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(54) Titre : COMPOSITIONS COMPRENANT UN OPIOIDE ET UN AUTRE PRINCIPE ACTIF PHARMACEUTIQUE POUR
OBTENIR UN EFFET ANALGESIQUE RAPIDE ET DURABLE, LES COMPOSITIONS POUVANT ETRE
ADMINISTREES INDEPENDAMMENT D'UNE PRISE ALIMENTAIRE

(54) Title: COMPOSITIONS COMPRISING AN OPIOID AND AN ADDITIONAL ACTIVE PHARMACEUTICAL
INGREDIENT FOR RAPID ONSET AND EXTENDED DURATION OF ANALGESIA THAT MAY BE ADMINISTERED
WITHOUT REGARD TO FOOD

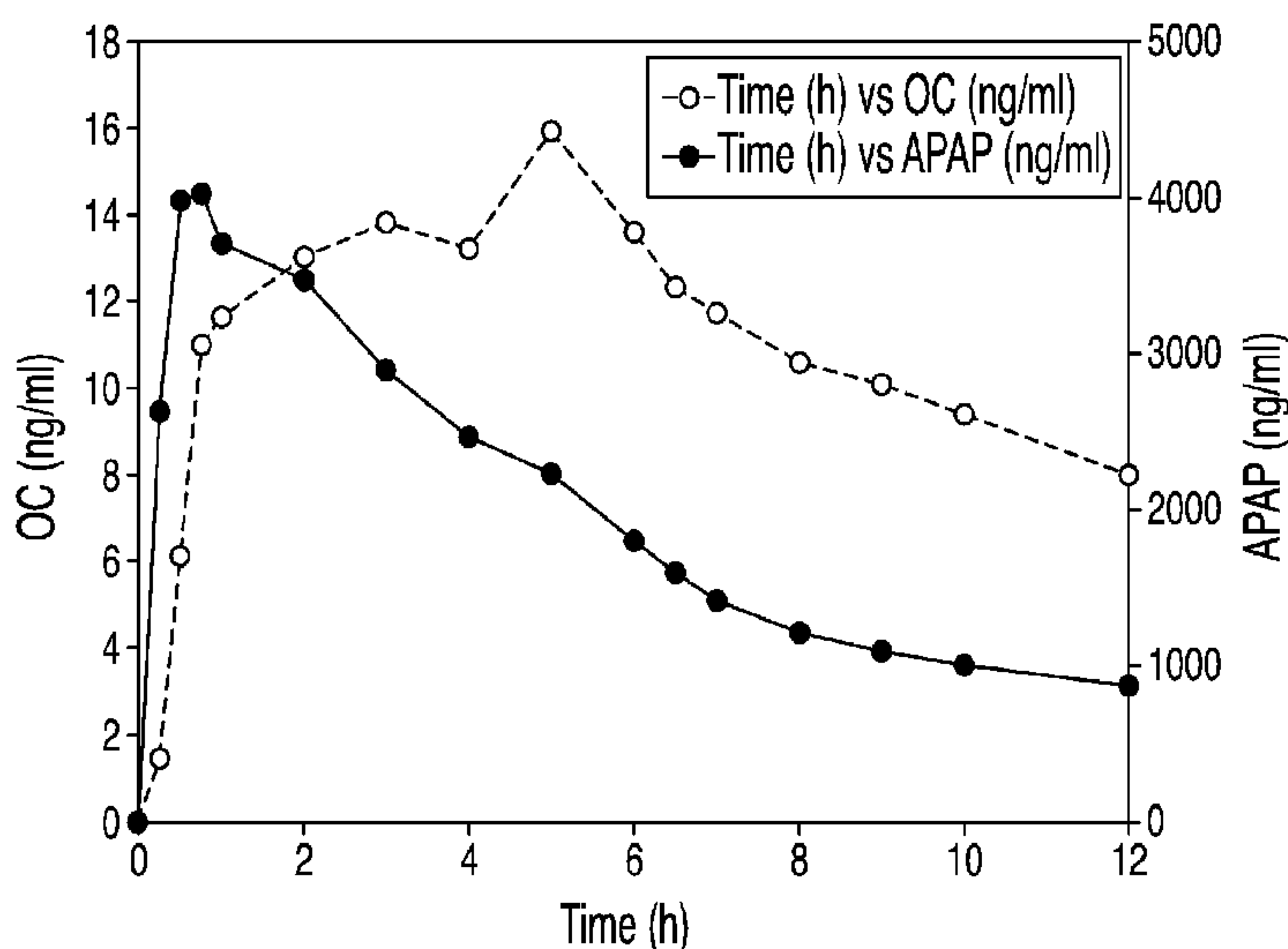


FIG. 107

(57) Abrégé/Abstract:

The present disclosure provides pharmaceutical compositions comprising an opioid and an additional active pharmaceutical ingredient, wherein the composition exhibits gastric retentive properties which are achieved by a combination of a physical property of the composition and release of the opioid, wherein upon administration to a subject, the composition has at least one pharmacokinetic parameter that differs by less than about 30% when the subject is in a fasted state as compared to a fed state. The present disclosure further provides pharmaceutical composition comprising oxycodone and acetaminophen that provides a rapid onset of analgesia, and reduced levels of acetaminophen near the end of the dosing interval. Also provided are an extended release pharmaceutical composition comprising oxycodone and acetaminophen that provides reduced abuse potential.

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[Continued on next page]

(54) Title: COMPOSITIONS COMPRISING AN OPIOID AND AN ADDITIONAL ACTIVE PHARMACEUTICAL INGREDIENT FOR RAPID ONSET AND EXTENDED DURATION OF ANALGESIA THAT MAY BE ADMINISTERED WITHOUT REGARD TO FOOD

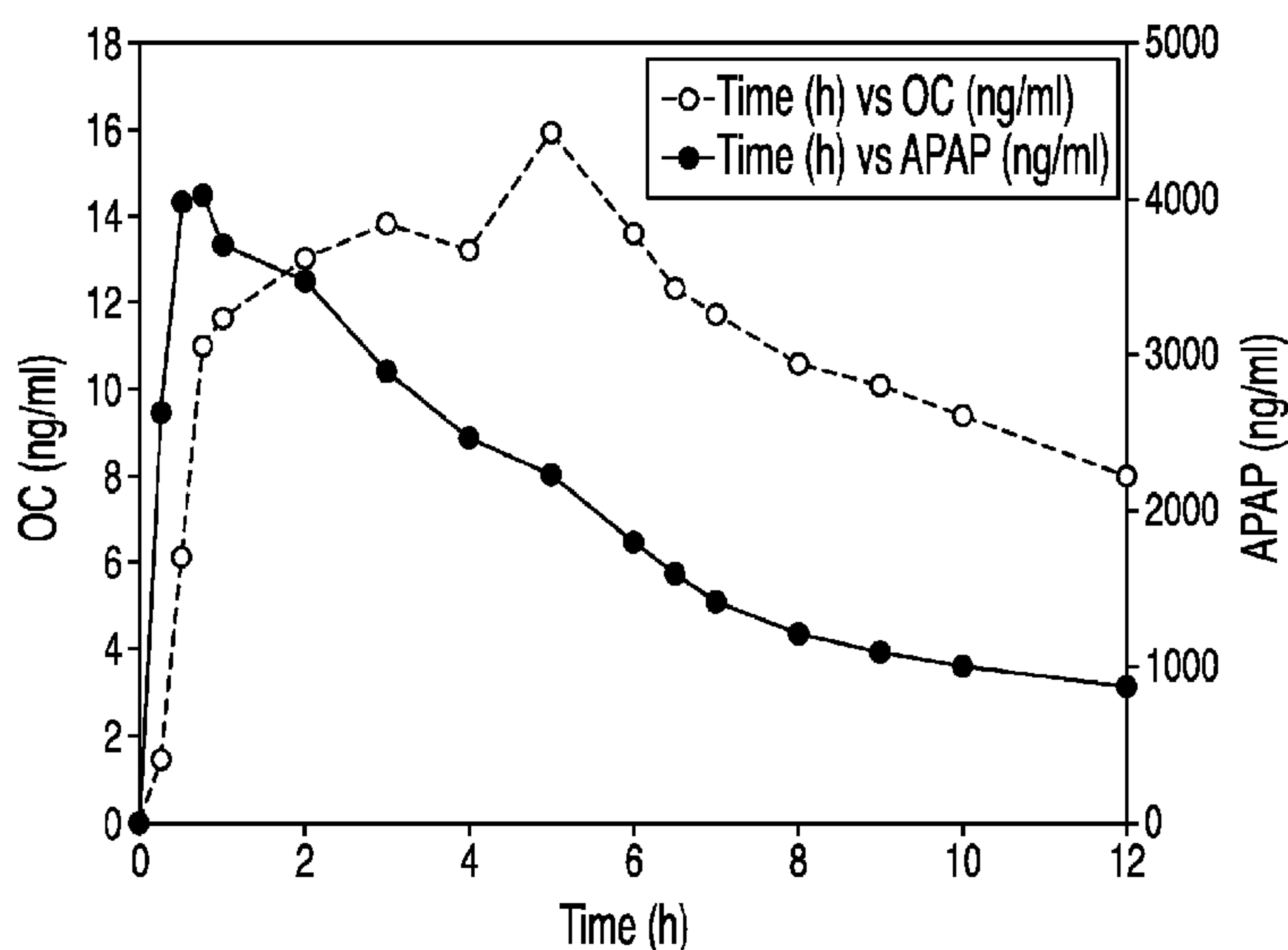


FIG. 107

(57) Abstract: The present disclosure provides pharmaceutical compositions comprising an opioid and an additional active pharmaceutical ingredient, wherein the composition exhibits gastric retentive properties which are achieved by a combination of a physical property of the composition and release of the opioid, wherein upon administration to a subject, the composition has at least one pharmacokinetic parameter that differs by less than about 30% when the subject is in a fasted state as compared to a fed state. The present disclosure further provides pharmaceutical composition comprising oxycodone and acetaminophen that provides a rapid onset of analgesia, and reduced levels of acetaminophen near the end of the dosing interval. Also provided are an extended release pharmaceutical composition comprising oxycodone and acetaminophen that provides reduced abuse potential.

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CONTENANT LES PAGES 1 À 144

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JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 3
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**COMPOSITIONS COMPRISING AN OPIOID AND AN ADDITIONAL ACTIVE
PHARMACEUTICAL INGREDIENT FOR RAPID ONSET AND EXTENDED DURATION
OF ANALGESIA THAT MAY BE ADMINISTERED WITHOUT REGARD TO FOOD**

RELATED CASES

[0001] This application claims priority to U.S. Provisional Application Nos. 61/794,848 and 61/798,525 filed on March 15, 2013, U.S. Provisional Application No. 61/871,956 filed on August 30, 2013, U.S. Provisional Application No. 61/871,690 U.S. filed on August 29, 2013, Provisional Application No. 61/926,027 filed on January 10, 2014, and U.S. Provisional Application No. 61/928,509 filed on January 17, 2014, which are incorporated herein by reference in their entirety to the full extent permitted by law.

FIELD OF THE INVENTION

[0002] The present disclosure relates to pharmaceutical compositions comprising an opioid and an additional active pharmaceutical ingredient wherein the compositions may be administered under fed or fasted conditions. The present disclosure further relates to extended release pharmaceutical compositions comprising oxycodone and acetaminophen that provide a rapid onset of analgesia, followed by an extended duration of analgesia of about 12 hours.

BACKGROUND OF THE INVENTION

[0003] Oral drug administration remains the route of choice for the majority of clinical applications. Modified release (MR) dosage forms that are administered once or twice daily offer advantages over their immediate release (IR) counterparts because they reduce the magnitude of peaks and troughs of drug plasma concentration, provide longer dosing intervals, sustained analgesic effect, and increased patient compliance. These modified release formulations may be referred to as controlled release (CR), sustained release (SR) and/or extended release (ER) etc. For certain types of patients, such as those suffering from pain, these MR products may permit the patient to sleep through the night without having to wake up during the night to take the next dose. Thus, these dosage forms can significantly increase the quality of life for such patients.

[0004] Gastroretentive (GR) dosage formulations have demonstrated successful delivery of drugs for extended durations of action. One way to improve drug absorption is to hold a drug delivery system above the preferred absorption site or window (proximal small intestine), and maintain the drug release at an appropriate rate. For

example, one strategy is to retain the formulation in the stomach (gastroretention). Over the last few decades, several gastroretentive drug delivery approaches have been designed and developed, including: high density (sinking) systems, which are retained in the bottom of the stomach, low density systems that float in gastric fluid due to buoyancy, mucoadhesive systems that release drugs following bio-adhesion to the gastric mucosa, superporous hydrogel systems, magnetic systems, and extendible or swellable systems that expand in the presence of water (gastric fluid) and fail to pass through the pyloric sphincter of stomach.

[0005] Parameters controlling the gastric retention of oral dosage forms include: density, size and shape of the dosage form, food intake and its nature (particularly fat content), total caloric content and frequency of intake, posture, gender, age, sex, sleep, body mass index, physical activity, disease states of the individual (e.g., diabetes), and administration of drugs with impact on gastrointestinal transit time, for example, drugs acting as anticholinergic agents (e.g., atropine, propantheline), opiates (e.g., codeine) and prokinetic agents (e.g., metoclopramide, cisapride).

[0006] Food intake (i.e., viscosity of food, food volume, caloric value, and frequency of feeding) may have a profound effect on the gastric retention of dosage forms. The presence or absence of food in the gastrointestinal tract (GIT) influences the gastric retention time (GRT) of the dosage form. Usually the presence of food in the gastrointestinal tract (GIT) improves the GRT of the dosage form and, thus, absorption increases because the drug stays at the preferred absorption site for a longer period of time. Indeed, GR formulations of the prior art should be administered with food in order to achieve the desired bioavailability.

[0007] There is a need, therefore, for extended release GR compositions comprising an opioid and a second active agent, wherein bioavailability of such composition is independent of food intake, thereby increasing the flexibility and ease of the administration of the composition.

[0008] Researchers have also combined various classes of pain drugs to provide better analgesia to patients. For example, a combination of acetaminophen-oxycodone hydrochloride is commercially available as Percocet and acetaminophen-hydrocodone bitartrate as Vicodin. In randomized controlled trials, it was

shown that the combination product Percocet was statistically superior to MR oxycodone in various outcome measures of pain relief. Other combination products such as Acetaminophen-Hydrocodone and Acetaminophen-Tramadol are either available or described in the literature. It is postulated that the combination of two analgesic drugs with complementary mechanisms of action results in enhanced analgesia due to an additive effect, an "opioid-sparing" effect, and an improved side effect and safety profile. The improved safety profile results from the use of reduced doses of two analgesics with different side-effects rather than an equieffective dose of a single agent.

[0009] Acetaminophen is absorbed from the small intestine and primarily metabolized by conjugation, like glucuronidation and sulfation, in the liver to nontoxic, water-soluble compounds that are eliminated in the urine. When the maximum daily dose is exceeded over a prolonged period, metabolism by conjugation becomes saturated, and excess acetaminophen is oxidatively metabolized by cytochrome P450 (CYP) enzymes (e.g., CYP2E1, 1A2, 2A6, 3A4) to a reactive metabolite, N-acetyl-p-benzoquinone-imine (NAPQI). NAPQI is a reactive free radical with an extremely short half-life that is rapidly inactivated by conjugation with glutathione, which is acting as a sulfhydryl donor. Once the pool of available glutathione is exhausted, the cysteines of cellular proteins become sulfhydryl donors to NAPQI, binding covalently and initiating a cascade of oxidative and cellular damage, resulting in necrosis and, ultimately, liver failure. Thus, avoiding excessive NAPQI formation is an important strategy when using acetaminophen, although to date acetaminophen-sparing has not been an approach any manufacturers have chosen to take. However, due to the prevalence of acetaminophen in many over-the-counter products, it is prudent to consider acetaminophen-sparing precautions when considering combination therapy lasting more than a few days to avoid an inadvertent reduction in glutathione stores.

[00010] Thus, various options for pain management are available that are both IR and MR, and contain either a single drug or a combination of analgesics. While these combination products provide the benefits associated with combining two analgesics as described above, both IR and MR, in itself, have a significant disadvantage. IR combination products lack the advantages of MR products described previously. MR combination products lack a significant benefit associated with IR products – rapid onset

of analgesia – that is extremely desirable for pain management. Because MR products retard the rate of drug release to sustain the drug effect over prolonged period, release of drug is slow resulting in significant time before effective analgesic drug concentration is attained in the bloodstream. There exists a clinical need for pain management that combines the desirable features of IR and MR in combination pain products.

SUMMARY OF THE INVENTION

[00011] Among the various aspects of the present disclosure is pharmaceutical composition comprising at least one extended release portion comprising an opioid, an additional active pharmaceutical ingredient, or a combination thereof, and at least one extended release component. At least one extended release portion comprises from about 60% to about 80% of the total amount of the opioid in the composition, and the composition has gastric retentive properties that are achieved by a combination of a physical property of the composition and release of the opioid. Moreover, when the composition is orally administered to a subject, the opioid or the additional active pharmaceutical ingredient produces a plasma profile characterized by at least one pharmacokinetic parameter that differs by less than about 30% when the subject is in a fasted state as compared to a fed.

[00012] A further aspect of the disclosure encompasses an extended release pharmaceutical composition comprising (a) at least one immediate release portion comprising an opioid, an additional active pharmaceutical ingredient, or a combination thereof, and (b) at least one extended release portion comprising an extended release component and an opioid, an additional active pharmaceutical ingredient, or a combination thereof. At least one immediate release portion comprises from about 20% to about 40% of the total amount of the opioid in the composition, and the composition has gastric retentive properties that are achieved by a combination of a physical property of the composition and release of the opioid. Additionally, when the composition is orally administered to a subject, the opioid or the additional active pharmaceutical ingredient in the composition produce a plasma profile characterized by at least one pharmacokinetic parameter that differs by less than about 30% when the subject is in a fasted state as compared to a fed state.

[00013] Still another aspect of the disclosure provides a method for administering a gastric retentive pharmaceutical composition comprising an opioid to a subject in need thereof. The method comprises orally administering an effective amount of the gastric retentive composition to the subject, the subject being in a fasted state, wherein the opioid in the composition produces a plasma profile characterized by at least one pharmacokinetic parameter that differs by less than about 30% when the subject is in a fasted state as compared to a fed state.

[00014] Still another aspect of the disclosure provides a method for administering a gastric retentive pharmaceutical composition comprising an opioid to a subject in need thereof. The method comprises orally administering an effective amount of the gastric retentive composition to the subject, the subject being in a fasted state, wherein the opioid in the composition produces a plasma profile characterized by at least one pharmacokinetic parameter that differs by less than about 30% when the subject is in a fasted state as compared to a fed state.

[00015] Yet another aspect of the disclosure encompasses a method for treating pain in a subject in need thereof. The method comprises orally administering an effective amount of a gastric retentive pharmaceutical composition comprising an opioid to the subject in a fasted state, wherein the opioid in the composition produces a plasma profile characterized by at least one pharmacokinetic parameter that differs by less than about 30% when the subject is in a fasted state as compared to a fed state.

[00016] Yet another aspect of the disclosure provides a pharmaceutical composition for oral administration in the treatment of pain, comprising (a) at least one immediate release portion comprising acetaminophen and oxycodone or a pharmaceutically acceptable salt thereof; and (b) at least one extended release portion comprising acetaminophen and oxycodone or salt thereof, and an extended release component, wherein the total amount of acetaminophen in the composition is about 325 mg to about 650 mg, and the total amount of oxycodone or salt in the composition is about 7.5 mg to about 15 mg, and wherein upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at a paddle speed of about 100 rpm in 900 ml of 0.1N HCl using a USP type II apparatus at a constant temperature of 37°C, about 30%, by weight, of the oxycodone or salt thereof is released at about 15 minutes in

the test and at least about 90%, by weight, of the acetaminophen is released at about 8 hours in the test. Further, upon oral administration of a single dose of the composition to a subject in need of analgesia, the composition provides a $C_{\max}$ for oxycodone from about 0.9 ng/mL/mg to about 1.6 ng/mL/mg, a $C_{\max}$ for acetaminophen from about 4.0 ng/mL/mg to about 11.0 ng/mL/mg, a $T_{\max}$ for oxycodone from about 2 hours to about 7 hours, and a $T_{\max}$ for acetaminophen from about 0.5 hour to about 6 hours.

[00017] In a further aspect of the disclosure provides a pharmaceutical composition for oral administration in the treatment of pain, comprising (a) at least one immediate release portion comprising acetaminophen and oxycodone or a pharmaceutically acceptable salt thereof, and (b) at least one extended release portion comprising acetaminophen and oxycodone or salt thereof, and an extended release component; wherein the total amount of acetaminophen in the composition is about 325 mg to about 650 mg, and the total amount of oxycodone or salt in the composition is about 7.5 mg to about 15 mg. Moreover, upon placement of the composition in an in vitro dissolution test comprising USP Paddle Method at a paddle speed of about 150 rpm in 900 ml of 0.1N HCl using a USP type II apparatus at a constant temperature of 37°C, no more than about 65%, by weight, of the total amount of the oxycodone or salt is released and no more than about 75%, by weight, of the total amount of the acetaminophen is released after 2 hours; from about 65% to about 85%, by weight, of the total amount of the oxycodone or salt is released and from about 70% to about 90%, by weight, of the total amount of the acetaminophen is released after 4 hours; from about 85% to about 100%, by weight, of the total amount of the oxycodone or salt is released and from about 85% to about 100%, by weight, of the total amount of the acetaminophen is released after 8 hours; and from about 95% to about 100%, by weight, of the total amount of the oxycodone or salt is released and from about 90% to about 100%, by weight, of the total amount of the acetaminophen is released after 12 hours.

[00018] An additional aspect of the disclosure provides for a pharmaceutical composition for oral administration in the treatment of pain, comprising (a) at least one immediate release portion comprising acetaminophen and oxycodone or a pharmaceutically acceptable salt thereof; and (b) at least one extended release portion comprising acetaminophen and oxycodone or salt thereof, and an extended release

component; wherein the total amount of acetaminophen in the composition is about 325 mg to about 650 mg, and the total amount of oxycodone or salt in the composition is about 7.5 mg to about 15 mg. And upon oral administration of the composition in an amount of about 15 mg oxycodone or salt and about 650 mg acetaminophen, the composition provides an $AUC_{0-1.7h}$ for acetaminophen of about 5.0 ng·h/mL/mg to about 13.0 ng·h/mL/mg; an $AUC_{1.7-48h}$ for acetaminophen of about 25.0 ng·h/mL/mg to about 75.0 ng·h/mL/mg; an $AUC_{0-2.8h}$ for oxycodone or salt of about 1.0 ng·h/mL/mg to about 3.0 ng·h/mL/mg ; and $AUC_{2.8-48h}$ of about 7.5 ng·h/mL/mg to about 15.0 ng·h/mL/mg.

[00019] Another aspect of the present disclosure is an extended release pharmaceutical composition comprising at least one extended release portion comprising oxycodone, acetaminophen, or a combination thereof, and at least one extended release component. At least one extended release portion comprises from about 60% to about 80% of the total amount of the oxycodone in the composition, and the composition has gastric retentive properties that are achieved by a combination of a physical property of the composition and release of the oxycodone. Moreover, when the composition is orally administered to a subject, the oxycodone or the acetaminophen produces a plasma profile characterized by at least one pharmacokinetic parameter that differs by less than about 30% when the subject is in a fasted state as compared to a fed state.

[00020] An additional aspect of the present disclosure provides a dosage form comprising from about 7.5 mg to about 30 mg of oxycodone and from about 325 mg to about 650 mg of acetaminophen. The dosage form comprises (a) at least one immediate release portion comprising about 25% of the total amount of oxycodone in the composition and about 50% of the total amount of acetaminophen in the composition; and (b) at least one extended release portion comprising about 75% of the total amount of oxycodone in the composition, about 50% of the total amount of acetaminophen in the composition, and about 35% to about 45%, by weight of the at least one extended release portion, of an extended release polymer comprising a polyethylene oxide.

[00021] A further aspect of the disclosure encompasses an extended release pharmaceutical composition comprising (a) at least one immediate release portion comprising oxycodone, acetaminophen, or a combination thereof, and (b) at least one extended release portion comprising an extended release component and oxycodone,

acetaminophen, or a combination thereof. At least one immediate release portion comprises from about 20% to about 40% of the total amount of the oxycodone in the composition, and the composition has gastric retentive properties that are achieved by a combination of a physical property of the composition and release of the oxycodone. Additionally, when the composition is orally administered to a subject, the oxycodone or the acetaminophen in the composition produce a plasma profile characterized by at least one pharmacokinetic parameter that differs by less than about 30% when the subject is in a fasted state as compared to a fed state.

[00022] A further aspect of the disclosure provides a method for reducing the risk of acetaminophen-induced hepatic damage in a subject being treated for pain with a dosage regimen that comprises administering to the subject at least two consecutive doses of a pharmaceutical composition comprising oxycodone and acetaminophen. The method comprises (a) administering a first dose of the pharmaceutical composition comprising at least one extended release portion comprising acetaminophen, oxycodone or a combination thereof, and an extended release component to the subject, wherein the composition maintains a therapeutic blood plasma concentration of oxycodone of at least 5 ng/mL from about 0.75 hours to about 10 hours after administration of the composition, and wherein at least about 90% of the acetaminophen is released from the composition by about 8 hours after administration of the composition such that, by about 10 hours after administration of the composition, acetaminophen has a blood plasma concentration that is less than about 30% of acetaminophen's maximum plasma concentration; and (b) administering a second dose of the pharmaceutical composition to the subject at about 12 hours after administration of the first dose.

[00023] Yet another aspect of the disclosure encompasses a method for treating pain in a subject in need thereof with a pharmaceutical composition that comprises oxycodone and acetaminophen. The method comprises orally administering to the subject an effective amount of pharmaceutical composition comprising least one extended release portion comprising oxycodone, acetaminophen or a combination thereof, and an extended release component, wherein the composition maintains a therapeutic plasma concentration of oxycodone of at least about 5 ng/mL from about 0.75 hour to about 10 hours after administration of the composition, and wherein at least about

90% of the acetaminophen is released from the composition by about 8 hours after administration of the composition such that, by about 10 hours after administration of the composition, the blood plasma concentration of acetaminophen is less than about 30% of acetaminophen's maximum plasma concentration.

[00024] A further aspect of the disclosure encompasses a pharmaceutical composition for extended release of oxycodone and acetaminophen comprising (a) at least one immediate release portion oxycodone, acetaminophen or a combination thereof, and (b) at least one extended release portion comprising oxycodone, acetaminophen or a combination thereof, and an extended release component wherein about 30% of the oxycodone in the pharmaceutical composition is released within about 15 minutes of administration and at least about 90% of the acetaminophen in the pharmaceutical composition is released in about 8 hours when measured in 900 ml of 0.1N HCl using a USP type II apparatus at a paddle speed of about 100 rpm and a constant temperature of 37°C.

[00025] Still another aspect of the disclosure provides a dosage form comprising (a) an immediate release portion comprising acetaminophen and oxycodone, wherein the immediate release portion comprises, by weight of the immediate release portion, from about 70% to about 80% of acetaminophen and from about 0.5% to about 1% of oxycodone; and (b) an extended release portion comprising acetaminophen, oxycodone, and an extended release polymer, wherein the extended release portion comprises, by weight of the extended release portion, from about 20% to about 40% of acetaminophen, from about 0.5% to about 2% of oxycodone, and from about 30% to about 50% of the extended release polymer.

[00026] Other features and aspects of the disclosure are described in detail below.

REFERENCE TO COLOR FIGURES

[00027] This application file contains at least one drawing executed in color. Copies of this patent application publication with color drawings will be provided by the Office upon request and payment of the necessary fee.

BRIEF DESCRIPTION OF THE DRAWINGS

[00028] FIG. 1 presents the *in vitro* release profile of oxycodone from oxycodone-acetaminophen bilayer tablets comprising either 15 or 30 mg of oxycodone, 500 mg of acetaminophen (APAP), and either 35% (w/w) POLYOX® 1105, 45% (w/w) POLYOX® 1105, or 45% (w/w) POLYOX® N60K, as indicated.

[00029] FIG. 2 shows the *in vitro* release profile of acetaminophen from oxycodone-acetaminophen bilayer tablets comprising either 15 or 30 mg of oxycodone, 500 mg of acetaminophen (APAP), and either 35% (w/w) POLYOX® 1105, 45% (w/w) POLYOX® 1105, or 45% (w/w) POLYOX® N60K, as indicated.

[00030] FIG. 3 presents the *in vitro* release profile of oxycodone from bilayer tablets comprising 7.5 mg of oxycodone and 325 mg of acetaminophen, and bilayer tablets comprising 15 mg of oxycodone and 650 mg of acetaminophen, as indicated.

[00031] FIG. 4 presents the *in vitro* release profile of acetaminophen from bilayer tablets comprising 7.5 mg of oxycodone and 325 mg of acetaminophen, and bilayer tablets comprising 15 mg of oxycodone and 650 mg of acetaminophen, as indicated.

[00032] FIG. 5 is a graphical representation of the mean plasma oxycodone concentrations as a function of time after administration of a single dose of bilayer tablet comprising 15 mg oxycodone/500 mg acetaminophen and having fast, medium, or slow release properties as compared to an immediate release 7.5 oxycodone/325 acetaminophen tablet administered twice at a 6 hr interval.

[00033] FIG. 6 is a graphical representation of the mean plasma acetaminophen concentrations as a function of time after administration of a single dose of bilayer tablet comprising 15 mg oxycodone/500 mg acetaminophen and having fast, medium, or slow release properties as compared to an immediate release 7.5 oxycodone/325 acetaminophen tablet administered twice at a 6 hr interval. The immediate release 7.5 oxycodone/325 acetaminophen tablet dose was normalized.

[00034] FIG. 7 is a graphical representation of the mean plasma oxycodone concentrations as a function of time after administration of a single dose of bilayer tablet comprising 30 mg oxycodone/500 mg acetaminophen and having fast, medium, or slow release properties as compared to an immediate release 7.5 oxycodone/325

acetaminophen tablet administered twice at a 6 hr interval. The immediate release 7.5 oxycodone/325 acetaminophen tablet dose was normalized.

[00035] FIG. 8 is a graphical representation of the mean plasma acetaminophen concentrations as a function of time after administration of a single dose of bilayer tablet comprising 30 mg oxycodone/500 mg acetaminophen and having fast, medium, or slow release properties as compared to an immediate release 7.5 oxycodone/325 acetaminophen tablet administered twice at a 6 hr interval. The immediate release 7.5 oxycodone/325 acetaminophen tablet dose was normalized.

[00036] FIG. 9 shows the mean plasma concentrations of oxycodone versus time by treatment. Treatment A was one tablet of 15 mg oxycodone/650 mg acetaminophen administered orally under fed conditions. Treatment B was two tablets of 15 mg oxycodone/650 mg acetaminophen administered orally one at a time under fed conditions. Treatment C was one tablet of an immediate release 7.5 oxycodone/325 acetaminophen tablet administered orally every 6 hours for 2 doses under fed conditions.

[00037] FIG. 10 presents the mean plasma concentrations of acetaminophen versus time by treatment. Treatment A was one tablet of 15 mg oxycodone/650 mg acetaminophen administered orally under fed conditions. Treatment B was two tablets of 15 mg oxycodone/650 mg acetaminophen administered orally one at a time under fed conditions. Treatment C was one tablet of an immediate release 7.5 oxycodone/325 acetaminophen tablet administered orally every 6 hours for 2 doses under fed conditions.

[00038] FIG. 11 shows the mean plasma concentrations of oxycodone versus time by treatment. Treatment A was one tablet of 15 mg oxycodone/650 mg acetaminophen administered orally every 12 hours for 4.5 days (9 doses) under fed conditions. Treatment B was two tablets of 15 mg oxycodone/650 mg acetaminophen administered orally one at a time every 12 hours for 4.5 days (9 doses) under fed conditions. Treatment C was two tablets of an immediate release 7.5 oxycodone/325 acetaminophen tablet administered orally every 6 hours for 4.5 days (18 doses) under fed conditions.

[00039] FIG. 12 shows the mean plasma concentrations of acetaminophen versus time by treatment. Treatment A was one tablet of 15 mg oxycodone/650 mg acetaminophen administered orally every 12 hours for 4.5 days (9 doses) under fed

conditions. Treatment B was two tablets of 15 mg oxycodone/650 mg acetaminophen administered orally one at a time every 12 hours for 4.5 days (9 doses) under fed conditions. Treatment C was two tablets of an immediate release 7.5 oxycodone/325 acetaminophen tablet administered orally every 6 hours for 4.5 days (18 doses) under fed conditions.

[00040] FIG. 13 presents the mean plasma concentrations of oxycodone versus time by treatment following oral administration of one tablet of 15 mg oxycodone/650 mg acetaminophen. Treatment A was under fed conditions. Treatment B was under fasted conditions.

[00041] FIG. 14 shows the mean plasma concentrations of oxycodone versus time by treatment following oral administration of two tablets of 15 mg oxycodone/650 mg acetaminophen. Treatment A was under fed conditions. Treatment B was under fasted conditions.

[00042] FIG. 15 presents the mean plasma concentrations of acetaminophen versus time by treatment following oral administration of one tablet of 15 mg oxycodone/650 mg acetaminophen. Treatment A was under fed conditions. Treatment B was under fasted conditions.

[00043] FIG. 16 shows mean plasma concentrations of acetaminophen versus time by treatment following oral administration of two tablets of 15 mg oxycodone/650 mg acetaminophen. Treatment A was under fed conditions. Treatment B was under fasted conditions.

[00044] FIG. 17 illustrates the *in vitro* release of oxycodone from a bilayer tablet comprising 7.5 mg of oxycodone/ 325 mg of acetaminophen tested in 0.1 N HCl at a paddle speed of 150 rpm containing 0%, 5%, 20%, or 40% ethanol. Plotted is the percent of oxycodone released over a period of 2 hours.

[00045] FIG. 18 presents the *in vitro* release of acetaminophen from a bilayer tablet comprising 7.5 mg of oxycodone/ 325 mg of acetaminophen tested in 0.1 N HCl at a paddle speed of 150 rpm containing 0%, 5%, 20%, or 40% ethanol. Plotted is the percent of acetaminophen released over a 2 hour period.

[00046] FIG. 19 shows the mean plasma concentrations of oxycodone as a function of time by treatment following oral administration of two tablets of 7.5 mg of

oxycodone/325 mg of acetaminophen. Treatment A was under fed (high fat) conditions. Treatment B was under fed (low fat) conditions. Treatment C was under fasted conditions.

[00047] FIG. 20 presents the mean plasma concentrations of acetaminophen as a function of time by treatment following oral administration of two tablets of 7.5 mg of oxycodone/325 mg of acetaminophen. Treatment A was under fed (high fat) conditions. Treatment B was under fed (low fat) conditions. Treatment C was under fasted conditions.

[00048] FIG. 21 shows the mean plasma concentrations of oxycodone versus time by treatment. Treatment A was one tablet of 7.5 mg oxycodone/325 mg acetaminophen administered orally under fasted conditions. Treatment B was two tablets of 7.5 mg oxycodone/325 mg acetaminophen administered orally under fasted conditions. Treatment C was one tablet of an immediate release 7.5 oxycodone/325 acetaminophen tablet administered orally every 6 hours for 2 doses under fasted conditions. Treatment D was two tablets of an immediate release 7.5 oxycodone/325 acetaminophen tablet administered orally every 6 hours for 2 doses under fasted conditions.

[00049] FIG. 22 presents the mean plasma concentrations of acetaminophen versus time by treatment. Treatment A was one tablet of 7.5 mg oxycodone/325 mg acetaminophen administered orally under fasted conditions. Treatment B was two tablets of 7.5 mg oxycodone/325 mg acetaminophen administered orally under fasted conditions. Treatment C was one tablet of an immediate release 7.5 oxycodone/325 acetaminophen tablet administered orally every 6 hours for 2 doses under fasted conditions. Treatment D was two tablets an immediate release 7.5 oxycodone/325 acetaminophen tablet administered orally every 6 hours for 2 doses under fasted conditions.

[00050] FIG. 23 shows a deconvolution plot of the biphasic absorption of oxycodone from tablets of the 7.5 mg oxycodone/325 mg acetaminophen formulation. The cumulative amount of oxycodone is plotted versus time. Circles represent one tablet of 7.5 mg oxycodone/325 mg acetaminophen; squares represent two tablets of 7.5 mg oxycodone/325 mg acetaminophen; and the immediate release 7.5 oxycodone/325 acetaminophen tablet is shown in a solid line with no symbols.

[00051] FIG. 24 presents a deconvolution plot of the biphasic absorption of acetaminophen from tablets of the 7.5 mg oxycodone/325 mg acetaminophen formulation. The cumulative amount of acetaminophen is plotted versus time. Circles represent one tablet of 7.5 mg oxycodone/325 mg acetaminophen; triangles represent two tablets of 7.5 mg oxycodone/325 mg acetaminophen; and squares represent the immediate release 7.5 oxycodone/325 acetaminophen product.

[00052] FIG. 25 shows the mean plasma concentrations of oxycodone versus time by treatment. Treatment A was one tablet of 7.5 mg oxycodone/325 mg acetaminophen administered orally every 12 hours for 4.5 days (9 doses) under fasted conditions. Treatment B was two tablets of 7.5 mg oxycodone/325 mg acetaminophen administered orally every 12 hours for 4.5 days (9 doses) under fasted conditions. Treatment C was one tablet of an immediate release 7.5 oxycodone/325 acetaminophen tablet administered orally every 6 hours for 4.5 days (18 doses) under fasted conditions.

[00053] FIG. 26 presents the mean plasma concentrations of acetaminophen versus time by treatment. Treatment A was one tablet of 7.5 mg oxycodone/325 mg acetaminophen administered orally every 12 hours for 4.5 days (9 doses) under fasted conditions. Treatment B was two tablets of 7.5 mg oxycodone/325 mg acetaminophen administered orally every 12 hours for 4.5 days (9 doses) under fasted conditions. Treatment C was one tablet of an immediate release 7.5 oxycodone/325 acetaminophen tablet administered orally every 6 hours for 4.5 days (18 doses) under fasted conditions.

[00054] FIG. 27A is a bar graph depicting the simulated fractional absorption of acetaminophen in the upper GIT of a human subject after treatment of a 7.5 mg oxycodone/325 mg acetaminophen immediate release formulation.

[00055] FIG. 27B is a bar graph depicting the simulated fractional absorption of acetaminophen in the upper GIT of a human subject after treatment of a 7.5 mg oxycodone/325 mg acetaminophen immediate release formulation, wherein the formulation's transit time from the stomach through ileum 3 has been doubled.

[00056] FIG. 27C is a bar graph depicting the simulated fractional absorption of acetaminophen in the upper GIT of a human subject after treatment of a 7.5 mg oxycodone/325 mg acetaminophen immediate release formulation, wherein the formulation's transit time in the stomach has been increased by two hours.

[00057] FIG. 28A is a bar graph depicting the simulated fractional absorption of oxycodone in the upper GIT of a human subject after treatment of a 7.5 mg oxycodone/325 mg acetaminophen immediate release formulation.

[00058] FIG. 28B is a bar graph depicting the simulated fractional absorption of oxycodone in the upper GIT of a human subject after treatment of a 7.5 mg oxycodone/325 mg acetaminophen immediate release formulation, wherein the formulation's transit time from the stomach through ileum 3 has been doubled.

[00059] FIG. 28C is a bar graph depicting the simulated fractional absorption of oxycodone in the upper GIT of a human subject after treatment of a 7.5 mg oxycodone/325 mg acetaminophen immediate release formulation, wherein the formulation's transit time in the stomach has been increased by two hours.

[00060] FIG. 29A presents the mean plasma concentrations and Partial AUCs of acetaminophen (e.g., $AUC_{0-1.7h}$ and $AUC_{1.7-48h}$) versus time by treatment: (1) Treatment B of Example 10, (2) Treatment C of Example 9, and (3) Treatment D of Example 10.

[00061] FIG. 29B presents the mean plasma concentrations and Partial AUCs of oxycodone (e.g., $AUC_{0-2.8h}$ and $AUC_{2.8-48h}$) versus time treatment: (1) Treatment B of Example 10, (2) Treatment C of Example 9, and (3) Treatment D of Example 10.

[00062] FIG. 30A presents the mean plasma concentrations and Partial AUCs of oxycodone versus time for Treatment A of Example 4, Treatment A of Example 6, and Treatment C of Example 4.

[00063] FIG. 30B presents the mean plasma concentrations and Partial AUCs of acetaminophen versus time for Treatment A of Example 4, Treatment A of Example 6, and Treatment C of Example 4.

[00064] FIG. 31 presents oxycodone dissolution data from crushed and intact immediate release tablets containing 7.5 mg oxycodone and 325 mg acetaminophen.

[00065] FIGS. 32A and 32B present acetaminophen dissolution data from crushed and intact pharmaceutical formulations described herein containing a total of 7.5 mg oxycodone and a total of 325 mg acetaminophen per tablet.

[00066] FIGS. 33A and 33B present oxycodone HCl dissolution data from crushed and intact pharmaceutical formulations described herein containing a total of 7.5 mg oxycodone and a total of 325 mg acetaminophen per tablet.

[00067] FIG. 34 presents acetaminophen dissolution data for three pharmaceutical formulations described herein. The dissolution data represents an extended release tablet with the immediate release data theoretically added. For each formulation, the tablet contained a total of 9 mg oxycodone HCl and a total of 250 mg acetaminophen. The three pharmaceutical formulations contained 25% by weight POLYOX® 205, 1105, and N-60K, respectively.

[00068] FIG. 35 presents oxycodone HCl dissolution data for the three pharmaceutical formulations described in FIG. 34.

[00069] FIG. 36 presents acetaminophen dissolution data for three pharmaceutical formulations described herein. The dissolution data represents an extended release tablet with the immediate release data theoretically added. For each formulation, the tablet contained a total of 9 mg oxycodone HCl and a total of 250 mg acetaminophen. The three pharmaceutical formulations contained 45% by weight POLYOX® 205, 1105, and N-60K, respectively.

[00070] FIG. 37 presents oxycodone HCl dissolution data for the three pharmaceutical formulations described in FIG. 36.

[00071] FIG. 38 presents acetaminophen dissolution data for four pharmaceutical formulations described herein. The dissolution data represents an extended release tablet with the immediate release data theoretically added. For each formulation, the tablet contained a total of 9 mg oxycodone HCl and a total of 250 mg acetaminophen. The four pharmaceutical compositions contained 25% by weight, 35% by weight, 45% by weight, and 55% by weight POLYOX® 1105, respectively.

[00072] FIG. 39 presents oxycodone HCl dissolution data for the three pharmaceutical formulations described in FIG. 38.

[00073] FIG. 40 presents the in vitro release of oxycodone from a bilayer tablet comprising 7.5 mg of oxycodone/ 325 mg of acetaminophen tested in 0.1 N HCl at a paddle speed of 100 rpm containing 0%, 5%, 20%, or 40% ethanol. Plotted is the percent of oxycodone released over a period of 8 hours.

[00074] FIG. 41 presents the in vitro release of acetaminophen from a bilayer tablet comprising 7.5 mg of oxycodone/ 325 mg of acetaminophen tested in 0.1 N HCl at

a paddle speed of 100 rpm containing 0%, 5%, 20%, or 40% ethanol. Plotted is the percent of acetaminophen released over a 8 hour period.

[00075] FIG. 42 presents the mean plasma concentrations of oxycodone versus time for A-F of Example 29.

[00076] FIG. 43 presents the mean plasma concentrations of acetaminophen versus time for Groups A-F of Example 29.

[00077] FIG. 44 presents the mean drug liking scores over time for Groups A-G of Example 29.

[00078] FIG. 45 presents the mean drug high scores over time for Groups A-G of Example 29.

[00079] FIG. 46 presents the mean good drug effects scores over time for Groups A-G of Example 29.

[00080] FIG. 47 presents the baseline adjusted pupillometry scores versus time for the subjects who completed the study set out in Example 29.

[00081] FIG. 48 presents the mean plasma concentrations of oxycodone versus time for Treatments A, B, and D of Example 30.

[00082] FIG. 49 presents the mean plasma concentrations of acetaminophen versus time for Treatments A, C, and D of Example 30.

[00083] FIG. 50 presents the mean plasma concentrations of oxycodone versus time for Treatments A, B, and D of Example 31.

[00084] FIG. 51 presents the mean plasma concentrations of acetaminophen versus time for Treatments A, C, and D of Example 31.

[00085] FIG. 52 presents the plasma oxycodone concentration over time, as well as half-value duration (HVD) and C_{max} in a single dose study in which patients received either a single dose of immediate-release oxycodone/acetaminophen (two total tablets, 7.5 mg oxycodone/ 325 mg acetaminophen per tablet administered at 0h and 6h) or a single dose of controlled-release oxycodone/acetaminophen (two total tablets, 7.5 mg oxycodone/ 325 mg acetaminophen per tablet, both administered at 0h).

[00086] FIG. 53 presents the plasma oxycodone concentration over time, as well as half-value duration (HVD) and mean C_{max} , during day 1 of a multi-dose study in which patients received either immediate-release oxycodone/acetaminophen (7.5 mg

oxycodone/ 325 mg acetaminophen per tablet administered as one tablet every 6 hours for 4.5 days) or controlled-release oxycodone/acetaminophen (two tablets of 7.5 mg oxycodone/ 325 mg acetaminophen per tablet (15 mg/650 mg total per dose) administered every 12 hours for 4.5 days).

[00087] FIG. 54 presents the plasma oxycodone concentration over time, as well as half-value duration (HVD) and mean C_{max} , during steady state (day 5) of a multi-dose study in which patients received either immediate-release oxycodone/acetaminophen (7.5 mg oxycodone/ 325 mg acetaminophen per tablet administered as one tablet every 6 hours for 4.5 days) or controlled-release oxycodone/acetaminophen (two tablets of 7.5 mg oxycodone/ 325 mg acetaminophen per tablet (15 mg/650 mg total per dose) administered every 12 hours for 4.5 days).

[00088] FIG. 55 presents the plasma acetaminophen concentration following single-dose of administration of controlled release oxycodone/acetaminophen. Patients received either 1 tablet (7.5 mg oxycodone/ 325 mg acetaminophen), 2 tablets (15 mg oxycodone/ 650 mg acetaminophen), or 4 tablets (30 mg oxycodone/ 1300 mg acetaminophen) as a single dose.

[00089] FIG. 56 presents the plasma acetaminophen concentration over days 1 to 4 during a multi-dose study of controlled-release oxycodone/acetaminophen. Patients received either 1 tablet (7.5 mg oxycodone/ 325 mg acetaminophen) every 12 hours or 2 tablets (15 mg oxycodone/ 650 mg acetaminophen) every 12 hours for 4.5 days (9 total doses).

[00090] FIG. 57 presents the steady-state plasma acetaminophen concentration (hours 96 to 144 on day 5) during a multi-dose study of controlled-release oxycodone/acetaminophen. Patients received either 1 tablet (7.5 mg oxycodone/ 325 mg acetaminophen) every 12 hours or 2 tablets (15 mg oxycodone/ 650 mg acetaminophen) every 12 hours for 4.5 days (9 total doses).

[00091] FIG. 58 presents the plasma oxycodone concentration following single-dose of administration of controlled release oxycodone/acetaminophen. Patients received either 1 tablet (7.5 mg oxycodone/ 325 mg acetaminophen), 2 tablets (15 mg oxycodone/ 650 mg acetaminophen), or 4 tablets (30 mg oxycodone/ 1300 mg acetaminophen) as a single dose.

[00092] FIG. 59 presents the plasma oxycodone concentration over days 1 to 4 during a multi-dose study of controlled-release oxycodone/acetaminophen. Patients received either 1 tablet (7.5 mg oxycodone/ 325 mg acetaminophen) every 12 hours or 2 tablets (15 mg oxycodone/ 650 mg acetaminophen) every 12 hours for 4.5 days (9 total doses).

[00093] FIG. 60 presents the steady-state plasma oxycodone concentration (hours 96 to 144 on day 5) during a multi-dose study of controlled-release oxycodone/acetaminophen. Patients received either 1 tablet (7.5 mg oxycodone/ 325 mg acetaminophen) every 12 hours or 2 tablets (15 mg oxycodone/ 650 mg acetaminophen) every 12 hours for 4.5 days (9 total doses).

[00094] FIG. 61 presents the participant-reported visual analog scale (VAS) scores for drug liking over time for patients receiving either low-dose intact controlled-release oxycodone/acetaminophen (2 tablets of 7.5 mg/325 mg, total dose of 15 mg/650 mg) or low-dose intact immediate-release oxycodone/acetaminophen (2 tablets of 7.5 mg/325 mg, total dose of 15 mg/650 mg).

[00095] FIG. 62 presents the participant-reported visual analog scale (VAS) scores for drug liking over time for patients receiving either high-dose intact controlled-release oxycodone/acetaminophen (4 tablets of 7.5 mg/325 mg, total dose of 30 mg/1300 mg) or high-dose intact immediate-release oxycodone/acetaminophen (4 tablets of 7.5 mg/325 mg, total dose of 30 mg/1300 mg).

[00096] FIG. 63 presents the participant-reported visual analog scale (VAS) scores for drug liking over time for patients receiving either high-dose intact controlled-release oxycodone/acetaminophen (4 tablets of 7.5 mg/325 mg, total dose of 30 mg/1300 mg) or high-dose crushed controlled-release oxycodone/ acetaminophen (4 tablets of 7.5 mg/325 mg crushed and encapsulated, total dose of 30 mg/1300 mg).

[00097] FIG. 64 presents the participant-reported visual analog scale (VAS) scores for drug liking over time for patients receiving either high-dose crushed controlled-release oxycodone/acetaminophen (4 tablets of 7.5 mg/325 mg crushed and encapsulated, total dose of 30 mg/1300 mg) or high-dose crushed immediate-release oxycodone/ acetaminophen (4 tablets of 7.5 mg/325 mg crushed and encapsulated, total dose of 30 mg/1300 mg).

[00098] FIG. 65 presents the participant-reported visual analog scale (VAS) scores for drug high over time for patients receiving either low-dose intact controlled-release oxycodone/acetaminophen (2 tablets of 7.5 mg/325 mg, total dose of 15 mg/650 mg) or low-dose intact immediate-release oxycodone/acetaminophen (2 tablets of 7.5 mg/325 mg, total dose of 15 mg/650 mg).

[00099] FIG. 66 presents the participant-reported visual analog scale (VAS) scores for drug high over time for patients receiving either high-dose intact controlled-release oxycodone/acetaminophen (4 tablets of 7.5 mg/325 mg, total dose of 30 mg/1300 mg) or high-dose intact immediate-release oxycodone/acetaminophen (4 tablets of 7.5 mg/325 mg, total dose of 30 mg/1300 mg).

[000100] FIG. 67 presents the participant-reported visual analog scale (VAS) scores for drug high over time for patients receiving either high-dose intact controlled-release oxycodone/acetaminophen (4 tablets of 7.5 mg/325 mg, total dose of 30 mg/1300 mg) or high-dose crushed controlled-release oxycodone/acetaminophen (4 tablets of 7.5 mg/325 mg crushed and encapsulated, total dose of 30 mg/1300 mg).

[000101] FIG. 68 presents the participant-reported visual analog scale (VAS) scores for drug high over time for patients receiving either high-dose crushed controlled-release oxycodone/acetaminophen (4 tablets of 7.5 mg/325 mg crushed and encapsulated, total dose of 30 mg/1300 mg) or high-dose crushed immediate-release oxycodone/acetaminophen (4 tablets of 7.5 mg/325 mg crushed and encapsulated, total dose of 30 mg/1300 mg).

[000102] FIG. 69 presents the least-squares mean $E_{\max}$ for drug liking for patients receiving either high-dose intact controlled-release oxycodone/acetaminophen (4 tablets of 7.5 mg/325 mg, total dose of 30 mg/1300 mg) or high-dose intact immediate-release oxycodone/acetaminophen (4 tablets of 7.5 mg/325 mg, total dose of 30 mg/1300 mg).

[000103] FIG. 70 presents the least-squares mean $E_{\max}$ for drug high and good drug effects for patients receiving either high-dose intact controlled-release oxycodone/acetaminophen (4 tablets of 7.5 mg/325 mg, total dose of 30 mg/1300 mg) or high-dose intact immediate-release oxycodone/acetaminophen (4 tablets of 7.5 mg/325 mg, total dose of 30 mg/1300 mg).

[000104] FIG. 71 presents the least-squares mean TE_{max} for drug liking, drug high, and good drug effects for patients receiving either high-dose intact controlled-release oxycodone/acetaminophen (4 tablets of 7.5 mg/325 mg, total dose of 30 mg/1300 mg) or high-dose intact immediate-release oxycodone/acetaminophen (4 tablets of 7.5 mg/325 mg, total dose of 30 mg/1300 mg).

[000105] FIG. 72 presents the mean pupillometry scores over time for patients receiving the following: low-dose intact controlled-release oxycodone/acetaminophen (2 tablets of 7.5 mg/325 mg, total dose of 15 mg/650 mg); low-dose intact immediate-release oxycodone/acetaminophen (2 tablets of 7.5 mg/325 mg, total dose of 15 mg/650 mg); high-dose intact controlled-release oxycodone/acetaminophen (4 tablets of 7.5 mg/325 mg, total dose of 30 mg/1300 mg); high-dose intact immediate-release oxycodone/acetaminophen (4 tablets of 7.5 mg/325 mg, total dose of 30 mg/1300 mg); high-dose crushed controlled-release oxycodone/acetaminophen (4 tablets of 7.5 mg/325 mg crushed and encapsulated, total dose of 30 mg/1300 mg); or high-dose crushed immediate-release oxycodone/ acetaminophen (4 tablets of 7.5 mg/325 mg crushed and encapsulated, total dose of 30 mg/1300 mg).

[000106] FIG. 73 presents simulated oxycodone plasma levels over time during multidose administration of either controlled-release oxycodone/acetaminophen or immediate-release oxycodone/acetaminophen. The solid line represents the simulated plasma levels for patients receiving two tablets of controlled-release 7.5 mg oxycodone /325 mg acetaminophen (total dose of 15 mg/650 mg) every 12 hours for 4.5 days (18 tablets total). The dashed line represents the simulated plasma levels for patients receiving one tablet of immediate-release 7.5 mg oxycodone /325 mg acetaminophen every 6 hours for 4.5 days (18 tablets total).

[000107] FIG. 74 presents the mean steady-state plasma concentration of oxycodone beginning at the point in time when patients in the study receiving controlled-release oxycodone/acetaminophen were administered their last dose. Patients in the study were administered oxycodone/acetaminophen according to one of the following three dosing regimens: Treatment A administered 1 tablet of controlled-release oxycodone/acetaminophen (7.5 mg oxycodone /325 mg acetaminophen) every 12 hours for 4.5 days; Treatment B administered 2 tablets of

controlled-release oxycodone/acetaminophen (15 mg oxycodone /650 mg acetaminophen total per dose) every 12 hours for 4.5 days; Treatment C administered 1 tablet of immediate-release oxycodone/acetaminophen (7.5 mg oxycodone /325 mg acetaminophen) every 6 hours for 4.5 days.

[000108] FIG. 75 presents the mean steady-state plasma concentration of acetaminophen beginning at the point in time when patients in the study receiving controlled-release oxycodone/acetaminophen were administered their last dose. Patients in the study were administered oxycodone/acetaminophen according to one of the following three dosing regimens: Treatment A administered 1 tablet of controlled-release oxycodone/acetaminophen (7.5 mg oxycodone /325 mg acetaminophen) every 12 hours for 4.5 days; Treatment B administered 2 tablets of controlled-release oxycodone/acetaminophen (15 mg oxycodone /650 mg acetaminophen total per dose) every 12 hours for 4.5 days; Treatment C administered 1 tablet of immediate-release oxycodone/acetaminophen (7.5 mg oxycodone /325 mg acetaminophen) every 6 hours for 4.5 days.

[000109] FIG. 76 presents the mean plasma concentration of oxycodone over time at steady state for patients completing all study periods of the study described in Example 37. Patients in the study received each of the following treatments separately, in one of four different sequences, with a washout period between them: 2 tablets of controlled-release 7.5 mg oxycodone/325 mg acetaminophen (15 mg oxycodone /650 mg acetaminophen total per dose) every 12 hours for 4.5 days; 1 tablet of commercially available oxycodone (15 mg) every 6 hours for 4.5 days; 1 tablet of immediate-release 37.5 mg tramadol/325 mg acetaminophen every 6 hours for 4.5 days; and 1 tablet of immediate-release 7.5 mg oxycodone /325 mg acetaminophen every 6 hours for 4.5 days. Only data for the three treatments with oxycodone are included in FIG. 76.

[000110] FIG. 77 presents the mean plasma concentration of acetaminophen over time at steady state for patients completing all study periods of the study described in Example 37. Patients in the study received each of the following treatments separately, in one of four different sequences, with a washout period between them: 2 tablets of controlled-release 7.5 mg oxycodone/325 mg acetaminophen (15 mg oxycodone /650 mg acetaminophen total per dose) every 12 hours for 4.5 days; 1 tablet of commercially

available oxycodone (15 mg) every 6 hours for 4.5 days; 1 tablet of immediate-release 37.5 mg tramadol/325 mg acetaminophen every 6 hours for 4.5 days; and 1 tablet of immediate-release 7.5 mg oxycodone /325 mg acetaminophen every 6 hours for 4.5 days. Only data for the three treatments with acetaminophen are included in FIG. 77.

[000111] FIG. 78 presents the mean plasma concentration of oxycodone over time for patients completing all study periods of the study described in Example 38. Patients in the study received each of the following treatments separately, in one of four different sequences, with a washout period between them: 2 tablets of controlled-release 7.5 mg oxycodone/325 mg acetaminophen (15 mg oxycodone /650 mg acetaminophen total per dose) administered once; 1 tablet of commercially available oxycodone (15 mg) every 6 hours for two doses; 1 tablet of immediate-release 37.5 mg tramadol/325 mg acetaminophen every 6 hours for two doses; and 1 tablet of immediate-release 7.5 mg oxycodone /325 mg acetaminophen every 6 hours for two doses. Only data for the three treatments with oxycodone are included in FIG. 78.

[000112] FIG. 79 presents the mean plasma concentration of acetaminophen over time for patients completing all study periods of the study described in Example 38. Patients in the study received each of the following treatments separately, in one of four different sequences, with a washout period between them: 2 tablets of controlled-release 7.5 mg oxycodone/325 mg acetaminophen (15 mg oxycodone /650 mg acetaminophen total per dose) administered once; 1 tablet of commercially available oxycodone (15 mg) every 6 hours for two doses; 1 tablet of immediate-release 37.5 mg tramadol/325 mg acetaminophen every 6 hours for two doses; and 1 tablet of immediate-release 7.5 mg oxycodone /325 mg acetaminophen every 6 hours for two doses. Only data for the three treatments with acetaminophen are included in FIG. 79.

[000113] FIG. 80 presents the plasma acetaminophen concentration over time during the first 12 hours after dosing, as well as half-value duration (HVD) and C_{max} , in a single dose study in which patients received either a single dose of immediate-release oxycodone/acetaminophen (two total tablets, 7.5 mg oxycodone/ 325 mg acetaminophen per tablet, 1 tablet administered at 0h and 1 tablet at 6h) or a single dose of controlled-release oxycodone/acetaminophen (two total tablets, 7.5 mg oxycodone/ 325 mg acetaminophen per tablet, both administered at 0h).

[000114] FIG. 81 presents the plasma acetaminophen concentration over time during the first 12 hours after initial dosing, as well as half-value duration (HVD) and C_{max} , in a multi-dose study in which patients received either 1 tablet of immediate-release 7.5 mg oxycodone/ 325 mg acetaminophen every 6 hours for 4.5 days, or 2 tablets of controlled-release 7.5 mg oxycodone/ 325 mg acetaminophen (15 mg/650 mg total per dose) every 12 hours for 4.5 days.

[000115] FIG. 82 presents the steady-state (day 5) plasma acetaminophen concentration over time, as well as half-value duration (HVD) and C_{max} , in a multi-dose study in which patients received either 1 tablet of immediate-release 7.5 mg oxycodone/ 325 mg acetaminophen every 6 hours for 4.5 days, or 2 tablets of controlled-release 7.5 mg oxycodone/ 325 mg acetaminophen (15 mg/650 mg total per dose) every 12 hours for 4.5 days.

[000116] FIG. 83 presents the plasma oxycodone concentrations and patient-reported visual analog scale (VAS) scores for drug liking over the first 12 hours after dosing in patients receiving either low-dose intact controlled-release oxycodone/acetaminophen (two tablets of 7.5 mg oxycodone/ 325 mg acetaminophen, 15 mg/650 mg total) or low-dose intact immediate-release oxycodone/acetaminophen (two tablets of 7.5 mg oxycodone/ 325 mg acetaminophen, 15 mg/650 mg total).

[000117] FIG. 84 presents the plasma oxycodone concentrations and patient-reported visual analog scale (VAS) scores for drug liking over the first 12 hours after dosing in patients receiving either high-dose intact controlled-release oxycodone/acetaminophen (four tablets of 7.5 mg oxycodone/ 325 mg acetaminophen, 30 mg/1300 mg total) or high-dose intact immediate-release oxycodone/acetaminophen (four tablets of 7.5 mg oxycodone/ 325 mg acetaminophen, 30 mg/1300 mg total).

[000118] FIG. 85 presents the plasma oxycodone concentrations and patient-reported visual analog scale (VAS) scores for drug liking over the first 12 hours after dosing in patients receiving either high-dose crushed controlled-release oxycodone/acetaminophen (four tablets of 7.5 mg oxycodone/ 325 mg acetaminophen, 30 mg/1300 mg total, crushed and encapsulated) or high-dose crushed immediate-release oxycodone/acetaminophen (four tablets of 7.5 mg oxycodone/ 325 mg acetaminophen, 30 mg/1300 mg total, crushed and encapsulated).

[000119] FIG. 86 presents the plasma oxycodone concentrations and patient-reported visual analog scale (VAS) scores for drug high over the first 12 hours after dosing in patients receiving either low-dose intact controlled-release oxycodone/acetaminophen (two tablets of 7.5 mg oxycodone/ 325 mg acetaminophen, 15 mg/650 mg total) or low-dose intact immediate-release oxycodone/acetaminophen (two tablets of 7.5 mg oxycodone/ 325 mg acetaminophen, 15 mg/650 mg total).

[000120] FIG. 87 presents the plasma oxycodone concentrations and patient-reported visual analog scale (VAS) scores for drug high over the first 12 hours after dosing in patients receiving either high-dose intact controlled-release oxycodone/acetaminophen (four tablets of 7.5 mg oxycodone/ 325 mg acetaminophen, 30 mg/1300 mg total) or high-dose intact immediate-release oxycodone/acetaminophen (four tablets of 7.5 mg oxycodone/ 325 mg acetaminophen, 30 mg/1300 mg total).

[000121] FIG. 88 presents the plasma oxycodone concentrations and patient-reported visual analog scale (VAS) scores for drug high over the first 12 hours after dosing in patients receiving either high-dose crushed controlled-release oxycodone/acetaminophen (four tablets of 7.5 mg oxycodone/ 325 mg acetaminophen, 30 mg/1300 mg total, crushed and encapsulated) or high-dose crushed immediate-release oxycodone/acetaminophen (four tablets of 7.5 mg oxycodone/ 325 mg acetaminophen, 30 mg/1300 mg total, crushed and encapsulated).

[000122] FIG. 89 presents a correlation plot for peak drug effects ($E_{\max}$) for drug liking versus $C_{\max}$. The correlation plot includes data from patients receiving the following forms of oxycodone/acetaminophen: low-dose intact controlled-release oxycodone/acetaminophen (two tablets of 7.5 mg oxycodone/ 325 mg acetaminophen, 15 mg/650 mg total); low-dose intact immediate-release oxycodone/acetaminophen (two tablets of 7.5 mg oxycodone/ 325 mg acetaminophen, 15 mg/650 mg total); high-dose intact controlled-release oxycodone/acetaminophen (four tablets of 7.5 mg oxycodone/ 325 mg acetaminophen, 30 mg/1300 mg total); high-dose intact immediate-release oxycodone/acetaminophen (four tablets of 7.5 mg oxycodone/ 325 mg acetaminophen, 30 mg/1300 mg total); high-dose crushed controlled-release oxycodone/acetaminophen (four tablets of 7.5 mg oxycodone/ 325 mg acetaminophen, 30 mg/1300 mg total, crushed and encapsulated); or high-dose crushed immediate-release oxycodone/acetaminophen

(four tablets of 7.5 mg oxycodone/ 325 mg acetaminophen, 30 mg/1300 mg total, crushed and encapsulated).

[000123] FIG. 90 presents a correlation plot for peak drug effects ($E_{\max}$) for drug high versus $C_{\max}$. The correlation plot includes data from patients receiving the following forms of oxycodone/acetaminophen: low-dose intact controlled-release oxycodone/acetaminophen (two tablets of 7.5 mg oxycodone/ 325 mg acetaminophen, 15 mg/650 mg total); low-dose intact immediate-release oxycodone/acetaminophen (two tablets of 7.5 mg oxycodone/ 325 mg acetaminophen, 15 mg/650 mg total); high-dose intact controlled-release oxycodone/acetaminophen (four tablets of 7.5 mg oxycodone/ 325 mg acetaminophen, 30 mg/1300 mg total); high-dose intact immediate-release oxycodone/acetaminophen (four tablets of 7.5 mg oxycodone/ 325 mg acetaminophen, 30 mg/1300 mg total); high-dose crushed controlled-release oxycodone/acetaminophen (four tablets of 7.5 mg oxycodone/ 325 mg acetaminophen, 30 mg/1300 mg total, crushed and encapsulated); or high-dose crushed immediate-release oxycodone/acetaminophen (four tablets of 7.5 mg oxycodone/ 325 mg acetaminophen, 30 mg/1300 mg total, crushed and encapsulated).

[000124] FIG. 91 presents a correlation plot for area under the drug effects curve (AUE) for drug liking versus area under the concentration-time curve (AUC) for oxycodone. The correlation plot includes data from patients receiving the following forms of oxycodone/acetaminophen: low-dose intact controlled-release oxycodone/acetaminophen (two tablets of 7.5 mg oxycodone/ 325 mg acetaminophen, 15 mg/650 mg total); low-dose intact immediate-release oxycodone/acetaminophen (two tablets of 7.5 mg oxycodone/ 325 mg acetaminophen, 15 mg/650 mg total); high-dose intact controlled-release oxycodone/acetaminophen (four tablets of 7.5 mg oxycodone/ 325 mg acetaminophen, 30 mg/1300 mg total); high-dose intact immediate-release oxycodone/acetaminophen (four tablets of 7.5 mg oxycodone/ 325 mg acetaminophen, 30 mg/1300 mg total); high-dose crushed controlled-release oxycodone/acetaminophen (four tablets of 7.5 mg oxycodone/ 325 mg acetaminophen, 30 mg/1300 mg total, crushed and encapsulated); or high-dose crushed immediate-release oxycodone/acetaminophen (four tablets of 7.5 mg oxycodone/ 325 mg acetaminophen, 30 mg/1300 mg total, crushed and encapsulated).

[000125] FIG. 92 presents a correlation plot for area under the drug effects curve (AUE) for drug high versus area under the concentration-time curve (AUC) for oxycodone. The correlation plot includes data from patients receiving the following forms of oxycodone/acetaminophen: low-dose intact controlled-release oxycodone/acetaminophen (two tablets of 7.5 mg oxycodone/ 325 mg acetaminophen, 15 mg/650 mg total); low-dose intact immediate-release oxycodone/acetaminophen (two tablets of 7.5 mg oxycodone/ 325 mg acetaminophen, 15 mg/650 mg total); high-dose intact controlled-release oxycodone/acetaminophen (four tablets of 7.5 mg oxycodone/ 325 mg acetaminophen, 30 mg/1300 mg total); high-dose intact immediate-release oxycodone/acetaminophen (four tablets of 7.5 mg oxycodone/ 325 mg acetaminophen, 30 mg/1300 mg total); high-dose crushed controlled-release oxycodone/acetaminophen (four tablets of 7.5 mg oxycodone/ 325 mg acetaminophen, 30 mg/1300 mg total, crushed and encapsulated); or high-dose crushed immediate-release oxycodone/acetaminophen (four tablets of 7.5 mg oxycodone/ 325 mg acetaminophen, 30 mg/1300 mg total, crushed and encapsulated).

[000126] FIG. 93 presents a summary of the study design for the study described in Example 12, which was a randomized, double-blind, placebo-controlled, phase 3 study was conducted to evaluate the safety and efficacy of controlled-release oxycodone/acetaminophen in patients with moderate to severe acute pain.

[000127] FIG. 94 presents the mean pain intensity scores during the first two hours after first metatarsal bunionectomy for patients receiving either placebo or controlled-release oxycodone/acetaminophen (two tablets of 7.5 mg oxycodone/ 325 mg acetaminophen, total of 15 mg/650 mg per dose) every 12 hours.

[000128] FIG. 95 presents the mean pain intensity scores during hours 0 to 48 after first metatarsal bunionectomy for patients receiving either placebo or controlled-release oxycodone/acetaminophen (two tablets of 7.5 mg oxycodone/ 325 mg acetaminophen, total of 15 mg/650 mg per dose) every 12 hours.

[000129] FIG. 96 presents the proportion of patients with $\geq 80\%$ reduction in pain intensity score at different times during the first 2 hours of treatment of the study described in Example 12.

[000130] FIG. 97 presents the proportion of patients “satisfied” or “very satisfied” with placebo or controlled-release oxycodone/ acetaminophen, respectively, according to several measures of the Global Assessment of Satisfaction as depicted, after 48 hours of the study described in Example 12, during which patients received either placebo or two tablets of controlled-release oxycodone/acetaminophen (total 15 mg oxycodone/ 650 mg acetaminophen per dose) every 12 hours after a first metatarsal bunionectomy.

[000131] FIG. 98 presents the proportion of patients “satisfied” or “very satisfied” with controlled-release oxycodone/ acetaminophen, according to several measures as depicted, after 7 or 14 days of open-label phase treatment, during which patients received two tablets of controlled-release oxycodone/ acetaminophen (total 15 mg oxycodone/ 650 mg acetaminophen per dose) every 12 hours.

[000132] FIG. 99 presents a summary of the study design for Example 13, which was a multicenter, phase 3, open-label study conducted to (1) evaluate the safety and tolerability of controlled-release oxycodone/ acetaminophen with up to 35 days of use in patients who were receiving only nonopioid analgesics but with pain sufficient to warrant escalation of treatment to opioid therapy and (2) evaluate the efficacy of controlled-release oxycodone/ acetaminophen using changes from baseline in pain intensity, pain-related quality of life, and disease-specific quality of life.

[000133] FIG. 100 presents a summary of patient disposition for the patients participating in the study described in Example 13.

[000134] FIG. 101 presents a summary of the pain intensity score (brief pain inventory)—both at baseline and at the end of treatment—for patients receiving two tablets of controlled-release oxycodone/ acetaminophen (total 15 mg oxycodone/ 650 mg acetaminophen per dose) every 12 hours for up to 35 days. As summarized in Example 13, patients participating in the study had either osteoarthritis of the knee or hip, or chronic low back pain.

[000135] FIG. 102 presents a summary of the Western Ontario and McMaster Universities Arthritis Index (WOMAC) domain for “pain”—both at baseline and at the end of treatment—for patients with osteoarthritis who received two tablets of controlled-release oxycodone/ acetaminophen (total 15 mg oxycodone/ 650 mg acetaminophen per dose) every 12 hours for up to 35 days.

[000136] FIG. 103 presents a summary of the Western Ontario and McMaster Universities Arthritis Index (WOMAC) domain for “stiffness”—both at baseline and at the end of treatment—for patients with osteoarthritis who received two tablets of controlled-release oxycodone/ acetaminophen (total 15 mg oxycodone/ 650 mg acetaminophen per dose) every 12 hours for up to 35 days.

[000137] FIG. 104 presents a summary of the Western Ontario and McMaster Universities Arthritis Index (WOMAC) domain for “physical function”—both at baseline and at the end of treatment—for patients with osteoarthritis who received two tablets of controlled-release oxycodone/ acetaminophen (total 15 mg oxycodone/ 650 mg acetaminophen per dose) every 12 hours for up to 35 days.

[000138] FIG. 105 presents a summary of the Western Ontario and McMaster Universities Arthritis Index (WOMAC) total across all domains—both at baseline and at the end of treatment—for patients with osteoarthritis who received two tablets of controlled-release oxycodone/ acetaminophen (total 15 mg oxycodone/ 650 mg acetaminophen per dose) every 12 hours for up to 35 days.

[000139] FIG. 106 presents stimulated human oxycodone pharmacokinetic profiles for oxycodone/acetaminophen formulations based on canine data.

[000140] FIG. 107 presents the pharmacokinetic profiles for oxycodone and acetaminophen achieved by an embodiment of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

[000141] Disclosed herein is a combination product of oxycodone and acetaminophen that has the desirable attributes of both IR and MR products. The extended release pharmaceutical composition disclosed herein comprises at least one extended release portion and, optionally, at least one immediate release portion. The extended release and immediate release portions may comprise oxycodone, acetaminophen, or combinations thereof. The at least one immediate release portion releases acetaminophen (APAP) and/or oxycodone instantly in an immediate release fashion that provides rapid onset for the attainment of therapeutically effective plasma concentrations within about the first 5 minutes, 10 minutes, 15 minutes, 20 minutes, 25 minutes, 30 minutes, 35 minutes, 40 minutes, 45 minutes, 50 minutes, 55 minutes, or 60 minutes after administration of the composition. The at least one extended release

portion releases acetaminophen and/or oxycodone in an extended release fashion to maintain plasma concentrations above the minimum effective concentration for about 8-12 hours. In addition, two other features of this composition are: 1) to allow the plasma concentrations of oxycodone to fall as rapidly as an immediate release formulation to provide the same rate of termination of drug effects as the immediate release product, and 2) to allow the concentrations of APAP to fall even quicker towards the later part of the dosing interval and bring down the levels of APAP lower than those of the immediate release product. The concentrations of APAP in the last quarter of the dosing interval are comparable to the pre-dose concentrations in a multiple dose setting, allowing for the glutathione synthase enzyme cycle to replenish the body's levels of glutathione to avoid the formation of toxic intermediates with subsequent doses of APAP. Moreover, the concentrations of APAP in the later part of the dosing interval are lower than those present when administered a conventional extended release formulation. This feature has been deliberately introduced to reduce the hepatic injury due to APAP and is termed "APAP time-off".

[000142] Abuse potential is a concern with any opioid product. The addition of APAP to the opioid, however, is likely to reduce the amount of abuse by illicit routes of administration, particularly intravenous or intranasal administration. This deterrence is likely due to the bulk (grams) that the APAP provides as well as the relative aqueous insolubility compared to freely soluble opioid salts. Further, APAP is known to be irritating to nasal passages and to make drug abusers sneeze violently when they are trying to snort it. In addition, embodiments disclosed herein may be tamper resistant in that the compositions are difficult to crush for administration intravenously or intranasally; difficult to extract with water or alcohol because the mixture becomes too viscous for injecting or snorting; and resistant to dose dumping in alcohol.

[000143] In one embodiment, the pharmaceutical composition disclosed herein, therefore, provides: 1) rapid onset of analgesia within about 15, 30, 45, or 60 minutes after administration of the composition mediated by both oxycodone and APAP, with APAP providing maximal contribution during the early phase; 2) prolonged analgesia for the entire 12 hours period, mainly contributed by oxycodone, with minimal fluctuations during this period; 3) relatively low levels of APAP toward end of dosing interval to allow

for recovery of the depleted hepatic glutathione system; 4) low abuse quotient; and 5) abuse deterrence.

[000144] In a further embodiment, gastric retentive extended release pharmaceutical compositions are disclosed comprising at least one opioid wherein gastric retention of the composition is achieved by a combination of a physical property of the composition and release of the opioid. In particular, the opioid is released at a rate that is sufficient to delay gastric emptying but insufficient to cause serious adverse gastrointestinal effects. Because gastric retention of the composition is aided by release of the opioid, oral administration of the composition is independent of food intake. That is, the composition may be administered to a subject in either a fed state or a fasted state. It was discovered that, upon oral administration to a subject, the composition produces a plasma profile characterized by at least one pharmacokinetic parameter that differs by less than about 30% when the subject is in a fasted state as compared to a fed state. The food independence of this gastric retentive composition increases the convenience of administration of the composition in that it may be administered with or without food. Moreover, this property of the composition increases patient/subject compliance. The present disclosure also provides methods for administering the gastric retentive extended release composition disclosed herein, wherein the composition may be administered to a subject without regard to meals.

[000145] Headings included herein are simply for ease of reference, and are not intended to limit the disclosure in any way.

I. Definitions

[000146] Compounds useful in the compositions and methods include those described herein in any of their pharmaceutically acceptable forms, including isomers such as diastereomers and enantiomers, salts, solvates, and polymorphs, as well as racemic mixtures and pure isomers of the compounds described herein, where applicable.

[000147] When introducing elements of the various embodiment(s) of the present disclosure, the articles "a", "an", "the" and "said" are intended to mean that there are one or more of the elements. The terms "comprising", "including" and "having" are intended to

be inclusive and mean that there may be additional elements other than the listed elements.

[000148] The use of individual numerical values are stated as approximations as though the values were preceded by the word “about” or “approximately.” Similarly, the numerical values in the various ranges specified in this application, unless expressly indicated otherwise, are stated as approximations as though the minimum and maximum values within the stated ranges were both preceded by the word “about” or “approximately.” In this manner, variations above and below the stated ranges can be used to achieve substantially the same results as values within the ranges. As used herein, the terms “about” and “approximately” when referring to a numerical value shall have their plain and ordinary meanings to a person of ordinary skill in the art to which the disclosed subject matter is most closely related or the art relevant to the range or element at issue. The amount of broadening from the strict numerical boundary depends upon many factors. For example, some of the factors which may be considered include the criticality of the element and/or the effect a given amount of variation will have on the performance of the claimed subject matter, as well as other considerations known to those of skill in the art. As used herein, the use of differing amounts of significant digits for different numerical values is not meant to limit how the use of the words “about” or “approximately” will serve to broaden a particular numerical value or range. Thus, as a general matter, “about” or “approximately” broaden the numerical value. Also, the disclosure of ranges is intended as a continuous range including every value between the minimum and maximum values plus the broadening of the range afforded by the use of the term “about” or “approximately.” Consequently, recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein.

[000149] The term “abuse quotient” for a pharmaceutical composition as used herein is the numerical value obtained via dividing the $C_{\max}$ for a drug by the $T_{\max}$ for the same drug. Generally speaking, the abuse quotient provides a means for predicting the degree of addictiveness of a given pharmaceutical composition. Pharmaceutical

compositions with lower abuse quotients typically are less addictive compared to pharmaceutical compositions with higher abuse quotients.

[000150] The term “active agent” or “drug,” as used herein, refers to any chemical that elicits a biochemical response when administered to a human or an animal. The drug may act as a substrate or product of a biochemical reaction, or the drug may interact with a cell receptor and elicit a physiological response, or the drug may bind with and block a receptor from eliciting a physiological response.

[000151] The term “bioequivalent,” as used herein, refers to two compositions, products or methods where the 90% Confidence Intervals (CI) for AUC, partial AUC and/or Cmax are between 0.80 to 1.25.

[000152] The term “bulk density,” as used herein, refers to a property of powders and is defined as the mass of many particles of the material divided by the total volume they occupy. The total volume includes particle volume, inter-particle void volume and internal pore volume.

[000153] The term “content uniformity,” as used herein refers to the testing of compressed tablets to provide an assessment of how uniformly the micronized or submicron active ingredient is dispersed in the powder mixture. Content uniformity is measured by use of USP Method (General Chapters, Uniformity of Dosage Forms), unless otherwise indicated. A plurality refers to five, ten or more tablet compositions.

[000154] The term “friability,” as used herein, refers to the ease with which a tablet will break or fracture. The test for friability is a standard test known to one skilled in the art. Friability is measured under standardized conditions by weighing out a certain number of tablets (generally 20 tablets or less), placing them in a rotating Plexiglas drum in which they are lifted during replicate revolutions by a radial lever, and then dropped approximately 8 inches. After replicate revolutions (typically 100 revolutions at 25 rpm), the tablets are reweighed and the percentage of composition abraded or chipped is calculated.

[000155] The term “ER” as used herein refers to extended release. The phrases “extended release layer,” “ER layer,” “ER portion,” and “extended release portion” are used interchangeable in this document. Further, as used herein the “extended release layer,” “ER layer,” “ER portion,” and “extended release portion” can be either (i) a discrete

part(s) of the pharmaceutical composition, (ii) integrated within the pharmaceutical composition, or (iii) a combination thereof.

[000156] The term "IR" as used herein refers to immediate release. The phrases "immediate release layer," "IR layer," "IR portion" and "immediate release portion" are used interchangeably in this document. In addition, as used herein the "immediate release layer," "IR layer," "IR portion" and "immediate release portion" can be either (i) a discrete part(s) of the pharmaceutical composition, (ii) integrated within the pharmaceutical composition, or (iii) a combination thereof.

[000157] The term "half life" as used herein refers to the time required for a drug's blood or plasma concentration to decrease by one half. This decrease in drug concentration is a reflection of its metabolism plus excretion or elimination after absorption is complete and distribution has reached an equilibrium or quasi equilibrium state. The half life of a drug in the blood may be determined graphically off of a pharmacokinetic plot of a drug's blood-concentration time plot, typically after intravenous administration to a sample population. The half life can also be determined using mathematical calculations that are well known in the art. Further, as used herein the term "half life" also includes the "apparent half-life" of a drug. The apparent half life may be a composite number that accounts for contributions from other processes besides elimination, such as absorption, reuptake, or enterohepatic recycling.

[000158] "Optional" or "optionally" means that the subsequently described element, component or circumstance may or may not occur, so that the description includes instances where the element, component, or circumstance occurs and instances where it does not.

[000159] "Partial AUC" means an area under the drug concentration-time curve (AUC) calculated using linear trapezoidal summation for a specified interval of time, for example, AUC(0-1hr) AUC(0-2hr), AUC(0-4hr), AUC(0-6hr), AUC(0-8hr), AUC(0-(T_{max} of IR product + 2SD)), AUC(0-(x)hr), AUC(x-yhr), AUC(T_{max}-t), AUC(0-(t)hr), AUC(T_{max} of IR product + 2SD)-t), or AUC(0-∞).

[000160] A drug "release rate," as used herein, refers to the quantity of drug released from a dosage form or pharmaceutical composition per unit time, e.g., milligrams of drug released per hour (mg/hr). Drug release rates for drug dosage forms are typically

measured as an *in vitro* rate of dissolution, *i.e.*, a quantity of drug released from the dosage form or pharmaceutical composition per unit time measured under appropriate conditions and in a suitable fluid. The specific results of dissolution tests claimed herein are performed on dosage forms or pharmaceutical compositions immersed in 900 mL of 0.1 N HCl using a USP Type II apparatus at a paddle speed of either about 100 rpm or about 150 rpm and a constant temperature of about 37°C. Suitable aliquots of the release rate solutions are tested to determine the amount of drug released from the dosage form or pharmaceutical composition. For example, the drug can be assayed or injected into a chromatographic system to quantify the amounts of drug released during the testing intervals.

[000161] The terms “subject” or “patient” are used interchangeably herein and refer to a vertebrate, preferably a mammal. Mammals include, but are not limited to, humans.

[000162] The term “tap density” or “tapped density,” as used herein, refers to a measure of the density of a powder. The tapped density of a pharmaceutical powder is determined using a tapped density tester, which is set to tap the powder at a fixed impact force and frequency. Tapped density by the USP method is determined by a linear progression of the number of taps.

II. ***Pharmaceutical Compositions Comprising an Opioid and an Additional Active Pharmaceutical Ingredient***

[000163] The present disclosure provides pharmaceutical compositions comprising at least one opioid (e.g., oxycodone) and its pharmaceutical salts and at least one other active pharmaceutical ingredient (API) (e.g., acetaminophen). It would be understood that when present in a pharmaceutical composition, the opioid would be in its salt form. For example, the pharmaceutical composition comprises at least one extended release portion comprising oxycodone, acetaminophen or a combination thereof, and an extended release component. The pharmaceutical composition may also comprise at least one immediate release portion comprising oxycodone, acetaminophen, or a combination thereof. The compositions disclosed herein are formulated to deliver therapeutic concentrations of oxycodone and acetaminophen within about the first hour

after oral administration and to maintain therapeutic concentrations of oxycodone and acetaminophen for an extended period of time (e.g., 10-12 hours).

[000164] The present disclosure further provides for gastric retentive, extended release compositions comprising at least one opioid (e.g., oxycodone) and at least one other (API) (e.g., acetaminophen) that is preferably absorbed in the upper gastrointestinal tract. In general, the gastric retentive, extended release composition comprises at least one extended release portion. The extended release portion(s) may comprise at least one opioid, at least one API, or combinations thereof. The gastric retentive, extended release composition disclosed herein may further comprise at least one immediate release portion. The immediate release portion(s) may comprise at least one opioid (e.g., oxycodone), at least one other API (e.g., acetaminophen), or combinations thereof.

(a) Active Agents

[000165] The composition disclosed herein comprises at least one opioid and at least one additional API, each of which is discussed in more detail below. In one embodiment, the same opioid or combination of opioids is present in both the at least one immediate release portion and the at least one extended release portion of the composition; and the same API or combination of APIs is present in both the at least one immediate release portion and the at least one extended release portion of the composition.

(i) *Opioids*

[000166] The opioid(s) useful in the present invention include adulmine, alfentanil, allocryptopine, allylprodine, alphaprodine, anileridine, aporphine, benzylmorphine, berberine, bicuculine, bicucine, bezitramide, buprenorphine, bulbocaprine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphine, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacymorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, nalbuphene, normorphine, norpipanone, opium, oxycodone,

oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propoxyphene, sufentanil, tapentadol, tilidine, tramadol, and pharmaceutical salts of any of the foregoing.

[000167] In various embodiments, the extended release dosage form may comprise one, two, three, four, or more than four opioids. In another embodiment, the opioid is selected from the group consisting of oxycodone, hydrocodone, tramadol, codeine, and pharmaceutical salts of any of the foregoing. In yet another embodiment, opioid is selected from the group consisting of adulmine, alfentanil, allocryptopine, allylprodine, alphaprodine, anileridine, aporphine, benzylmorphine, berberine, bicuculine, bicucine, bezitramide, buprenorphine, bulbocaprine, butorphanol, clonitazene, desomorphine, dextromoramide, dezocine, diampromide, diamorphine, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacymorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, nalbuphene, normorphine, norpipanone, opium, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propoxyphene, sufentanil, tapentadol, tilidine, and pharmaceutical salts of any of the foregoing. In one embodiment, the extended release dosage form comprises one opioid. In a further embodiment, the dosage form comprises oxycodone.

[000168] In one embodiment, the composition may comprise from about 1.0 mg to about 500 mg of the opioid. In another embodiment, the composition may comprise from about 1.4 mg to about 400 mg of the opioid. In yet another embodiment, the amount of opioid in the composition may range from about 5 mg to about 300 mg. In still another embodiment, the amount of opioid in the composition may range from about 4 mg to about 30 mg. In another embodiment, the amount of opioid in the composition may range from about 30 mg to about 60 mg. In yet another embodiment, the amount of opioid in the

composition may range from about 60 mg to about 120 mg. In an alternate embodiment, the amount of opioid in the composition may range from about 120 mg to about 300 mg. In various embodiments, the amount of opioid in the composition may be about 4 mg, 4.5 mg, 5 mg, 5.5 mg, 6 mg, 6.5 mg, 7 mg, 7.5 mg, 8 mg, 8.5 mg, 9 mg, 9.5 mg, 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg, 16 mg, 17 mg, 18 mg, 19 mg, 20 mg, 22 mg, 24 mg, 26 mg, 28 mg, 30 mg, 32 mg, 34 mg, 36 mg, 38 mg, 40 mg, 42 mg, 44 mg, 46 mg, 48 mg, 50 mg, 52 mg, 54 mg, 56 mg, 58 mg, 60 mg, 62 mg, 64 mg, 66 mg, 68 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 220 mg, 240 mg, 260 mg, 280 mg, 300 mg, 320 mg, 340 mg, 360 mg, 380 mg, or 400 mg. In one embodiment, the amount of opioid in the composition may range from about 7.5 mg to about 30 mg. In another embodiment, the amount of opioid in the composition may range from about 7.5 mg to about 15 mg. In still another embodiment, the amount of opioid in the composition may range from about 15 mg to about 30 mg.

[000169] In additional embodiments, the dosage form comprises oxycodone, and the total amount of oxycodone present in the pharmaceutical composition can and will vary. In some embodiments, the total amount of oxycodone present in the pharmaceutical composition may range from about 2 mg to about 160 mg, about 5 mg to about 75 mg, about 5 mg to about 40 mg, or about 10 mg to about 30 mg. In another embodiment, the total amount of oxycodone in the pharmaceutical composition may range from about 5 mg to about 30 mg. In additional embodiments, the total amount of oxycodone present in the pharmaceutical composition may be about 5 mg, 5.5 mg, 6.0 mg, 6.5 mg, 7.0 mg, 7.5 mg, 8.0 mg, 8.5 mg, 9.0 mg, 9.5 mg, 10 mg, 10.5 mg, 11 mg, 11.5 mg, 12 mg, 12.5 mg, 13 mg, 13.5 mg, 14 mg, 14.5 mg, 15 mg, 15.5 mg, 16 mg, 16.5 mg, 17 mg, 17.5 mg, 18 mg, 18.5 mg, 19 mg, 19.5 mg, 20 mg, 22.5 mg, 25 mg, 27.5 mg, 30 mg, 32.5 mg, 35 mg, 37.5 mg, 40 mg, 45 mg, 50 mg, 60 mg, 70 mg, 80 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, or 160 mg. In one embodiment, the total amount of oxycodone in the pharmaceutical composition may be about 30 mg. In another embodiment, the total amount of oxycodone in the pharmaceutical composition may be about 15 mg. In still another embodiment, the total amount of oxycodone in the pharmaceutical composition may be about 7.5 mg.

(ii) Other API

[000170] The composition disclosed herein may also comprise at least one other API. In general, the other API is preferentially absorbed in the upper gastrointestinal tract (GIT). Accordingly, optimal absorption of the API may occur in the upper GIT (i.e., duodenum, jejunum, and ileum of the small intestine), with little or no absorption in the lower GIT (i.e., cecum and colon of the large intestine).

[000171] In some embodiments, the other API may be a non-opioid analgesic. Suitable non-opioid analgesics include acetaminophen (also known as paracetamol), acetylsalicylic acid, diclofenac, diflunisol, ibuprofen, indomethacin, ketoprofen, ketorolac, naproxen, mefamanic acid, phenacetin, piroxicam, sulindac, and tolmetin. In other embodiments, the other API may be a steroidal anti-inflammatory agent such as celecoxib, deracoxib, ketoprofen, lumiracoxib, meloxicam, parecoxib, rofecoxib, or valdecoxib. In a further embodiment, the other API may be a steroidal anti-inflammatory agent such as alclometasone, dexamethasone, fluocinonide, hydrocortisone, methylprednisolone, prednisone, prednisolone, or triamcinolone. In further embodiments, the other API may be a norepinephrine transporter modulator such as tapentadol, a tricyclic antidepressant such as amitriptyline, an alpha-2 adrenergic agonist such as clonidine, a calcium channel blocker such as nimodipine, a GABA B agonist such as baclofen, a cannabinoid, a NMDA receptor antagonist, a CCK receptor antagonist, a beta blocker, or a serotonin receptor antagonist. Any of the aforementioned APIs may be in the form of a pharmaceutically acceptable salt. In various embodiments, the at least one extended release portion may comprise one, two, three, four, or more APIs. In one embodiment, one extended release portion may comprise one of the other APIs.

[000172] The amount of the other API in the gastric retentive, extended release composition can and will vary. In one embodiment, the composition may comprise from about 1.0 mg to about 1500 mg of the API. In another embodiment, the amount of API in the composition may range from about 100 mg to about 1000 mg. In still another embodiment, the amount of API in the composition may range from about 50 mg to about 500 mg. In another embodiment, the amount of API in the composition may range from about 10 mg to about 100 mg. In yet another embodiment, the amount of API in the composition may range from about 1.0 mg to about 10 mg. In one embodiment, the

amount of API in the composition may range from about 250 mg to about 1300 mg. In another embodiment, the amount of API in the composition may range from about 325 mg to about 650 mg. In still another embodiment, the amount of API in the composition may range from about 650 mg to about 1300 mg.

[000173] In additional embodiments, the dosage form comprises acetaminophen, and the total amount of acetaminophen present in the pharmaceutical composition can and will vary. In one embodiment, the total amount of acetaminophen present in the pharmaceutical composition may range from about 80 mg to about 1600 mg. In another embodiment, the total amount of acetaminophen present in the pharmaceutical composition may be about 250 mg to about 1300 mg. In a further embodiment, the total amount of acetaminophen present in the pharmaceutical composition may be about 300 mg to about 600 mg. In yet another embodiment, the total amount of acetaminophen present in the pharmaceutical composition may be about 325 mg to about 650 mg. In another embodiment, the total amount of acetaminophen present in the pharmaceutical composition may be about 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 375 mg, 400 mg, 425 mg, 450 mg, 475 mg, 500 mg, 525 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 1000 mg, or 1300 mg. In one embodiment, the total amount of acetaminophen in the pharmaceutical composition may be about 650 mg. In another embodiment, the total amount of acetaminophen in the pharmaceutical composition may be about 500 mg. In yet another embodiment, the total amount of acetaminophen in the pharmaceutical composition may be about 325 mg.

(b) Immediate Release Portion

[000174] The pharmaceutical composition disclosed herein may comprise at least one immediate release portion. In one embodiment, the at least one immediate release portion may comprise oxycodone. In another embodiment, the at least one immediate release portion may comprise acetaminophen. In a further embodiment, the at least one immediate release portion may comprise oxycodone and acetaminophen.

[000175] The at least one immediate release portion of the pharmaceutical composition is designed to release more than 80%, more than 90%, or essentially all of the opioid(s) and / or the other API(s) in the at least one immediate release portion(s) within about one hour. In one embodiment, more than 80%, more than 90%, or

essentially all of the opioid(s) and/or the other API(s) in the at least one immediate release portion(s) may be released in less than about 45 minutes. In another embodiment, more than 80%, more than 90%, or essentially all of the opioid(s) and/or the other API(s) in the at least one immediate release portion(s) may be released in less than about 30 minutes. In a further embodiment, more than 80%, more than 90%, or essentially all of the opioid(s) and/or the other API(s) in the at least one immediate release portion(s) may be released in less than about 20 minutes. In yet another embodiment, more than 80%, more than 90%, or essentially all of the opioid(s) and/or the other API(s) in the at least one immediate release portion(s) may be released in less than about 15 minutes. In an alternate embodiment, more than 80%, more than 90%, or essentially all of the opioid(s) and/or the other API(s) in the at least one immediate release portion(s) may be released in less than about 10 minutes. In yet another embodiment, more than 80%, more than 90%, or essentially all of the opioid(s) and/or the other API(s) in the at least one immediate release portion may be released in less than about 5 minutes.

[000176] In some embodiments, the immediate release portion may be part of or homogeneously mixed with the extended release portion.

(i) Opioid(s)

[000177] At least one immediate release portion of the composition may comprise at least one opioid. Suitable opioids are detailed above in Section (II)(a)(i). In one embodiment, the opioid may be codeine or a salt thereof. In another embodiment, the opioid may be hydrocodone or a salt thereof. In yet another embodiment, the opioid may be hydromorphone or a salt thereof. In still another embodiment, the opioid may be morphine or a salt thereof. In a further embodiment, the opioid may be oxymorphone or a salt thereof. In an alternate embodiment, the opioid may be tramadol or a salt thereof. In another embodiment, the opioid may be oxycodone or a salt thereof.

[000178] The amount of opioid present in the at least one immediate release portion of the pharmaceutical composition can and will vary. In one embodiment, the amount of opioid in the at least one immediate release portion may range from about 0.4 mg to about 100 mg. In another embodiment, the amount of opioid in the at least one immediate release portion may range from about 1.25 mg to about 75 mg. In another embodiment, the amount of opioid in the at least one immediate release portion may

range from about 1 mg to about 20 mg. In still another embodiment, the amount of opioid in the at least one immediate release portion may range from about 0.5 mg to about 10 mg. In another embodiment, the amount of opioid in the at least one immediate release portion may range from about 7.5 mg to about 15 mg. In yet another embodiment, the amount of opioid in the at least one immediate release portion may range from about 15 mg to about 30 mg. In an alternate embodiment, the amount of opioid in the at least one immediate release portion may range from about 30 mg to about 75 mg. In various embodiments, the amount of opioid in the at least one immediate release portion may be about 1.25 mg, 1.3 mg, 1.325 mg, 1.35 mg, 1.375 mg, 1.4 mg, 1.425 mg, 1.45 mg, 1.475 mg, 1.5 mg, 1.525 mg, 1.55 mg, 1.575 mg, 1.6 mg, 1.625 mg, 1.65 mg, 1.675 mg, 1.7 mg, 1.725 mg, 1.75 mg, 1.775 mg, 1.8 mg, 1.825 mg, 1.85 mg, 1.875 mg, 1.9 mg, 1.925 mg, 1.95 mg, 1.975 mg, 2.0 mg, 2.25 mg, 2.5 mg, 2.75 mg, 3.0 mg, 3.25 mg, 3.5 mg, 3.75 mg, 4.0 mg, 4.25 mg, 4.5 mg, 4.75 mg, 5.0 mg, 5.25 mg, 5.5 mg, 5.75 mg, 6.0 mg, 6.25 mg, 6.5 mg, 6.75 mg, 7.0 mg, 7.25 mg, 7.5 mg, 7.75 mg, 8.0 mg, 8.25 mg, 8.5 mg, 8.75 mg, 9.0 mg, 9.25 mg, 9.5 mg, 9.75 mg, 10.0 mg, 12.0 mg, 13.0 mg, 14.0 mg, 15.0 mg, 20.0 mg, 25 mg, 30 mg, 35 mg or 40.0 mg. In one embodiment, the amount of opioid in the at least one immediate release portion may range from about 1.0 mg and about 2.0 mg, for example, about 1.25 mg, or in another example, about 1.875 mg. In yet another embodiment, the amount of opioid in the at least one immediate release portion may range from about 2.0 mg and about 3.0 mg, for example, about 2.25 mg, or in a further example, about 2.5 mg. In an additional embodiment, the amount of opioid in the at least one immediate release portion may range from 3 mg and about 4.0 mg, for example, about 3.75 mg. In another embodiment, the amount of opioid in the at least one immediate release portion may range from 7.0 mg and about 8.0 mg, for example, about 7.5 mg. In a further embodiment, the amount of opioid in the at least one immediate release portion may range from about 1.0 mg and about 5.0 mg. In yet another embodiment, the amount of opioid in the at least one immediate release portion may range from about 1.0 mg and about 4.5 mg. In another embodiment, the amount of opioid in the at least one immediate release portion may range from about 1.0 mg and about 4.0 mg. In still another embodiment, the amount of opioid in the at least one immediate release portion may range from about 1.0 mg and about 3.75 mg. In yet another

embodiment, the amount of opioid in the at least one immediate release portion may range from about 1.0 mg and about 3.5 mg.

[000179] The amount of opioid present in the at least one immediate release portion(s) may be expressed as a percentage (w/w) of the total amount of opioid in the pharmaceutical composition. In one embodiment, the at least one immediate release portion may comprise from about 20% to about 40% (w/w) of the total amount of opioid present in the pharmaceutical composition. In certain embodiments, the percentage of opioid present in the at least one immediate release portion of the pharmaceutical composition may be about 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, or 40% (w/w) of the total amount of opioid present in the composition. In one embodiment, the percentage of opioid present in the at least one immediate release portion may range from about 20% to about 30% (w/w) of the total amount of opioid present in the composition. In another embodiment, the percentage of opioid present in the at least one immediate release portion of the pharmaceutical composition may be about 25% (w/w) of the total amount of opioid present in the pharmaceutical composition.

[000180] The amount of opioid in the at least one immediate release portion also may be expressed as a percentage (w/w) of the total weight of the immediate release portion(s) of the pharmaceutical composition. In one embodiment, the amount of opioid in an immediate release portion may range from about 0.2% (w/w) to about 20% (w/w) of the total weight of such immediate release portion of the pharmaceutical composition. In another embodiment, the amount of opioid in an immediate release portion may range from about 0.5% (w/w) to about 5% (w/w) of the total weight of such immediate release portion. In various embodiments, an immediate release portion may comprise an amount of opioid that is approximately 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1.0%, 1.1%, 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%, 1.8%, 1.9%, 2.0%, 2.1%, 2.2%, 2.3%, 2.4%, 2.5%, 2.6%, 2.7%, 2.8%, 2.9%, 3.0%, 3.25%, 3.5%, 3.75%, 4.0%, 4.25%, 4.5%, 4.75%, 5.0%, 5.25%, 5.5%, 5.75%, 6.0%, 6.25%, 6.5%, 6.75%, 7.0%, 7.25%, 7.5%, 7.75%, 8.0%, 8.25%, 8.5%, 8.75%, 9.0%, 9.25%, 9.5%, 9.75%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, or 20% (w/w) of the total weight of such immediate release portion of the pharmaceutical composition. In yet another embodiment, the amount of

opioid in an immediate release portion may be about 0.5% (w/w) to about 1.0% (w/w) of the total weight of such immediate release portion of the pharmaceutical composition.

[000181] In some embodiments, the opioid in the at least one immediate release portion(s) of the pharmaceutical composition may be in the form of particles comprising opioid and at least one excipient. The at least one immediate release portion, therefore, may comprise particles of opioid(s) that are admixed with other API(s) and optional excipient(s). Suitable oxycodone particles are described in co-pending application U.S. Appl. Ser. No. 13/166,770, filed June 22, 2011, which is incorporated herein by reference in its entirety. The opioid particles may be coated or uncoated. The average size or average diameter of the particles may vary. In general, the average diameter of the particles may range from about 50 microns to about 2000 microns, from about 100 microns to about 1000 microns, or from about 150 microns to about 200 microns. In one embodiment, the maximum diameter of about 50% of the particles (d50) may be about 40 microns, 50 microns, 100 microns, 150 microns, 200 microns, 250 microns, 300 microns, 400 microns, or 500 microns. In another embodiment, the maximum diameter of about 90% of the particles (d90) may be about 100 microns, 150 microns, 200 microns, 250 microns, 300 microns, 400 microns, or 500 microns.

[000182] In one embodiment, the opioid found in the at least one immediate release portion of the pharmaceutical composition is oxycodone. The amount of oxycodone in the at least one immediate release portion of the pharmaceutical composition can and will vary. In one embodiment, the amount of oxycodone in the at least one immediate release portion may range from about 0.4 mg to about 100 mg. In an additional embodiment, the amount of oxycodone in the at least one immediate release portion may range from about 1 mg to about 40 mg. In a further embodiment, the amount of oxycodone in the at least one immediate release portion of the pharmaceutical composition may range from about 1 mg to about 7.5 mg. In another embodiment, the amount of oxycodone in the at least one immediate release portion may range from about 7.5 mg to about 15 mg. In yet another embodiment, the amount of oxycodone in the at least one immediate release portion may range from about 15 mg to about 40 mg. In various embodiments, the amount of oxycodone in the at least one immediate release portion may be about 1.25 mg, 1.3 mg, 1.325 mg, 1.35 mg, 1.375 mg, 1.4 mg, 1.425 mg,

1.45 mg, 1.475 mg, 1.5 mg, 1.525 mg, 1.55 mg, 1.575 mg, 1.6 mg, 1.625 mg, 1.65 mg, 1.675 mg, 1.7 mg, 1.725 mg, 1.75 mg, 1.775 mg, 1.8 mg, 1.825 mg, 1.85 mg, 1.875 mg, 1.9 mg, 1.925 mg, 1.95 mg, 1.975 mg, 2.0 mg, 2.25 mg, 2.5 mg, 2.75 mg, 3.0 mg, 3.25 mg, 3.5 mg, 3.75 mg, 4.0 mg, 4.25 mg, 4.5 mg, 4.75 mg, 5.0 mg, 5.25 mg, 5.5 mg, 5.75 mg, 6.0 mg, 6.25 mg, 6.5 mg, 6.75 mg, 7.0 mg, 7.25 mg, 7.5 mg, 7.75 mg, 8.0 mg, 8.25 mg, 8.5 mg, 8.75 mg, 9.0 mg, 9.25 mg, 9.5 mg, 9.75 mg, 10.0 mg, 11.0 mg, 12.0 mg, 12.5 mg, 13.0 mg, 14.0 mg, 15.0 mg, 17.5 mg, 20.0 mg, 22.5 mg, 25 mg, 27.5 mg, 30 mg, 40.0 mg, 75 mg, or 100 mg. In one embodiment, the amount of oxycodone in the at least one immediate release portion may range from about 7.0 mg and about 8.0 mg, for example, about 7.5 mg. In another embodiment, the amount of oxycodone in the at least one immediate release portion may be between about 3.0 mg and about 4.0 mg, for example, about 3.75 mg. In still another embodiment, the amount of opioid in the at least one immediate release portion may range from about 1.0 mg and about 2.0 mg, for example, about 1.875 mg. In a further embodiment, the amount of oxycodone in the at least one immediate release portion may range from about 1.0 mg and about 5.0 mg. In yet another embodiment, the amount of oxycodone in the at least one immediate release portion may range from about 1.0 mg and about 4.5 mg. In another embodiment, the amount of oxycodone in the at least one immediate release portion may range from about 1.0 mg and about 4.0 mg. In still another embodiment, the amount of oxycodone in the at least one immediate release portion may range from about 1.0 mg and about 3.5 mg. In yet another embodiment, the amount of oxycodone in the at least one immediate release portion may range from about 1.0 mg and about 3.0 mg.

[000183] The amount of oxycodone present in the at least one immediate release portion(s) may be expressed as a percentage (w/w) of the total amount of oxycodone in the pharmaceutical composition. In one embodiment, the at least one immediate release portion may comprise from about 20% to about 40% (w/w) of the total amount of oxycodone present in the pharmaceutical composition. In certain embodiments, the percentage of oxycodone present in the at least one immediate release portion of the pharmaceutical composition may be about 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, or 40% (w/w) of the total amount of oxycodone. In another embodiment, the percentage of oxycodone

present in the at least one immediate release portion of the pharmaceutical composition may be about 25% (w/w) of the total amount of oxycodone present in the pharmaceutical composition.

[000184] The amount of oxycodone in the at least one immediate release portion also may be expressed as a percentage (w/w) of the total weight of the immediate release portion(s) of the pharmaceutical composition. In one embodiment, the amount of oxycodone in an immediate release portion may range from about 0.2% (w/w) to about 20% (w/w) of the total weight of such immediate release portion of the pharmaceutical composition. In another embodiment, the amount of oxycodone in an immediate release portion may range from about 0.5% (w/w) to about 5% (w/w) of the total weight of such immediate release portion. In various embodiments, an immediate release portion may comprise an amount of oxycodone that is approximately 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1.0%, 1.1%, 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%, 1.8%, 1.9%, 2.0%, 2.1%, 2.2%, 2.3%, 2.4%, 2.5%, 2.6%, 2.7%, 2.8%, 2.9%, 3.0%, 3.25%, 3.5%, 3.75%, 4.0%, 4.25%, 4.5%, 4.75%, 5.0%, 5.25%, 5.5%, 5.75%, 6.0%, 6.25%, 6.5%, 6.75%, 7.0%, 7.25%, 7.5%, 7.75%, 8.0%, 8.25%, 8.5%, 8.75%, 9.0%, 9.25%, 9.5%, 9.75%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, or 20% (w/w) of the total weight of such immediate release portion of the pharmaceutical composition. In yet another embodiment, the amount of oxycodone in an immediate release portion may be about 0.5% (w/w) to about 1.0% (w/w) of the total weight of such immediate release portion of the pharmaceutical composition.

[000185] In some embodiments, the oxycodone of the at least one immediate release portion(s) of the pharmaceutical composition may be in the form of particles comprising oxycodone and at least one excipient. The at least one immediate release portion, therefore, may comprise particles of oxycodone that are admixed with other API(s), such as acetaminophen and optional excipient(s). Suitable oxycodone particles are described in co-pending application U.S. Appl. Ser. No. 13/166,770, filed June 22, 2011, which is incorporated herein by reference in its entirety. The oxycodone particles may be coated or uncoated. The average size or average diameter of the particles may vary. In general, the average diameter of the particles may range from about 50 microns to about 2000 microns, from about 100 microns to about 1000 microns, or from about 150

microns to about 200 microns. In one embodiment, the maximum diameter of about 50% of the particles (d50) may be about 40 microns, 50 microns, 100 microns, 150 microns, 200 microns, 250 microns, 300 microns, 400 microns, or 500 microns. In another embodiment, the maximum diameter of about 90% of the particles (d90) may be about 100 microns, 150 microns, 200 microns, 250 microns, 300 microns, 400 microns, or 500 microns.

(ii) Other API(s)

[000186] At least one immediate release portion of the composition may comprise at least one other API. Examples of suitable APIs that may be included in the at least one immediate release portion are presented above in Section (II)(a)(ii). In one embodiment, the other API may be acetylsalicylic acid or a salt thereof. In another embodiment, the other API may be diclofenac or a salt thereof. In yet another embodiment, the other API may be ibuprofen or a salt thereof. In still another embodiment, the other API may be indomethacin or a salt thereof. In a further embodiment, the other API may be ketoprofen or a salt thereof. In an alternate embodiment, the other API may be naproxen or a salt thereof. In another embodiment, the other API may be piroxicam or a salt thereof. In still another embodiment, the other API may be prednisolone or a salt thereof. In one embodiment, the other API may be acetaminophen or salt thereof.

[000187] The amount of the other API in the at least one immediate release portion can and will vary. In one embodiment, the immediate release portion may comprise from about 0.5 mg to about 750 mg of the API. In another embodiment, the amount of API in the at least one immediate release portion may range from about 50 mg to about 500 mg. In another embodiment, the amount of API in the at least one immediate release portion may range from about 25 mg to about 250 mg. In another embodiment, the amount of API in the at least one immediate release portion may range from about 150 mg to about 500 mg. In yet another embodiment, the amount of API in the at least one immediate release portion may range from about 0.5 mg to about 5 mg. In one embodiment, the amount of API in the at least one immediate release portion may range from about 125 mg to about 650 mg. In another embodiment, the amount of API in the at least one immediate release portion may range from about 162.5 mg to about 325 mg. In still another embodiment, the amount of API in the at least one immediate release portion

may range from about 325 mg to about 650 mg. In an additional embodiment, the amount of API in the at least one immediate release portion may range from about 100 mg to about 400 mg. In still another embodiment, the amount of API in the at least one immediate release portion may range from about 125 mg to about 325 mg.

[000188] The amount of other API in the at least one immediate release portion of the pharmaceutical composition can and will vary. In general, the amount of other API present in the at least one immediate release portion may range from about 30% to about 70% (w/w) of the total amount of other API in the composition. In one embodiment, the amount of other API present in the at least one immediate release portion ranges from about 40% to about 60% (w/w) of the total amount of API in the composition. In various embodiments, the at least one immediate release portion of the composition may comprise about 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, or 70% (w/w) of the total amount of API in the composition.

[000189] The amount of other API in an immediate release portion of the composition may range from about 15% to about 95% (w/w) of the total weight of such immediate release portion of the composition. In various embodiments, the amount of other API(s) in an immediate release portion may be about 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 82%, 84%, 86%, 88%, 90%, 92%, or 95% (w/w) of the total weight of such immediate release portion.

[000190] In embodiments in which the other API is acetaminophen, the amount of acetaminophen in the at least one immediate release may range from about 40 mg to about 800 mg. In still another embodiment, the at least one immediate release portion of the pharmaceutical composition may comprise from about 100 mg to about 600 mg of acetaminophen. In another embodiment, the at least one immediate release portion may comprise from about 150 mg to about 400 mg of acetaminophen. In a further embodiment, the amount of acetaminophen in the at least one immediate release portion may range from about 160 mg to about 325 mg. In an additional embodiment, the amount of acetaminophen in the at least one immediate release portion may range from about

100 mg to about 400 mg. In still another embodiment, the amount of acetaminophen in the at least one immediate release portion may range from about 125 mg to about 325 mg. In yet another embodiment, the amount of acetaminophen in the at least one immediate release portion may range from about 125 mg to about 400 mg.

[000191] In yet another embodiment, the amount of acetaminophen in the at least one immediate release portion may be about 120 mg, 125 mg, 130 mg, 135 mg, 140 mg, 145 mg, 150 mg, 155 mg, 160 mg, 162.5 mg, 165 mg, 170 mg, 175 mg, 180 mg, 185 mg, 190 mg, 195 mg, 200 mg, 205 mg, 210 mg, 215 mg, 220 mg, 225 mg, 230 mg, 235 mg, 240 mg, 245 mg, 250 mg, 255 mg, 260 mg, 265 mg, 270 mg, 275 mg, 280 mg, 285 mg, 290 mg, 295 mg, 300 mg, 305 mg, 310 mg, 315 mg, 320 mg, 325 mg, 330 mg, 335 mg, 340 mg, 345 mg, 350 mg, 355 mg, 360 mg, 365 mg, 370 mg, 375 mg, 380 mg, 385 mg, 390 mg, 395 mg, 400 mg, 500 mg, 520 mg, 600 mg, 650 mg, 700 mg, 750 mg, or 780 mg. In one embodiment, the at least one immediate release portion may comprise about 325 mg of acetaminophen. In another embodiment, the amount of acetaminophen in the at least one immediate release portion may be about 250 mg. In yet another embodiment, the amount of acetaminophen in the at least one immediate release portion may be about 162.5 mg. In still another embodiment, the amount of acetaminophen in the at least one immediate release portion may be about 125 mg.

[000192] The at least one immediate release portion(s) of the pharmaceutical composition may comprise from about 40% to about 60% (w/w) of the total amount of acetaminophen present in the pharmaceutical composition. The amount of acetaminophen in the at least one immediate release portion may be about 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, or 60% (w/w) of the total amount of acetaminophen present in the pharmaceutical composition. In one embodiment, the percentage of acetaminophen present in the at least one immediate release portion may be about 50% (w/w) of the total amount of acetaminophen present in the pharmaceutical composition.

[000193] The amount of acetaminophen in an immediate release portion(s) of the pharmaceutical composition may range from about 20% (w/w) to about 95% (w/w) of the total weight of such immediate release portion of the composition. In various embodiments, an immediate release portion may comprise an amount of acetaminophen

that is approximately about 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, or 95% (w/w) of the total weight of such immediate release portion. In one embodiment, the amount of acetaminophen in an immediate release portion may range from about 70% to about 80% (w/w) of the total weight of such immediate release portion of the pharmaceutical composition.

(iii) Excipients

[000194] The at least one immediate release portion(s) of pharmaceutical composition may further comprise at least one excipient. Suitable excipients include binders, fillers, disintegrants, lubricants, antioxidants, chelating agents, and color agents.

[000195] In one embodiment, the at least one immediate release portion(s) of the pharmaceutical composition may comprise at least one binder. Suitable binders include, without limit, starches (including corn starch and pregelatinized starch), gelatin, sugars (including sucrose, glucose, dextrose and lactose), polyethylene glycol, polyols, polyvinylalcohols, C12-C18 fatty acid alcohols, waxes, gums (e.g., guar gum, arabic gum, acacia gum, xanthan gum, etc.), gelatin, pectin, sodium alginate, polyvinylpyrrolidone, cellulosic polymers (including hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxycellulose, methylcellulose, microcrystalline cellulose, ethylcellulose, hydroxyethyl cellulose, and the like), polyacrylamides, and polyvinylloxazolidone. In one embodiment, the amount of binder or binders in an immediate release portion of the pharmaceutical composition may range from about 5% to about 10% (w/w) of the total weight of such immediate release portion. In various embodiments, an immediate release portion of the pharmaceutical composition may comprise at least one binder that is present in an amount that is about 5.0%, 5.25%, 5.5%, 5.75%, 6.0%, 6.25%, 6.5%, 6.75%, 7.0%, 7.1%, 7.2%, 7.3%, 7.4%, 7.5%, 7.6%, 7.7%, 7.8%, 7.9%, 8.0%, 8.1%, 8.2%, 8.3%, 8.4%, 8.5%, 8.6%, or 8.7%, 8.8%, 8.9%, or 9.0% (w/w) of such immediate release portion of the composition.

[000196] In another embodiment, the at least one immediate release portion(s) of the pharmaceutical composition may comprise at least one filler. Suitable fillers include but are not limited to microcrystalline cellulose (MCC), dibasic calcium phosphate, tribasic

calcium phosphate, magnesium carbonate, magnesium oxide, calcium silicate, magnesium aluminum silicate, silicon dioxide, titanium dioxide, alumina, talc, kaolin, polyvinylpyrrolidone, dibasic calcium sulfate, tribasic calcium sulfate, starch, calcium carbonate, magnesium carbonate, carbohydrates, modified starches, lactose, sucrose, dextrose, mannitol, sorbitol, and inorganic compounds. In one embodiment, the amount of filler or fillers in an immediate release portion may range from about 1.0% to about 10.0% (w/w) of the total weight of such immediate release portion. In various embodiments, an immediate release portion of the pharmaceutical composition may comprise at least one filler that is present in an amount that is about 1.0%, 1.5%, 2.0%, 2.5%, 3.0%, 3.5%, 4.0%, 4.5%, 5.0%, 5.5%, 6.0%, 6.1%, 6.2%, 6.3%, 6.4%, 6.5%, 6.6%, 6.7%, 6.8%, 6.9%, 7.0%, 7.1%, 7.2%, 7.3%, 7.4%, 7.5%, 7.6%, 7.7%, 7.8%, 7.9%, 8.0%, 8.1%, 8.2%, 8.3%, 8.4%, 8.5%, 8.6%, 8.7%, 8.8%, 8.9%, 9.0%, 9.1%, 9.2%, 9.3%, 9.4%, 9.5%, 9.6%, 9.7%, 9.8%, 9.9%, or 10.0%, (w/w), of such immediate release portion of the pharmaceutical composition.

[000197] In still another embodiment, the at least one immediate release portion(s) of the pharmaceutical composition may further comprise at least one disintegrant. The disintegrant may be selected from the group consisting of croscarmellose sodium, crospovidone, alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium, low substituted hydroxypropylcellulose, microcrystalline cellulose, and sodium starch glycolate. In one embodiment, the amount of disintegrant in an immediate release portion may range from about 2.0% to about 15.0% (w/w) of the total weight of such immediate release portion. In some embodiments, the amount of disintegrant in an immediate release portion may be about 4.0%, 4.2%, 4.4%, 4.6%, 4.8%, 5.0%, 5.2%, 5.4%, 5.6%, 5.8%, 6.0%, 6.2%, 6.4%, 6.6%, 6.8%, or 7.0% (w/w) of such immediate release portion of the pharmaceutical composition.

[000198] In a further embodiment, the at least one immediate release portion(s) of the pharmaceutical composition may further comprise a lubricant. Useful lubricants include magnesium stearate, calcium stearate, stearic acid, and hydrogenated vegetable oil (preferably comprised of hydrogenated and refined triglycerides of stearic and palmitic acids). The lubricant may be present in an amount ranging from about 0.1% to about 3.0% (w/w) of the total weight of an immediate release portion. In certain embodiments,

the amount of lubricant in at least one immediate release portion may be about 0.25%, 0.5%, 0.75%, 1.0%, 1.5%, 1.55%, 1.6%, 1.65%, 1.7%, 1.75%, 1.80%, 1.85%, 1.90%, 1.95%, or 2.0% (w/w) of the total weight of such immediate release portion.

[000199] In yet another embodiment, the at least one immediate release portion(s) of the pharmaceutical composition may comprise at least one antioxidant. Suitable antioxidants include, without limitation, ascorbic acid, citric acid, ascorbyl palmitate, butylated hydroxyanisole, a mixture of 2 and 3 tertiary-butyl-4-hydroxyanisole, butylated hydroxytoluene, sodium isoascorbate, dihydroguaric acid, potassium sorbate, sodium bisulfate, sodium metabisulfate, sorbic acid, potassium ascorbate, vitamin E, 4-chloro-2,6-ditertiarybutylphenol, alphatocopherol, and propylgallate. The amount of antioxidant present in an immediate release portion of the pharmaceutical composition may range from about 0.01% to about 4.0% (w/w), or from about 0.02% to about 0.10% (w/w) of the total weight of such immediate release portion. In various embodiments, the amount of antioxidant present in an immediate release portion of the pharmaceutical composition may be about 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.10%, 0.12%, 0.14%, 0.16%, 0.18%, 0.20%, 0.25%, 0.50%, 0.75%, 1.00%, 1.50%, or 2.00% (w/w) of the total weight of such immediate release portion.

[000200] In still another embodiment, the at least one immediate release portion(s) of the pharmaceutical composition may comprise at least one chelating agent. Suitable chelating agents include ethylenediamine tetracetic acid (EDTA) and its salts, N-(hydroxy-ethyl)ethylenediaminetriacetic acid, nitrilotriacetic acid (NIA), ethylene-bis(oxyethylene-nitrilo)tetraacetic acid, 1,4,7,10-tetraazacyclodecane-N,N',N'',N'''-tetraacetic acid, 1,4,7,10-tetraaza-cyclododecane-N,N',N''-triacetic acid, 1,4,7-tris(carboxymethyl)-10-(2'-hydroxypropyl)-1,4,7,10-tetraazocyclodecane, 1,4,7-triazacyclonane-N,N',N''-triacetic acid, 1,4,8,11-tetraazacyclotetra-decane-N,N',N'',N'''-tetraacetic acid; diethylenetriamine-pentaacetic acid (DTPA), ethylenedicysteine, bis(aminoethanethiol)carboxylic acid, triethylenetetraamine-hexaacetic acid, and 1,2-diaminocyclohexane-N,N',N''-tetraacetic acid. In one embodiment, the chelating agent may be the sodium salt of EDTA. The amount of chelating agent present in an

immediate release portion of the pharmaceutical composition may range from about 0.001% to about 0.20% (w/w) of such immediate release portion. In some embodiments, the amount of chelating agent present in an immediate release portion of the pharmaceutical composition may be about 0.001%, 0.002%, 0.003%, 0.004%, 0.005%, 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.10%, 0.11%, 0.12%, 0.13%, 0.14%, or 0.15% (w/w) of the total weight of such immediate release portion.

[000201] In an alternate embodiment, the at least one immediate release portion of the pharmaceutical composition may comprise a color agent. Suitable color additives include, but are not limited to, food, drug and cosmetic colors (FD&C), drug and cosmetic colors (D&C), and external drug and cosmetic colors (Ext. D&C). In various embodiments, the amount of color agent present in an immediate release portion may range from about 2.0% to about 5.0% (w/w) of the total weight of such immediate release portion of the composition. In other embodiments, the amount of color agent present in an immediate release portion may be about 1.0 %, 1.5 %, 2.0%, 2.5%, 3.0%, 3.5%, 4.0%, 4.5%, or 5.0% (w/w) of the total weight of such immediate release portion.

(c) Extended Release Portion

[000202] The pharmaceutical composition disclosed herein comprises at least one extended release portion. The at least one extended release portion may comprise at least one opioid, such as oxycodone, at least one other API, such as acetaminophen, or combinations thereof. The at least one extended release portion(s) further comprises at least one extended release component. The extended release component may comprise at least one extended release polymer.

[000203] The at least one extended release portion of the pharmaceutical composition is designed to release the active agents over an extended period of time. In general, the at least one extended release portion(s) provides release of the opioid(s), such as oxycodone, and/or the API(s), such as acetaminophen, for a period of time ranging from at least about 3 hours (hrs) to at least about 12 hrs. In one embodiment, the opioid(s) and/or the other API(s) may be released from the at least one extended release portion over a period of at least about 5 hours (hrs), or over a period of at least about 6 hours (hrs). In another embodiment, the at least one extended release portion may

release the opioid(s) and/or the other API(s) over a period of at least about 7 hours (hrs), or over a period of at least about 8 hours (hrs). In still another embodiment, the opioid(s) and/or the other API(s) may be released from the at least one extended release portion over a period of at least about 9 hours(hrs), or over a period of at least about 10 hours (hrs). In a further embodiment, the at least one extended release portion may release the opioid(s) and/or the other API(s) over a period of at least about 11 hours (hrs), or over a period of at least about 12 hours (hrs).

(i) Opioids

[000204] At least one extended release portion of the pharmaceutical composition comprises at least one opioid. Suitable opioids are detailed above in Section (II)(a)(i). In one embodiment, the opioid may be codeine or a salt thereof. In another embodiment, the opioid may be hydrocodone or a salt thereof. In yet another embodiment, the opioid may be hydromorphone or a salt thereof. In still another embodiment, the opioid may be morphine or a salt thereof. In a further embodiment, the opioid may be oxymorphone or a salt thereof. In an alternate embodiment, the opioid may be tramadol or a salt thereof. In another embodiment, the opioid may be oxycodone or a salt thereof.

[000205] The amount of opioid present in the at least one extended release portion(s) can and will vary. In one embodiment, the amount of opioid in the at least one extended release portion may range from about 1 mg to about 300 mg. In another embodiment, the amount of opioid in the at least one extended release portion may range from about 3.75 mg to about 225 mg. In yet another embodiment, the amount of opioid in the at least one extended release portion may range from about 3.75 mg to about 120 mg. In a further embodiment, the at least one extended release portion of the pharmaceutical composition may comprise from about 1 mg to about 22.5 mg of opioid. In an additional embodiment, the at least one extended release portion of the pharmaceutical composition may comprise from about 1 mg to about 15 mg of opioid. In another embodiment, the amount of opioid in the at least one extended release portion may be from about 22.5 mg to about 45 mg. In yet another embodiment, the amount opioid in the at least one extended release portion may be from about 45 mg to about 90 mg. In still another embodiment, the amount of opioid in the at least one extended release portion

may be from about 90 mg to about 225 mg. In yet another embodiment, the amount of opioid in the at least one extended release portion may be about 10 mg to about 30 mg. In yet another embodiment, the amount of opioid in the at least one extended release portion may be about 30 mg to about 60 mg.

[000206] In one embodiment, the amount of opioid in the at least one extended release portion may be from about 22 mg to about 23 mg, for example, about 22.5 mg. In another embodiment, the amount of opioid in the at least one extended release portion may be about 10 mg to about 12 mg, for example, about 11.25 mg.

[000207] In a further embodiment, the amount of opioid in the at least one extended release portion may be about 5.625 mg. In an additional embodiment, the amount of opioid in the at least one extended release portion may be about 10 mg to about 12.5 mg. In a further embodiment, the amount of opioid in the at least one extended release portion may be about 12 mg to about 18 mg. In another embodiment, the amount of opioid in the at least one extended release portion may be about 20 mg to about 25 mg. In a yet another embodiment, the amount of opioid in the at least one extended release portion may be about 2.5 mg to about 12.5 mg. In a further embodiment, the amount of opioid in the at least one extended release portion may be about 3 mg to about 8 mg. In another embodiment, the at least one extended release portion comprises about 5 mg to about 7 mg of opioid. In a further embodiment, the amount of opioid may be about 5.625 mg to about 11.25 mg. In a yet another embodiment, the amount of opioid in the at least one extended release portion may be about 3.75 mg. In a yet another embodiment, the amount of opioid in the at least one extended release portion may be about 5.625 mg. In still another embodiment, the amount of opioid in the at least one extended release portion may be about 7.5 mg. In still another embodiment, the amount of opioid in the at least one extended release portion may be about 11.25 mg. In an additional embodiment, the amount of opioid in the at least one extended release portion may be about 2.0 mg to about 7.0 mg. In a further embodiment, the amount of opioid in the at least one extended release portion may be about 3.0 mg to about 7.0 mg. In still a further embodiment, the amount of opioid in the at least one extended release portion may be about 4.0 mg to about 7.0 mg. In a another embodiment, the amount of opioid in the at least one extended release portion may be

about 4.0 mg to about 6.5 mg. In yet another embodiment, the amount of opioid in the at least one extended release portion may be about 4.5 mg to about 6.5 mg.

[000208] In yet another embodiment, the amount of opioid in the at least one extended release portion may be about 1.0 mg, 1.5 mg, 2.0 mg, 2.5 mg, 3.0 mg, 3.5 mg, 3.75 mg, 4.0 mg, 4.5 mg, 5.0 mg, 5.5 mg, 5.625 mg, 6.0 mg, 6.5 mg, 7.0 mg, 7.5 mg, 8.0 mg, 8.5 mg, 9.0 mg, 9.5 mg, 10.0 mg, 10.5 mg, 11.0 mg, 11.25 mg, 11.5 mg, 12.0 mg, 12.5 mg, 13.0 mg, 13.5 mg, 14.0 mg, 14.5 mg, 15.0 mg, 15.5 mg, 16.0 mg, 16.5 mg, 17.0 mg, 17.5 mg, 18.0 mg, 18.5 mg, 19.0 mg, 19.5 mg, 20.0 mg, 22.5 mg, or 25 mg, 27.5 mg, 30 mg, 35 mg, 40 mg, 45 mg, or 50 mg.

[000209] The amount of opioid present in the at least one extended release portion(s) may be expressed as a percentage of the total amount of opioid in the pharmaceutical composition. In one embodiment, the at least one extended release portion of the pharmaceutical composition comprises from about 60% to about 80% (w/w) of the total amount of opioid present in the pharmaceutical composition. In certain embodiments, the percentage of opioid present in the at least one extended release portion of the pharmaceutical composition may be about 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, or 80% (w/w) of the total amount of opioid present in the composition. In one embodiment, the percentage of opioid present in the at least one extended release portion of the pharmaceutical composition may be about 75% of the total amount of opioid present in the pharmaceutical composition.

[000210] The amount of opioid in the extended release portion(s) also may be expressed as a percentage of the total weight of the extended release portion(s) of the pharmaceutical composition. In one embodiment, the amount of opioid in an extended release portion may range from about 0.3% to about 8.0% (w/w) of the total weight of the extended release portion of the pharmaceutical composition. In various embodiments, an extended release portion may comprise an amount of opioid that is approximately 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1.0%, 1.1%, 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%, 1.8%, 1.9%, 2.0%, 2.1%, 2.2%, 2.3%, 2.4%, 2.5%, 2.6%, 2.7%, 2.8%, 2.9%, 3.0%, 3.1%, 3.2%, 3.3%, 3.4%, 3.5%, 3.6%, 3.7%, 3.8%, 3.9%, or 4.0%, 4.5%, 5%, 5.5%, 6%, 6.5%, 7%, 7.5%, or 8% (w/w) of the total weight of such extended release portion of the

pharmaceutical composition. In one embodiment, the amount of opioid in an extended release portion comprises about 0.5% to about 2% (w/w) of the total weight of such extended release portion of the pharmaceutical composition.

[000211] In some embodiments, the opioid of the at least one extended release portion of the composition(s) may be in the form of particles comprising the opioid and at least one excipient. Thus, the at least one extended release portion may comprise particles of opioid(s) which are admixed with the additional API(s), such as acetaminophen, and the extended release component, both of which are detailed below, as well as optional excipient(s). Suitable oxycodone particles are described in co-pending application U.S. Appl. Ser. No. 13/166,770, filed June 22, 2011, which is incorporated herein by reference in its entirety. The opioid particles may be coated or uncoated. The average size or average diameter of the particles may vary. In general, the average diameter of the particles may range from about 50 microns to about 2000 microns, from about 100 microns to about 1000 microns, or from about 150 microns to about 200 microns. In one embodiment, the maximum diameter of about 50% of the particles (d50) may be about 40 microns, 50 microns, 100 microns, 150 microns, 200 microns, 250 microns, 300 microns, 400 microns, or 500 microns. In another embodiment, the maximum diameter of about 90% of the particles (d90) may be about 100 microns, 150 microns, 200 microns, 250 microns, 300 microns, 400 microns, or 500 microns.

[000212] In embodiments in which the opioid is oxycodone, the amount of oxycodone in the at least one extended release portion(s) can and will vary. In one embodiment, the amount of oxycodone in the at least one extended release portion may range from about 1 mg to about 300 mg. In another embodiment, the amount of opioid in the at least one extended release portion may range from about 3.75 mg to about 225 mg. In another embodiment, the amount of opioid in the at least one extended release portion may range from about 3.75 mg to about 120 mg. In still another embodiment, the amount of opioid in the at least one extended release portion may range from about 45 mg to about 90 mg.

[000213] In a further embodiment, the at least one extended release portion of the pharmaceutical composition may comprise from about 1 mg to about 22.5 mg of

oxycodone. In another embodiment, the amount of in the at least one extended release portion may be about 10 mg to about 30 mg. In yet another embodiment, the amount of oxycodone in the at least one extended release portion may be about 30 mg to about 60 mg. In still another embodiment, the amount of oxycodone in the at least one extended release portion may be about 22.5 mg to about 45 mg. In another embodiment, the at least one extended release portion comprises about 5 mg to about 7 mg of oxycodone. In a further embodiment, the amount of oxycodone may be about 5.625 mg to about 11.25 mg. In an additional embodiment, the amount of oxycodone may be about 10 mg to about 12.5 mg. In a further embodiment, the amount of oxycodone may be about 12 mg to about 18 mg. In another embodiment, the amount of oxycodone in the at least one extended release portion may be about 20 mg to about 25 mg. In an additional embodiment, the amount of oxycodone may be about 2.0 mg to about 7.0 mg. In a further embodiment, the amount of oxycodone may be about 3.0 mg to about 7.0 mg. In still a further embodiment, the amount of oxycodone may be about 4.0 mg to about 7.0 mg. In a another embodiment, the amount of oxycodone may be about 4.0 mg to about 6.5 mg. In yet another embodiment, the amount of oxycodone may be about 4.5 mg to about 6.5 mg.

[000214] In yet another embodiment, the amount of oxycodone may be about 1.0 mg, 1.5 mg, 2.0 mg, 2.5 mg, 3.0 mg, 3.5 mg, 4.0 mg, 4.5 mg, 5.0 mg, 5.5 mg, 5.625 mg, 6.0 mg, 6.5 mg, 7.0 mg, 7.5 mg, 8.0 mg, 8.5 mg, 9.0 mg, 9.5 mg, 10.0 mg, 10.5 mg, 11.0 mg, 11.25 mg, 11.5 mg, 12.0 mg, 12.5 mg, 13.0 mg, 13.5 mg, 14.0 mg, 14.5 mg, 15.0 mg, 15.5 mg, 16.0 mg, 16.5 mg, 17.0 mg, 17.5 mg, 18.0 mg, 18.5 mg, 19.0 mg, 19.5 mg, 20.0 mg, 22.5 mg, 25 mg, 27.5 mg, 30 mg, 35 mg, 40 mg, 45 mg, or 50 mg. In one embodiment, the amount of oxycodone in the at least one extended release portion may be from about 22 mg to about 23 mg, for example, about 22.5 mg. In another embodiment, the amount of oxycodone in the at least one extended release portion may be about 10 mg to about 12 mg, for example, about 11.25 mg. In still another embodiment, the amount of oxycodone in the at least one extended release portion may be from about 5 mg to about 6 mg, for example, about 5.625 mg.

[000215] The amount of oxycodone present in the at least one extended release portion(s) may be expressed as a percentage of the total amount of oxycodone in the

pharmaceutical composition. In one embodiment, the at least one extended release portion of the pharmaceutical composition comprises from about 60% to about 80% (w/w) of the total amount of oxycodone present in the pharmaceutical composition. In certain embodiments, the percentage of oxycodone present in the at least one extended release portion of the pharmaceutical composition may be about 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, or 80% (w/w) of the total amount of oxycodone present in the composition. In one embodiment, the percentage of oxycodone present in the at least one extended release portion of the pharmaceutical composition may be about 75% of the total amount of oxycodone present in the pharmaceutical composition.

[000216] The amount of oxycodone in the extended release portion(s) also may be expressed as a percentage of the total weight of the extended release portion(s) of the pharmaceutical composition. In one embodiment, the amount of oxycodone in an extended release portion may range from about 0.3% to about 8.0% (w/w) of the total weight of the extended release portion of the pharmaceutical composition. In various embodiments, an extended release portion may comprise an amount of oxycodone that is approximately 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1.0%, 1.1%, 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%, 1.8%, 1.9%, 2.0%, 2.1%, 2.2%, 2.3%, 2.4%, 2.5%, 2.6%, 2.7%, 2.8%, 2.9%, 3.0%, 3.1%, 3.2%, 3.3%, 3.4%, 3.5%, 3.6%, 3.7%, 3.8%, 3.9%, or 4.0%, 4.5%, 5%, 5.5%, 6%, 6.5%, 7%, 7.5%, or 8% (w/w) of the total weight of such extended release portion of the pharmaceutical composition. In one embodiment, the amount of oxycodone in an extended release portion comprises about 0.5% to about 2% (w/w) of the total weight of such extended release portion of the pharmaceutical composition.

[000217] In some embodiments, the oxycodone of the at least one extended release portion of the composition(s) may be in the form of particles comprising oxycodone and at least one excipient. Thus, the at least one extended release portion may comprise particles of oxycodone which are admixed with the additional API(s), such as acetaminophen and the extended release component, both of which are detailed below, as well as optional excipients. Suitable oxycodone particles are described in co-pending application U.S. Appl. Ser. No. 13/166,770, filed June 22, 2011, which is incorporated herein by reference in its entirety. The oxycodone particles may be coated

or uncoated. The average size or average diameter of the particles may vary. In general, the average diameter of the particles may range from about 50 microns to about 2000 microns, from about 100 microns to about 1000 microns, or from about 150 microns to about 200 microns. In one embodiment, the maximum diameter of about 50% of the particles (d50) may be about 40 microns, 50 microns, 100 microns, 150 microns, 200 microns, 250 microns, 300 microns, 400 microns, or 500 microns. In another embodiment, the maximum diameter of about 90% of the particles (d90) may be about 100 microns, 150 microns, 200 microns, 250 microns, 300 microns, 400 microns, or 500 microns.

(ii) Other API(s)

[000218] The at least one extended release portion of the pharmaceutical composition may comprise at least one other API. Examples of suitable APIs that may be included in the at least one extended release portion are presented above in Section (I)(a)(ii). In one embodiment, the other API may be acetylsalicylic acid or a salt thereof. In another embodiment, the API may be diclofenac or a salt thereof. In yet another embodiment, the API may be ibuprofen or a salt thereof. In still another embodiment, the API may be indomethacin or a salt thereof. In a further embodiment, the API may be ketoprofen or a salt thereof. In an alternate embodiment, the API may be naproxen or a salt thereof. In another embodiment, the API may be piroxicam or a salt thereof. In still another embodiment, the API may be prednisolone or a salt thereof. In one embodiment, the API may be acetaminophen or salt thereof.

[000219] The amount of the other API in the at least one extended release portion can and will vary. In one embodiment, the at least one extended release portion may comprise from about 0.5 mg to about 750 mg of the API. In another embodiment, the amount of API in the at least one extended release portion may range from about 50 mg to about 500 mg. In another embodiment, the amount of API in the at least one extended release portion may range from about 25 mg to about 250 mg. In another embodiment, the amount of API in the at least one extended release portion may range from about 150 mg to about 500 mg. In yet another embodiment, the amount of API in the at least one extended release portion may range from about 0.5 mg to about 5 mg. In one embodiment, the amount of API in the at least one extended release portion may range

from about 125 mg to about 650 mg. In another embodiment, the amount of API in the at least one extended release portion may range from about 162.5 mg to about 325 mg. In still another embodiment, the amount of API in the at least one extended release portion may range from about 325 mg to about 650 mg. In yet another embodiment, the amount of API in the at least one extended release portion may range from about 100 mg to about 400 mg. In an additional embodiment, the amount of API in the at least one extended release portion may range from about 125 mg to about 325 mg.

[000220] The amount of other API(s) in the at least one extended release portion of the pharmaceutical composition can and will vary, depending upon the identity of the API(s). In general, the amount of other API present in the at least one extended release portion may range from about 30% to about 70% (w/w) of the total amount of other API in the composition. In one embodiment, the amount of other API present in the at least one extended release portion may range from about 40% to about 60% (w/w) of the total amount of other API in the composition. In various embodiments, the at least one extended release portion of the pharmaceutical composition may comprise about 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, or 70% (w/w) of the total amount of other API in the composition.

[000221] The amount of other API in an extended release portion also may be expressed as a percentage of the total weight of such extended release portion of the pharmaceutical composition. In various embodiments, the amount of other API in an extended release portion may range from about 10% to about 70% (w/w) of the total weight of such extended release portion of the composition. In various embodiments, the amount of other API in an extended release portion may be about 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 32%, 34%, 36%, 38%, 40%, 42%, 44%, 46%, 48%, 50%, 52%, 54%, 56%, 58%, 60%, 62%, 64%, 66%, 68%, or 70% (w/w) of the total weight of such extended release portion of the composition.

[000222] In embodiments in which the other API is acetaminophen, the amount of acetaminophen in the at least one extended release portion may range from about 40 mg

to about 800 mg. In still another embodiment, the at least one extended release portion of the pharmaceutical composition may comprise from about 100 mg to about 600 mg of acetaminophen. In another embodiment, the at least one extended release portion may comprise from about 125 mg to about 400 mg of acetaminophen. In a further embodiment, the amount of acetaminophen in the at least one extended release portion may range from about 160 mg to about 325 mg. In yet another embodiment, the amount of acetaminophen in the at least one extended release portion may range from about 100 mg to about 400 mg. In an additional embodiment, the amount of acetaminophen in the at least one extended release portion may range from about 125 mg to about 325 mg.

[000223] In yet another embodiment, the amount of acetaminophen in the at least one extended release portion may be about 100 mg, 110 mg, 120 mg, 125 mg, 130 mg, 135 mg, 140 mg, 145 mg, 150 mg, 155 mg, 160 mg, 162.5 mg, 165 mg, 170 mg, 175 mg, 180 mg, 185 mg, 190 mg, 195 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, 300 mg, 310 mg, 320 mg, 325 mg, 330 mg, 340 mg, 350 mg, 360 mg, 370 mg, 380 mg, 390 mg, 400 mg, 450 mg, 500 mg, 520 mg, 550 mg, 600 mg, 625 mg, 650 mg, 700 mg, 750 mg, 775 mg, 780 mg, or 800 mg. In one embodiment, the at least one extended release portion comprises about 325 mg of acetaminophen. In another embodiment, the amount of acetaminophen in the at least one extended release portion may be about 250 mg. In yet another embodiment, the amount of acetaminophen in the at least one extended release portion may be about 162.5 mg. In still another embodiment, the amount of acetaminophen in the at least one extended release portion may be about 125 mg.

[000224] The amount of acetaminophen in the at least one extended release portion(s) of the pharmaceutical composition may comprise from about 40% to about 60% of the total amount of acetaminophen present in the pharmaceutical composition. The amount of acetaminophen in the at least one extended release portion may be about 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, or 60% (w/w) of the total amount of acetaminophen present in the pharmaceutical composition. In one embodiment, the percentage of acetaminophen present in the at least one extended release portion(s) of the

pharmaceutical composition may be about 50% (w/w) of the total amount of acetaminophen present in the composition.

[000225] The amount of acetaminophen in an extended release portion of the pharmaceutical composition may range from about 15% to about 60% (w/w) of the total weight of such extended release portion of the pharmaceutical composition. In various embodiments, the amount of acetaminophen in an extended release portion may comprise an amount of acetaminophen that is approximately about 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 32%, 35%, 37%, 40%, 42%, 45%, 47%, 50%, 52%, 55%, 57%, or 60% (w/w) of the total weight of such extended release portion. In one embodiment, the amount of acetaminophen in an extended release portion may range from about 20% to about 40% (w/w) of the total weight of such extended release portion of the pharmaceutical composition.

(iii) Extended release component

[000226] The extended release portion(s) of the composition also comprise(s) an extended release component. Suitable extended release components include polymers, resins, hydrocolloids, hydrogels, and the like.

[000227] In one embodiment, the extended release component may comprise at least one extended release polymer. Suitable polymers for inclusion in the at least one extended release portion of the composition may be linear, branched, dendrimeric, or star polymers, and include synthetic hydrophilic polymers as well as semi-synthetic and naturally occurring hydrophilic polymers. The polymers may be homopolymers or copolymers, such as random copolymers, block copolymers, and graft copolymers. Suitable hydrophilic polymers include, but are not limited to: polyalkylene oxides, particularly poly(ethylene oxide), polyethylene glycol and poly(ethylene oxide)-poly(propylene oxide) copolymers; cellulosic polymers, such as methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and carboxymethylcellulose, microcrystalline cellulose, and polysaccharides and their derivatives; acrylic acid and methacrylic acid polymers, copolymers and esters thereof, preferably formed from acrylic acid, methacrylic acid, methyl acrylate, ethyl acrylate, methyl methacrylate, ethyl methacrylate, and copolymers thereof, with each other or with additional acrylate species such as aminoethyl acrylate;

maleic anhydride copolymers; polymaleic acid; poly(acrylamides) such as polyacrylamide *per se*, poly(methacrylamide), poly(dimethylacrylamide), and poly(N-isopropyl-acrylamide); polyalkylene oxides; poly(olefinic alcohol)s such as poly(vinyl alcohol); poly(N-vinyl lactams) such as poly(vinyl pyrrolidone), poly(N-vinyl caprolactam), and copolymers thereof; polyols such as glycerol, polyglycerol (particularly highly branched polyglycerol), propylene glycol and trimethylene glycol substituted with one or more polyalkylene oxides, e.g., mono-, di- and tri-polyoxyethylated glycerol, mono- and di-polyoxyethylated propylene glycol, and mono- and di-polyoxyethylated trimethylene glycol; polyoxyethylated sorbitol and polyoxyethylated glucose; polyoxazolines, including poly(methyloxazoline) and poly(ethyloxazoline); polyvinylamines; polyvinylacetates, including polyvinylacetate *per se* as well as ethylene-vinyl acetate copolymers, polyvinyl acetate phthalate, and the like, polyimines, such as polyethyleneimine; starch and starch-based polymers; polyurethane hydrogels; chitosan; polysaccharide gums; xanthan gum; zein; and shellac, ammoniated shellac, shellac-acetyl alcohol, and shellac n-butyl stearate. The polymers may be used individually or in combination. Certain combinations will often provide a more controlled release of opioid(s), such as oxycodone, and API(s), such as acetaminophen, than their components when used individually. Suitable combinations include cellulose-based polymers combined with gums, such as hydroxyethyl cellulose or hydroxypropyl cellulose combined with xanthan gum, and poly(ethylene oxide) combined with xanthan gum.

[000228] In one embodiment, the extended release polymer(s) may be a cellulosic polymer, such as an alkyl substituted cellulose derivative as detailed above. In terms of their viscosities, one class of exemplary alkyl substituted celluloses includes those whose viscosity is within the range of about 100 to about 110,000 centipoise as a 2% aqueous solution at 20°C. Another class includes those whose viscosity is within the range of about 1,000 to about 4,000 centipoise as a 1% aqueous solution at 20°C.

[000229] In one embodiment, the extended release polymer(s) may be a polyalkylene oxide. In another aspect, the polyalkylene oxide may be poly(ethylene) oxide. In a further embodiment, the poly(ethylene) oxide may have an approximate molecular weight between 500,000 Daltons (Da) to about 10,000,000 Da or about 900,000 Da to about 7,000,000 Da. In yet a further embodiment, the poly(ethylene) oxide

may have a molecular weight of approximately about 600,000 Da, about 700,000 Da, about 800,000 Da, about 900,000 Da, about 1,000,000 Da, about 2,000,000 Da, about 3,000,000 Da, about 4,000,000 Da, about 5,000,000 Da, about 6,000,000 Da, about 7,000,000 Da, about 8,000,000 Da, 9,000,000 Da, or 10,000,000 Da.

[000230] In another embodiment, the polyethylene oxide may be any desirable grade of POLYOX™ or any combination thereof. By way of example and without limitation, the POLYOX™ grade may be WSR N-10, WSR N-80, WSR N-750, WSR 205, WSR 1105, WSR N-12K, WSR N-60K, WSR-301, WSR Coagulant, WSR-303, WSR-308, WSR N-3000, UCARFLOC Polymer 300, UCARFLOC Polymer 302, UCARFLOC Polymer 304, and UCARFLOC Polymer 309. In one embodiment, the polyethylene oxide may have an average molecular weight of from about 100,000 Da to about 8,000,000 Da. In another embodiment, the polyethylene oxide may have an average molecular weight of about 100,000 Da, about 200,000 Da, about 300,000 Da, about 400,000 Da, about 500,000 Da, about 600,000 Da, about 700,000 Da, about 800,000 Da, about 900,000 Da, about 1,000,000 Da, about 2,000,000 Da, about 3,000,000 Da, about 4,000,000 Da, about 5,000,000 Da, about 6,000,000 Da, about 7,000,000 Da, or about 8,000,000 Da. In still another embodiment, the polyethylene oxide may have an average number of repeating ethylene oxide units (-CH₂CH₂O-) of about 2,000 to about 160,000. In yet another embodiment, the polyethylene oxide may have an average number of repeating ethylene oxide units of about 2,275, about 4,500, about 6,800, about 9,100, about 14,000, about 20,000, about 23,000, about 45,000, about 90,000, about 114,000, or about 159,000.

[000231] The release profile of the extended release compositions disclosed herein will depend partially upon the molecular weight of the extended release polymer(s). In certain embodiments, the polymers are of a moderate to high molecular weight (900,000 Da to 4,000,000 Da) to control release of the opioid, such as oxycodone and/or the API(s), such as acetaminophen from the composition via diffusion of the opioid(s) and/or other API out of the polymer and/or erosion of the polymer. An example of suitable polyethylene oxide polymers are those having molecular weights (viscosity average) on the order of about 900,000 Da to about 2,000,000 Da. Using a lower molecular weight ("MW") polyethylene oxide, such as POLYOX® 1105 (900,000 MW),

the release rates for drugs are higher. Using a higher molecular weight polyethylene oxide (such as POLYOX® N-60K (2,000,000 MW) or POLYOX® WSR-301 (4,000,000 MW) reduces the rate of release for drugs. In another embodiment of the invention, a hydroxypropylmethylcellulose polymer of such molecular weight is utilized so that the viscosity of a 2% aqueous solution is about 4000 cps to greater than about 100,000 cps.

[000232] The release profile of the extended release pharmaceutical composition disclosed herein may also depend upon the amount of the extended release polymer(s) in the pharmaceutical composition. In general, the release rates for all active agents may be decreased by increasing the amount of the extended release polymer(s) in the pharmaceutical composition. Stated another way, the release rates for the opioid, such as oxycodone, and/or the additional API, such as acetaminophen, may be slowed by increasing the amount of the extended release polymer(s) in the pharmaceutical composition. By way of example and without limitation, the release profile of all active agents (e.g., acetaminophen and oxycodone) may be decreased by increasing the amount of POLYOX® 1105 from about 25% by weight of the ER portion to about 35% by weight of the ER portion:

[000233] The amount of extended release polymer or polymers present in the extended release portion(s) of the pharmaceutical composition can and will vary. In one embodiment, the polymer present in an extended release portion of the composition may range from about 15% to about 70% (w/w), or about 20% to about 60 % (w/w), or about 25% to about 55% (w/w) of the total weight of such extended release portion of the composition. In another embodiment, the amount of polymer present in an extended release portion of the pharmaceutical composition may range from about 30% to about 50% (w/w) of the total weight of such extended release portion. In still another embodiment, the amount of polymer present in an extended release portion of the pharmaceutical composition may range from about 35% to about 45% (w/w) of the total weight of such extended release portion. In yet another embodiment, the amount of polymer present in an extended release portion of the pharmaceutical composition may be about 30%, 35%, 40%, 45%, 50%, 55%, or 60% (w/w) of the total weight of such extended release portion. In one embodiment, the amount of polymer present in an extended release portion of the pharmaceutical composition may be about 35% (w/w) of

the total weight of such extended release portion. In another embodiment, the amount of polymer present in an extended release portion of the pharmaceutical composition may be about 45% (w/w) of the total weight of such extended release portion. In one embodiment, the ER layer swells upon imbibition of fluid to a size which is about 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 100% larger than the size of the ER layer prior to imbibition of fluid. In another embodiment, the ER layer swells upon imbibition of fluid to a size at least about 25% larger than the size of the ER layer prior to imbibition of fluid within about 15 minutes of the start of fluid imbibition. In still another embodiment, the ER layer swells upon imbibition of fluid to a size at least about 100% larger than the size of the ER layer prior to imbibition of fluid within about 45 min, 50 min, 60 min, 75 min, or 90 min of the start of fluid imbibitions.

(iv) Excipients

[000234] The extended release portion(s) of the pharmaceutical composition may further comprise at least one excipient. Suitable excipients include binders, fillers, lubricants, antioxidants, chelating agents, and color agents.

[000235] In one embodiment, the extended release portion(s) of the pharmaceutical composition may comprise at least one binder. Suitable binders include, without limit, starches (including corn starch and pregelatinized starch), gelatin, sugars (including sucrose, glucose, dextrose and lactose), polyethylene glycol, polyols, polyvinylalcohols, C12-C18 fatty acid alcohols, waxes, gums (e.g., guar gum, arabic gum, acacia gum, xanthan gum, etc.), gelatin, pectin, sodium alginate, polyvinylpyrrolidone, cellulosic polymers (including hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxylcellulose, methylcellulose, microcrystalline cellulose, ethylcellulose, hydroxyethyl cellulose, and the like), polyacrylamides, and polyvinylloxazolidone. In one embodiment, the amount of binder or binders in an extended release portion of the pharmaceutical composition may range from about 0.5% to about 8.0% (w/w) of such extended release portion. In various embodiments, an extended release portion of the pharmaceutical composition may comprise at least one binder that is present in an amount that is about 0.5%, 1.0%, 1.1%, 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%, 1.8%,

1.9%, 2.0%, 2.5%, 3.0%, 3.5%, 4.0%, 4.5%, 5.0%, 5.5%, or 6.0%, 6.5%, 7.0%, 7.5%, or 8.0% (w/w) of such extended release portion of the composition.

[000236] In another embodiment, the at least one extended release portion(s) of the pharmaceutical composition may comprise at least one filler. Suitable fillers include but are not limited to microcrystalline cellulose (MCC), dibasic calcium phosphate, tribasic calcium phosphate, magnesium carbonate, magnesium oxide, calcium silicate, magnesium aluminum silicate, silicon dioxide, titanium dioxide, alumina, talc, kaolin, polyvinylpyrrolidone, dibasic calcium sulfate, tribasic calcium sulfate, starch, calcium carbonate, magnesium carbonate, carbohydrates, modified starches, lactose, sucrose, dextrose, mannitol, sorbitol, and inorganic compounds. In one embodiment, the amount of filler or fillers in an extended release portion may range from about 2% to about 50% (w/w) of the total weight of such extended release portion. In various embodiments, an extended release portion of the pharmaceutical composition may comprise at least one filler that is present in an amount that is about 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, or 50% (w/w) of such extended release portion of the composition.

[000237] In a further embodiment, the extended release portion(s) of the pharmaceutical composition may further comprise a lubricant. Useful lubricants include magnesium stearate, calcium stearate, stearic acid, and hydrogenated vegetable oil (preferably comprised of hydrogenated and refined triglycerides of stearic and palmitic acids). The lubricant may be present in an amount ranging from about 0.1% to about 3.0% (w/w) of the total weight of the extended release portion. In certain embodiments, the amount of lubricant in an extended release portion may be about 0.25%, 0.5%, 0.75%, 1.0%, 1.5%, 1.75%, 1.80%, 1.85%, 1.90%, or 2.0% (w/w) of the total weight of such extended release portion of the composition.

[000238] In yet another embodiment, the extended release portion(s) of the pharmaceutical composition may comprise at least one antioxidant. Suitable antioxidants include, without limit, ascorbic acid, citric acid, ascorbyl palmitate, butylated hydroxyanisole, a mixture of 2 and 3 tertiary-butyl-4-hydroxyanisole, butylated

hydroxytoluene, sodium isoascorbate, dihydroguaric acid, potassium sorbate, sodium bisulfate, sodium metabisulfate, sorbic acid, potassium ascorbate, vitamin E, 4-chloro-2,6-ditertiarybutylphenol, alphanatocopherol, and propylgallate. The amount of antioxidant present in an extended release portion of the pharmaceutical composition may range from about 0.01% to about 4.0% (w/w), or from about 0.02% to about 0.10% (w/w). In various embodiments, the amount of antioxidant present in an extended release portion of the pharmaceutical composition may be about 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.10%, 0.12%, 0.14%, 0.16%, 0.18%, 0.20%, 0.25%, 0.50%, 0.75%, 1.00%, 1.50%, or 2.00% (w/w) of the total weight of such extended release portion.

[000239] In still another embodiment, the extended release portion(s) of the pharmaceutical composition may comprise at least one chelating agent. Suitable chelating agents include ethylenediamine tetracetic acid (EDTA) and its salts, N-(hydroxy-ethyl)ethylenediaminetriacetic acid, nitrilotriacetic acid (NIA), ethylene-bis(oxyethylene-nitrilo)tetraacetic acid, 1,4,7,10-tetraazacyclodecane-N,N',N'',N'''-tetraacetic acid, 1,4,7,10-tetraaza-cyclododecane-N,N',N''-triacetic acid, 1,4,7-tris(carboxymethyl)-10-(2'-hydroxypropyl)-1,4,7,10-tetraazocyclodecane, 1,4,7-triazacyclonane-N,N',N''-triacetic acid, 1,4,8,11-tetraazacyclotetra-decane-N,N',N'',N'''-tetraacetic acid; diethylenetriamine-pentaacetic acid (DTPA), ethylenedicysteine, bis(aminoethanethiol)carboxylic acid, triethylenetetraamine-hexaacetic acid, and 1,2-diaminocyclohexane-N,N,N',N'-tetraacetic acid. In one embodiment, the chelating agent may be the sodium salt of EDTA. The amount of chelating agent present in an extended release portion of the pharmaceutical composition may range from about 0.001% to about 0.20% (w/w) of such extended release portion. In some embodiments, the amount of chelating agent present in an extended release portion of the pharmaceutical composition may be about 0.001%, 0.002%, 0.003%, 0.004%, 0.005%, 0.006%, 0.007%, 0.008%, 0.009%, 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.10%, 0.11%, 0.12%, 0.13%, 0.14%, or 0.15% (w/w) of the total weight of such extended release portion.

[000240] In an alternate embodiment, the extended release portion(s) of the pharmaceutical composition may comprise a color agent. Suitable color additives include, but are not limited to, food, drug and cosmetic colors (FD&C), drug and cosmetic colors (D&C), and external drug and cosmetic colors (Ext. D&C). In various embodiments, the amount of color agent present in an extended release portion may range from about 2.0% to about 5.0% (w/w) of such extended release portion of the composition. In other embodiments, the amount of color agent present in an extended release portion may be about 1.0%, 1.5%, 2.0%, 2.5%, 3.0%, 3.5%, 4.0%, 4.5%, or 5.0% (w/w) of such extended release portion.

(d) **Dosage forms of the pharmaceutical composition**

(i) ***Physical Properties***

[000241] The physical form of the pharmaceutical composition disclosed herein can and will vary. In general, the pharmaceutical composition is a solid dosage form comprising at least one extended release portion and, optionally, at least one immediate release portion. Suitable solid dosage forms include tablets, caplets, capsules, encapsulated beads, and gelcaps. Non-limiting types of tablets include coated tablets, uncoated tablets, bilayer tablets, multiparticulate tablets, monolithic tablets, matrix tablets, compressed tablets, and molded tablets. Non-limiting types of capsules include hard capsules and multi-layer capsules.

[000242] In one embodiment, the dosage form may be a capsule. Non-limiting examples of suitable hard capsules include hard starch capsules, hard gelatin capsules, hard cellulose capsules, and hydrogel capsules. In one example, the core of the capsule may comprise the at least one extended release portion and the shell of the capsule may comprise the at least one immediate release portion of the composition. In another example, the core of the capsule may comprises one extended release portion, comprising oxycodone, acetaminophen and an extended release component, and the shell of the capsule may comprise one immediate release portion of the composition comprising oxycodone and acetaminophen. In yet another example, the core of the capsule may comprise two extended release portions, each comprising an extended release component and one of oxycodone or acetaminophen, and the shell of the capsule may comprise two immediate release portions of the composition, each comprising one of

the oxycodone and the acetaminophen. In still another embodiment, the dosage form may be a sustained release capsule comprising the oxycodone or the acetaminophen and exhibiting immediate release and/or extended release properties. In yet another embodiment, the dosage form may be a delayed release capsule comprising the oxycodone and/or acetaminophen and exhibiting immediate release and/or extended release properties. The capsule may comprise a coating. In one embodiment, the capsule may comprise an enteric coating.

[000243] In another embodiment, the dosage form may be a tablet comprising at least one extended release portion and at least one immediate release portion. The at least one immediate release portion may be adjacent to, abutting, or surrounding the at least one extended release portion. In one embodiment, the dosage form may be a bilayer tablet comprising one extended release layer comprising the oxycodone and the acetaminophen and one immediate release layer comprising the oxycodone and the acetaminophen. The bilayer tablet may comprise a coating. In another embodiment, the dosage form may be a multilayer tablet comprising two extended release portions, each comprising one of the oxycodone and the acetaminophen, and one immediate release portion comprising both the oxycodone and the acetaminophen. In yet another embodiment, the dosage form may be a multilayer tablet comprising two extended release portions, each comprising one of the oxycodone and the acetaminophen, and two immediate release portions, each comprising one of the oxycodone and the acetaminophen. In still another embodiment, the dosage form may be a sustained release tablet comprising the oxycodone and/or acetaminophen and exhibiting immediate release and/or extended release properties. In yet another embodiment, the dosage form may be a delayed release tablet comprising the oxycodone and/or acetaminophen and exhibiting immediate release and/or extended release properties. The bilayer tablet may comprise a coating. In one embodiment, the bilayer tablet may comprise an enteric coating.

[000244] In certain embodiments, the tablet may have a friability of no greater than about 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.7% or 1.0%. In another embodiment, the tablet may have a friability of greater than 0 but less than about 1.0%, greater than 0 but

less than about 0.5%, greater than 0 but less than about 0.3%, or greater than 0 but less than about 0.2%. In still another embodiment, the tablet may have a friability of zero.

[000245] In another embodiment, the tablet may have a hardness of at least about 10 Kilopond (also known as kilopons) (kp). In some embodiments, the tablet may have a hardness of about 9 kp to about 25 kp, or about 12 kp to about 20 kp. In further embodiments, the tablet may have a hardness of about 11 kp, 12 kp, 13 kp, 14 kp, 15 kp, 16 kp, 17 kp, 18 kp, 19 kp, or 20 kp.

[000246] In additional embodiments, the tablet may have a content uniformity of from about 85 to about 115 percent by weight or from about 90 to about 110 percent by weight, or from about 95 to about 105 percent by weight. In other embodiments, the content uniformity may have a relative standard deviation (RSD) equal to or less than about 3.5%, 3.0%, 2.5%, 2.0%, 1.5%, 1.0%, or 0.5%.

[000247] The pharmaceutical composition disclosed herein includes one or more dosage forms that are designed to achieve the therapeutic concentrations of the active ingredients. In some embodiments, therefore, a therapeutically effective dose of the pharmaceutical composition may comprise one dosage form. In other embodiments, a therapeutically effective dose of the pharmaceutical composition may comprise two dosage forms. In additional embodiments, a therapeutically effective dose of the pharmaceutical composition may comprise three or more dosage forms.

[000248] In still other embodiments, prior to administration to a patient or immersion in fluid, the pharmaceutical composition may have (i) a length of approximately 18 mm, 18.01 mm, 18.02 mm, 18.03 mm, 18.04 mm, 18.05 mm, 18.06 mm, 18.07 mm, 18.08 mm, 18.09 mm, 18.1 mm, 18.11 mm, 18.12 mm, 18.13 mm, 18.14 mm, 18.15 mm, 18.16 mm, 18.17 mm, 18.18 mm, 18.19 mm, 18.2 mm, 18.21 mm, 18.22 mm, 18.23 mm, 18.24 mm, 18.25 mm, 18.26 mm, 18.27 mm, 18.28 mm, 18.29 mm, 18.3 mm, 18.31 mm, 18.32 mm, 18.33 mm, 18.34 mm, 18.35 mm, 18.36 mm, 18.37 mm, 18.38 mm, 18.39 mm, 18.4 mm, 18.41 mm, 18.42 mm, 18.43 mm, 18.44 mm, 18.45 mm, 18.46 mm, 18.47 mm, 18.48 mm, 18.49 mm, 18.5 mm, 18.51 mm, 18.52 mm, 18.53 mm, 18.54 mm, 18.55 mm, 18.56 mm, 18.57 mm, 18.58 mm, 18.59 mm, 18.6 mm, 18.61 mm, 18.62 mm, 18.63 mm, 18.64 mm, 18.65 mm, 18.66 mm, 18.67 mm, 18.68 mm, 18.69 mm, 18.7 mm, 18.71 mm, 18.72 mm, 18.73 mm, 18.74 mm, 18.75 mm, 18.76 mm, 18.77 mm, 18.78 mm, 18.79 mm,

18.8 mm, 18.81 mm, 18.82 mm, 18.83 mm, 18.84 mm, 18.85 mm, 18.86 mm, 18.87 mm, 18.88 mm, 18.89 mm, 18.9 mm, 18.91 mm, 18.92 mm, 18.93 mm, 18.94 mm, 18.95 mm, 18.96 mm, 18.97 mm, 18.98 mm, 18.99 mm, 19 mm, 19.01 mm, 19.02 mm, 19.03 mm, 19.04 mm, 19.05 mm, 19.06 mm, 19.07 mm, 19.08 mm, 19.09 mm, 19.1 mm, 19.11 mm, 19.12 mm, 19.13 mm, 19.14 mm, 19.15 mm, 19.16 mm, 19.17 mm, 19.18 mm, 19.19 mm, 19.2 mm, 19.21 mm, 19.22 mm, 19.23 mm, 19.24 mm, 19.25 mm, 19.26 mm, 19.27 mm, 19.28 mm, 19.29 mm, 19.3 mm, 19.31 mm, 19.32 mm, 19.33 mm, 19.34 mm, 19.35 mm, 19.36 mm, 19.37 mm, 19.38 mm, 19.39 mm, 19.4 mm, 19.41 mm, 19.42 mm, 19.43 mm, 19.44 mm, 19.45 mm, 19.46 mm, 19.47 mm, 19.48 mm, 19.49 mm, 19.5 mm, 19.51 mm, 19.52 mm, 19.53 mm, 19.54 mm, 19.55 mm, 19.56 mm, 19.57 mm, 19.58 mm, 19.59 mm, 19.6 mm, 19.61 mm, 19.62 mm, 19.63 mm, 19.64 mm, 19.65 mm, 19.66 mm, 19.67 mm, 19.68 mm, 19.69 mm, 19.7 mm, 19.71 mm, 19.72 mm, 19.73 mm, 19.74 mm, 19.75 mm, 19.76 mm, 19.77 mm, 19.78 mm, 19.79 mm, 19.8 mm, 19.81 mm, 19.82 mm, 19.83 mm, 19.84 mm, 19.85 mm, 19.86 mm, 19.87 mm, 19.88 mm, 19.89 mm, 19.9 mm, 19.91 mm, 19.92 mm, 19.93 mm, 19.94 mm, 19.95 mm, 19.96 mm, 19.97 mm, 19.98 mm, 19.99 mm, or 20 mm as measured on the major axis, (ii) a width of approximately 11 mm, 11.01 mm, 11.02 mm, 11.03 mm, 11.04 mm, 11.05 mm, 11.06 mm, 11.07 mm, 11.08 mm, 11.09 mm, 11.1 mm, 11.11 mm, 11.12 mm, 11.13 mm, 11.14 mm, 11.15 mm, 11.16 mm, 11.17 mm, 11.18 mm, 11.19 mm, 11.2 mm, 11.21 mm, 11.22 mm, 11.23 mm, 11.24 mm, 11.25 mm, 11.26 mm, 11.27 mm, 11.28 mm, 11.29 mm, 11.3 mm, 11.31 mm, 11.32 mm, 11.33 mm, 11.34 mm, 11.35 mm, 11.36 mm, 11.37 mm, 11.38 mm, 11.39 mm, 11.4 mm, 11.41 mm, 11.42 mm, 11.43 mm, 11.44 mm, 11.45 mm, 11.46 mm, 11.47 mm, 11.48 mm, 11.49 mm, 11.5 mm, 11.51 mm, 11.52 mm, 11.53 mm, 11.54 mm, 11.55 mm, 11.56 mm, 11.57 mm, 11.58 mm, 11.59 mm, 11.6 mm, 11.61 mm, 11.62 mm, 11.63 mm, 11.64 mm, 11.65 mm, 11.66 mm, 11.67 mm, 11.68 mm, 11.69 mm, 11.7 mm, 11.71 mm, 11.72 mm, 11.73 mm, 11.74 mm, 11.75 mm, 11.76 mm, 11.77 mm, 11.78 mm, 11.79 mm, 11.8 mm, 11.81 mm, 11.82 mm, 11.83 mm, 11.84 mm, 11.85 mm, 11.86 mm, 11.87 mm, 11.88 mm, 11.89 mm, 11.9 mm, 11.91 mm, 11.92 mm, 11.93 mm, 11.94 mm, 11.95 mm, 11.96 mm, 11.97 mm, 11.98 mm, 11.99 mm, 12 mm, 12.01 mm, 12.02 mm, 12.03 mm, 12.04 mm, 12.05 mm, 12.06 mm, 12.07 mm, 12.08 mm, 12.09 mm, 12.1 mm, 12.11 mm, 12.12 mm, 12.13 mm, 12.14 mm, 12.15 mm, 12.16 mm, 12.17 mm, 12.18 mm, 12.19 mm, 12.2 mm, 12.21 mm,

12.22 mm, 12.23 mm, 12.24 mm, 12.25 mm, 12.26 mm, 12.27 mm, 12.28 mm, 12.29 mm, 12.3 mm, 12.31 mm, 12.32 mm, 12.33 mm, 12.34 mm, 12.35 mm, 12.36 mm, 12.37 mm, 12.38 mm, 12.39 mm, 12.4 mm, 12.41 mm, 12.42 mm, 12.43 mm, 12.44 mm, 12.45 mm, 12.46 mm, 12.47 mm, 12.48 mm, 12.49 mm, 12.5 mm, 12.51 mm, 12.52 mm, 12.53 mm, 12.54 mm, 12.55 mm, 12.56 mm, 12.57 mm, 12.58 mm, 12.59 mm, 12.6 mm, 12.61 mm, 12.62 mm, 12.63 mm, 12.64 mm, 12.65 mm, 12.66 mm, 12.67 mm, 12.68 mm, 12.69 mm, 12.7 mm, 12.71 mm, 12.72 mm, 12.73 mm, 12.74 mm, 12.75 mm, 12.76 mm, 12.77 mm, 12.78 mm, 12.79 mm, 12.8 mm, 12.81 mm, 12.82 mm, 12.83 mm, 12.84 mm, 12.85 mm, 12.86 mm, 12.87 mm, 12.88 mm, 12.89 mm, 12.9 mm, 12.91 mm, 12.92 mm, 12.93 mm, 12.94 mm, 12.95 mm, 12.96 mm, 12.97 mm, 12.98 mm, 12.99 mm, or 13 mm, and (iii) a height or thickness of approximately 5 mm, 5.01 mm, 5.02 mm, 5.03 mm, 5.04 mm, 5.05 mm, 5.06 mm, 5.07 mm, 5.08 mm, 5.09 mm, 5.1 mm, 5.11 mm, 5.12 mm, 5.13 mm, 5.14 mm, 5.15 mm, 5.16 mm, 5.17 mm, 5.18 mm, 5.19 mm, 5.2 mm, 5.21 mm, 5.22 mm, 5.23 mm, 5.24 mm, 5.25 mm, 5.26 mm, 5.27 mm, 5.28 mm, 5.29 mm, 5.3 mm, 5.31 mm, 5.32 mm, 5.33 mm, 5.34 mm, 5.35 mm, 5.36 mm, 5.37 mm, 5.38 mm, 5.39 mm, 5.4 mm, 5.41 mm, 5.42 mm, 5.43 mm, 5.44 mm, 5.45 mm, 5.46 mm, 5.47 mm, 5.48 mm, 5.49 mm, 5.5 mm, 5.51 mm, 5.52 mm, 5.53 mm, 5.54 mm, 5.55 mm, 5.56 mm, 5.57 mm, 5.58 mm, 5.59 mm, 5.6 mm, 5.61 mm, 5.62 mm, 5.63 mm, 5.64 mm, 5.65 mm, 5.66 mm, 5.67 mm, 5.68 mm, 5.69 mm, 5.7 mm, 5.71 mm, 5.72 mm, 5.73 mm, 5.74 mm, 5.75 mm, 5.76 mm, 5.77 mm, 5.78 mm, 5.79 mm, 5.8 mm, 5.81 mm, 5.82 mm, 5.83 mm, 5.84 mm, 5.85 mm, 5.86 mm, 5.87 mm, 5.88 mm, 5.89 mm, 5.9 mm, 5.91 mm, 5.92 mm, 5.93 mm, 5.94 mm, 5.95 mm, 5.96 mm, 5.97 mm, 5.98 mm, 5.99 mm, or 6 mm. In yet another embodiment, the pharmaceutical composition may have (i) a length of approximately 19.1 mm, 19.11 mm, 19.12 mm, 19.13 mm, 19.14 mm, 19.15 mm, 19.16 mm, 19.17 mm, 19.18 mm, 19.19 mm, 19.2 mm, 19.21 mm, 19.22 mm, 19.23 mm, 19.24 mm, 19.25 mm, 19.26 mm, 19.27 mm, 19.28 mm, 19.29 mm, or 19.3 mm as measured on the major axis, (ii) a width of approximately 12.4 mm, 12.41 mm, 12.42 mm, 12.43 mm, 12.44 mm, 12.45 mm, 12.46 mm, 12.47 mm, 12.48 mm, 12.49 mm, or 12.5 mm, and (iii) a height or thickness of approximately 5.6 mm, 5.61 mm, 5.62 mm, 5.63 mm, 5.64 mm, 5.65 mm, 5.66 mm, 5.67 mm, 5.68 mm, 5.69 mm, 5.7 mm, 5.71 mm, 5.72 mm, 5.73 mm, 5.74 mm, 5.75 mm, 5.76 mm, 5.77 mm, 5.78 mm, 5.79 mm, or 5.8 mm.

[000249] In additional embodiments, the pharmaceutical composition may expand upon immersion in fluid to have (i) a length of about 18.5 mm, 18.6 mm, 18.7 mm, 18.8 mm, 18.9 mm, 19 mm, 19.1 mm, 19.2 mm, 19.3 mm, 19.4 mm, 19.5 mm, 19.6 mm, 19.7 mm, 19.8 mm, 19.9 mm, 20 mm, 20.1 mm, 20.2 mm, 20.3 mm, 20.4 mm, 20.5 mm, 20.6 mm, 20.7 mm, 20.8 mm, 20.9 mm, or 21 mm; and (ii) a width of about 11 mm, 11.1 mm, 11.2 mm, 11.3 mm, 11.4 mm, 11.5 mm, 11.6 mm, 11.7 mm, 11.8 mm, 11.9 mm, 12 mm, 12.1 mm, 12.2 mm, 12.3 mm, 12.4 mm, 12.5 mm, 12.6 mm, 12.7 mm, 12.8 mm, 12.9 mm, 13 mm, 13.1 mm, 13.2 mm, 13.3 mm, 13.4 mm, 13.5 mm, 13.6 mm, 13.7 mm, 13.8 mm, 13.9 mm, or 14 mm within about 5 minutes of immersion in fluid. In other embodiments, the pharmaceutical composition may expand upon immersion in fluid to (i) a length of about 18.5 mm, 18.6 mm, 18.7 mm, 18.8 mm, 18.9 mm, 19 mm, 19.1 mm, 19.2 mm, 19.3 mm, 19.4 mm, 19.5 mm, 19.6 mm, 19.7 mm, 19.8 mm, 19.9 mm, 20 mm, 20.1 mm, 20.2 mm, 20.3 mm, 20.4 mm, 20.5 mm, 20.6 mm, 20.7 mm, 20.8 mm, 20.9 mm, 21 mm, 21.1 mm, 21.2 mm, 21.3 mm, 21.4 mm, 21.5 mm, 21.6 mm, 21.7 mm, 21.8 mm, 21.9 mm, or 22 mm; and (ii) a width of about 11 mm, 11.1 mm, 11.2 mm, 11.3 mm, 11.4 mm, 11.5 mm, 11.6 mm, 11.7 mm, 11.8 mm, 11.9 mm, 12 mm, 12.1 mm, 12.2 mm, 12.3 mm, 12.4 mm, 12.5 mm, 12.6 mm, 12.7 mm, 12.8 mm, 12.9 mm, 13 mm, 13.1 mm, 13.2 mm, 13.3 mm, 13.4 mm, 13.5 mm, 13.6 mm, 13.7 mm, 13.8 mm, 13.9 mm, 14 mm, 14.1 mm, 14.2 mm, 14.3 mm, 14.4 mm, 14.5 mm, 14.6 mm, 14.7 mm, 14.8 mm, 14.9 mm, or 15 mm within about 10 minutes to about 15 minutes of immersion in fluid. In still other embodiments, the pharmaceutical composition may expand upon immersion in fluid to (i) a length of about 19 mm, 19.1 mm, 19.2 mm, 19.3 mm, 19.4 mm, 19.5 mm, 19.6 mm, 19.7 mm, 19.8 mm, 19.9 mm, 20 mm, 20.1 mm, 20.2 mm, 20.3 mm, 20.4 mm, 20.5 mm, 20.6 mm, 20.7 mm, 20.8 mm, 20.9 mm, 21 mm, 21.1 mm, 21.2 mm, 21.3 mm, 21.4 mm, 21.5 mm, 21.6 mm, 21.7 mm, 21.8 mm, 21.9 mm, 22 mm, 22.1 mm, 22.2 mm, 22.3 mm, 22.4 mm, or 22.5 mm; and (ii) a width of about 12 mm, 12.1 mm, 12.2 mm, 12.3 mm, 12.4 mm, 12.5 mm, 12.6 mm, 12.7 mm, 12.8 mm, 12.9 mm, 13 mm, 13.1 mm, 13.2 mm, 13.3 mm, 13.4 mm, 13.5 mm, 13.6 mm, 13.7 mm, 13.8 mm, 13.9 mm, 14 mm, 14.1 mm, 14.2 mm, 14.3 mm, 14.4 mm, 14.5 mm, 14.6 mm, 14.7 mm, 14.8 mm, 14.9 mm, or 15 mm within about 20 minutes to about 25 minutes of immersion in fluid. In additional embodiments, the pharmaceutical composition may expand upon immersion in fluid to (i) a length of

about 19 mm, 19.1 mm, 19.2 mm, 19.3 mm, 19.4 mm, 19.5 mm, 19.6 mm, 19.7 mm, 19.8 mm, 19.9 mm, 20 mm, 20.1 mm, 20.2 mm, 20.3 mm, 20.4 mm, 20.5 mm, 20.6 mm, 20.7 mm, 20.8 mm, 20.9 mm, 21 mm, 21.1 mm, 21.2 mm, 21.3 mm, 21.4 mm, 21.5 mm, 21.6 mm, 21.7 mm, 21.8 mm, 21.9 mm, 22 mm, 22.1 mm, 22.2 mm, 22.3 mm, 22.4 mm, 22.5 mm, 22.6 mm, 22.7 mm, 22.8 mm, 22.9 mm, or 23 mm; and (ii) a width of about 12.5 mm, 12.6 mm, 12.7 mm, 12.8 mm, 12.9 mm, 13 mm, 13.1 mm, 13.2 mm, 13.3 mm, 13.4 mm, 13.5 mm, 13.6 mm, 13.7 mm, 13.8 mm, 13.9 mm, 14 mm, 14.1 mm, 14.2 mm, 14.3 mm, 14.4 mm, 14.5 mm, 14.6 mm, 14.7 mm, 14.8 mm, 14.9 mm, or 15 mm within about 30 minutes to about 35 minutes of immersion in fluid. In still other embodiments, the pharmaceutical composition may expand upon immersion in fluid to (i) a length of about 18 mm, 18.1 mm, 18.2 mm, 18.3 mm, 18.4 mm, 18.5 mm, 18.6 mm, 18.7 mm, 18.8 mm, 18.9 mm, 19 mm, 19.1 mm, 19.2 mm, 19.3 mm, 19.4 mm, 19.5 mm, 19.6 mm, 19.7 mm, 19.8 mm, 19.9 mm, 20 mm, 20.1 mm, 20.2 mm, 20.3 mm, 20.4 mm, 20.5 mm, 20.6 mm, 20.7 mm, 20.8 mm, 20.9 mm, 21 mm, 21.1 mm, 21.2 mm, 21.3 mm, 21.4 mm, 21.5 mm, 21.6 mm, 21.7 mm, 21.8 mm, 21.9 mm, 22 mm, 22.1 mm, 22.2 mm, 22.3 mm, 22.4 mm, 22.5 mm, 22.6 mm, 22.7 mm, 22.8 mm, 22.9 mm, 23 mm, 23.1 mm, 23.2 mm, 23.3 mm, 23.4 mm, or 23.5; (ii) a width of about 11.5 mm, 11.6 mm, 11.7 mm, 11.8 mm, 11.9 mm, 12 mm, 12.1 mm, 12.2 mm, 12.3 mm, 12.4 mm, 12.5 mm, 12.6 mm, 12.7 mm, 12.8 mm, 12.9 mm, 13 mm, 13.1 mm, 13.2 mm, 13.3 mm, 13.4 mm, 13.5 mm, 13.6 mm, 13.7 mm, 13.8 mm, 13.9 mm, 14 mm, 14.1 mm, 14.2 mm, 14.3 mm, 14.4 mm, 14.5 mm, 14.6 mm, 14.7 mm, 14.8 mm, 14.9 mm, 15 mm, 15.1 mm, 15.2 mm, 15.3 mm, 15.4 mm, 15.5 mm, 15.6 mm, 15.7 mm, 15.8 mm, 15.9 mm, or 16 mm; and (iii) a height or thickness of about 5.5 mm, 5.6 mm, 5.7 mm, 5.8 mm, 5.9 mm, 6 mm, 6.1 mm, 6.2 mm, 6.3 mm, 6.4 mm, 6.5 mm, 6.6 mm, 6.7 mm, 6.8 mm, 6.9 mm, or 7 mm within about 50 minutes to about 55 minutes of immersion in fluid. In yet another embodiment, the pharmaceutical composition may expand upon immersion in fluid to (i) a length of about 19.5 mm, 19.6 mm, 19.7 mm, 19.8 mm, 19.9 mm, 20 mm, 20.1 mm, 20.2 mm, 20.3 mm, 20.4 mm, 20.5 mm, 20.6 mm, 20.7 mm, 20.8 mm, 20.9 mm, 21 mm, 21.1 mm, 21.2 mm, 21.3 mm, 21.4 mm, 21.5 mm, 21.6 mm, 21.7 mm, 21.8 mm, 21.9 mm, 22 mm, 22.1 mm, 22.2 mm, 22.3 mm, 22.4 mm, 22.5 mm, 22.6 mm, 22.7 mm, 22.8 mm, 22.9 mm, 23 mm, 23.1 mm, 23.2 mm, 23.3 mm, 23.4 mm, or 23.5; (ii) a width of about 13 mm, 13.1 mm, 13.2 mm, 13.3

mm, 13.4 mm, 13.5 mm, 13.6 mm, 13.7 mm, 13.8 mm, 13.9 mm, 14 mm, 14.1 mm, 14.2 mm, 14.3 mm, 14.4 mm, 14.5 mm, 14.6 mm, 14.7 mm, 14.8 mm, 14.9 mm, 15 mm, 15.1 mm, 15.2 mm, 15.3 mm, 15.4 mm, 15.5 mm, 15.6 mm, 15.7 mm, 15.8 mm, 15.9 mm, or 16 mm; and (iii) a height or thickness of about 5.5 mm, 5.6 mm, 5.7 mm, 5.8 mm, 5.9 mm, 6 mm, 6.1 mm, 6.2 mm, 6.3 mm, 6.4 mm, 6.5 mm, 6.6 mm, 6.7 mm, 6.8 mm, 6.9 mm, or 7 mm within about 60 minutes of immersion in fluid.

[000250] In yet another embodiment, the length of the pharmaceutical composition increases by about 4%, 4.25%, 4.5%, 4.75%, 5%, 5.25%, 5.5%, 5.75%, 6%, 6.25%, 6.5%, 6.75%, 7%, 7.25%, 7.5%, 7.75%, 8%, 8.25%, 8.5%, 8.75%, 9%, 9.25%, 9.5%, 9.75%, 10%, 10.25%, 10.5%, 10.75%, 11%, 11.25%, 11.5%, 11.75%, 12%, 12.25%, 12.5%, 12.75%, or 13% within about 10 minutes of immersion in fluid. In still another embodiment, the length of the pharmaceutical composition increases by about 5%, 5.25%, 5.5%, 5.75%, 6%, 6.25%, 6.5%, 6.75%, 7%, 7.25%, 7.5%, 7.75%, 8%, 8.25%, 8.5%, 8.75%, 9%, 9.25%, 9.5%, 9.75%, 10%, 10.25%, 10.5%, 10.75%, 11%, 11.25%, 11.5%, 11.75%, 12%, 12.25%, 12.5%, 12.75%, 13%, 13.25%, 13.5%, 13.75%, 14%, 14.25%, 14.5%, 14.75%, or 15% within about 15 minutes of immersion in fluid. In yet another embodiment, the length of the pharmaceutical composition increases by about 5%, 5.25%, 5.5%, 5.75%, 6%, 6.25%, 6.5%, 6.75%, 7%, 7.25%, 7.5%, 7.75%, 8%, 8.25%, 8.5%, 8.75%, 9%, 9.25%, 9.5%, 9.75%, 10%, 10.25%, 10.5%, 10.75%, 11%, 11.25%, 11.5%, 11.75%, 12%, 12.25%, 12.5%, 12.75%, 13%, 13.25%, 13.5%, 13.75%, 14%, 14.25%, 14.5%, 14.75%, or 15% within about 20 minutes of immersion in fluid. In a further embodiment, the length of the pharmaceutical composition increases by about 7%, 7.25%, 7.5%, 7.75%, 8%, 8.25%, 8.5%, 8.75%, 9%, 9.25%, 9.5%, 9.75%, 10%, 10.25%, 10.5%, 10.75%, 11%, 11.25%, 11.5%, 11.75%, 12%, 12.25%, 12.5%, 12.75%, 13%, 13.25%, 13.5%, 13.75%, 14%, 14.25%, 14.5%, 14.75%, 15%, 15.25%, 15.5%, 15.75%, 16%, 16.25%, 16.5%, 16.75%, 17%, 17.25%, 17.5%, 17.75%, or 18% within about 30 minutes of immersion in fluid. In another embodiment, the length of the pharmaceutical composition increases by about 8%, 8.25%, 8.5%, 8.75%, 9%, 9.25%, 9.5%, 9.75%, 10%, 10.25%, 10.5%, 10.75%, 11%, 11.25%, 11.5%, 11.75%, 12%, 12.25%, 12.5%, 12.75%, 13%, 13.25%, 13.5%, 13.75%, 14%, 14.25%, 14.5%, 14.75%, 15%, 15.25%, 15.5%, 15.75%, 16%, 16.25%, 16.5%, 16.75%, 17%, 17.25%, 17.5%,

17.75%, 18%, 18.25%, 18.5%, 18.75%, or 19% within about 45 minutes of immersion in fluid. In yet another embodiment, the length of the pharmaceutical composition increases by about 8%, 8.25%, 8.5%, 8.75%, 9%, 9.25%, 9.5%, 9.75%, 10%, 10.25%, 10.5%, 10.75%, 11%, 11.25%, 11.5%, 11.75%, 12%, 12.25%, 12.5%, 12.75%, 13%, 13.25%, 13.5%, 13.75%, 14%, 14.25%, 14.5%, 14.75%, 15%, 15.25%, 15.5%, 15.75%, 16%, 16.25%, 16.5%, 16.75%, 17%, 17.25%, 17.5%, 17.75%, 18%, 18.25%, 18.5%, 18.75%, or 19% within about 55 minutes of immersion in fluid. In still another embodiment, the length of the pharmaceutical composition increases by about 8%, 8.25%, 8.5%, 8.75%, 9%, 9.25%, 9.5%, 9.75%, 10%, 10.25%, 10.5%, 10.75%, 11%, 11.25%, 11.5%, 11.75%, 12%, 12.25%, 12.5%, 12.75%, 13%, 13.25%, 13.5%, 13.75%, 14%, 14.25%, 14.5%, 14.75%, 15%, 15.25%, 15.5%, 15.75%, 16%, 16.25%, 16.5%, 16.75%, 17%, 17.25%, 17.5%, 17.75%, 18%, 18.25%, 18.5%, 18.75%, 19%, 19.25%, 19.5%, 19.75%, or 20% within about 60 minutes of immersion in fluid.

[000251] In a further embodiment, the width of the pharmaceutical composition increases by about 6%, 6.25%, 6.5%, 6.75%, 7%, 7.25%, 7.5%, 7.75%, 8%, 8.25%, 8.5%, 8.75%, 9%, 9.25%, 9.5%, 9.75%, 10%, 10.25%, 10.5%, 10.75%, 11%, 11.25%, 11.5%, 11.75%, 12%, 12.25%, 12.5%, 12.75%, 13%, 13.25%, 13.5%, 13.75%, 14%, 14.25%, 14.5%, 14.75%, or 15% within about 10 minutes of immersion in fluid. In still another embodiment, the width of the pharmaceutical composition increases by about 6%, 6.25%, 6.5%, 6.75%, 7%, 7.25%, 7.5%, 7.75%, 8%, 8.25%, 8.5%, 8.75%, 9%, 9.25%, 9.5%, 9.75%, 10%, 10.25%, 10.5%, 10.75%, 11%, 11.25%, 11.5%, 11.75%, 12%, 12.25%, 12.5%, 12.75%, 13%, 13.25%, 13.5%, 13.75%, 14%, 14.25%, 14.5%, 14.75%, 15%, 15.25%, 15.5%, 15.75%, 16%, 16.25%, 16.5%, 16.75%, 17%, 17.25%, 17.5%, 17.75%, or 18%, within about 15 minutes of immersion in fluid. In yet another embodiment, the width of the pharmaceutical composition increases by about 6%, 6.25%, 6.5%, 6.75%, 7%, 7.25%, 7.5%, 7.75%, 8%, 8.25%, 8.5%, 8.75%, 9%, 9.25%, 9.5%, 9.75%, 10%, 10.25%, 10.5%, 10.75%, 11%, 11.25%, 11.5%, 11.75%, 12%, 12.25%, 12.5%, 12.75%, 13%, 13.25%, 13.5%, 13.75%, 14%, 14.25%, 14.5%, 14.75%, 15%, 15.25%, 15.5%, 15.75%, 16%, 16.25%, 16.5%, 16.75%, 17%, 17.25%, 17.5%, 17.75%, or 18%, within about 20 minutes of immersion in fluid. In a further embodiment, the width of the pharmaceutical composition increases by about 10%, 10.25%, 10.5%, 10.75%,

11%, 11.25%, 11.5%, 11.75%, 12%, 12.25%, 12.5%, 12.75%, 13%, 13.25%, 13.5%, 13.75%, 14%, 14.25%, 14.5%, 14.75%, 15%, 15.25%, 15.5%, 15.75%, 16%, 16.25%, 16.5%, 16.75%, 17%, 17.25%, 17.5%, 17.75%, 18%, 18.25%, 18.5%, 18.75%, 19%, 19.25%, 19.5%, 19.75%, 20%, 20.25%, 20.5%, 20.75%, 21%, 21.25%, 21.5%, 21.75%, 22%, 22.25%, 22.5%, 22.75%, 23%, 23.25%, 23.5%, 23.75%, or 24% within about 30 minutes of immersion in fluid. In another embodiment, the width of the pharmaceutical composition increases by about 12%, 12.25%, 12.5%, 12.75%, 13%, 13.25%, 13.5%, 13.75%, 14%, 14.25%, 14.5%, 14.75%, 15%, 15.25%, 15.5%, 15.75%, 16%, 16.25%, 16.5%, 16.75%, 17%, 17.25%, 17.5%, 17.75%, 18%, 18.25%, 18.5%, 18.75%, 19%, 19.25%, 19.5%, 19.75%, 20%, 20.25%, 20.5%, 20.75%, 21%, 21.25%, 21.5%, 21.75%, 22%, 22.25%, 22.5%, 22.75%, 23%, 23.25%, 23.5%, 23.75%, 24%, 24.25%, 24.5%, 24.75%, or 25% within about 45 minutes of immersion in fluid. In yet another embodiment, the width of the pharmaceutical composition increases by about 12%, 12.25%, 12.5%, 12.75%, 13%, 13.25%, 13.5%, 13.75%, 14%, 14.25%, 14.5%, 14.75%, 15%, 15.25%, 15.5%, 15.75%, 16%, 16.25%, 16.5%, 16.75%, 17%, 17.25%, 17.5%, 17.75%, 18%, 18.25%, 18.5%, 18.75%, 19%, 19.25%, 19.5%, 19.75%, 20.25%, 20.5%, 20.75%, 21%, 21.25%, 21.5%, 21.75%, 22%, 22.25%, 22.5%, 22.75%, 23%, 23.25%, 23.5%, 23.75%, 24%, 24.25%, 24.5%, 24.75%, or 25% within about 55 minutes of immersion in fluid. In still another embodiment, the width of the pharmaceutical composition increases by about 14%, 14.25%, 14.5%, 14.75%, 15%, 15.25%, 15.5%, 15.75%, 16%, 16.25%, 16.5%, 16.75%, 17%, 17.25%, 17.5%, 17.75%, 18%, 18.25%, 18.5%, 18.75%, 19%, 19.25%, 19.5%, 19.75%, 20%, 20.25%, 20.5%, 20.75%, 21%, 21.25%, 21.5%, 21.75%, 22%, 22.25%, 22.5%, 22.75%, 23%, 23.25%, 23.5%, 23.75%, 24%, 24.25%, 24.5%, 24.75%, 25%, 25.25%, 25.5%, 25.75%, or 26% within about 60 minutes of immersion in fluid.

[000252] In some embodiments, the composition disclosed herein may have gastric retentive properties. These gastric retentive properties of the composition may be due to a combination of a physical property of the composition and/or the release of the opioid. In one embodiment, the gastric retentive properties of the opioid-containing extended release composition is provided by the use of a polymer. In one embodiment, the opioid-containing extended release composition comprises a gastric retentive

polymer in an amount of about 1% to about 99%. In another embodiment, the opioid-containing extended release composition comprises a gastric retentive polymer in an amount of about 10% to about 80%. In yet another embodiment, the opioid-containing extended release composition comprises a gastric retentive polymer in an amount of about 20% to about 60%. In other embodiments, the opioid-containing extended release composition comprises a gastric retentive polymer in an amount of about 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%.

[000253] In another embodiment, the composition may be expandable. That is, the composition has size that is small enough for oral intake, but the composition absorbs water from the gastric fluid and swells to a size that prevents its passage through the pylorus. Such a composition comprises at least one swellable, expandable material, such as a polymer, resin, hydrocolloid, hydrogel, or the like. In various embodiments, the composition may swell to a size that is about 110% to about 200% of the original volume within about 30 minutes of administration. For example, the composition may swell to approximately 115% of its original volume within 30 minutes of administration, and at a later time may swell to a volume that is 130% or more of the original volume. In other embodiments, the composition may exhibit a volume increase of two-fold or more. Additionally, the composition may become slippery upon absorption of water, which provides resistance to peristalsis and further promotes gastric retention. The swellable material degrades or erodes over a specified period of time (e.g., the dosing interval) such that the composition is no longer retained in the stomach. In one embodiment, the ER layer swells upon imbibition of fluid to a size which is about 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 100% larger than the size of the ER layer prior to imbibition of fluid. In another embodiment, the ER layer swells upon imbibition of fluid to a size at least about 25% larger than the size of the ER

layer prior to imbibition of fluid within about 15 minutes of the start of fluid imbibition. In still another embodiment, the ER layer swells upon imbibition of fluid to a size at least about 100% larger than the size of the ER layer prior to imbibition of fluid within about 45 min, 50 min, 60 min, 75 min, or 90 min of the start of fluid imbibitions.

[000254] In a further embodiment, the composition contains at least one swellable polymer. For example, the composition may include chitosan, methylcellulose, polyvinyl acetate, purified shellac, polyethylene oxide, polypropylene oxide, or an expansive polymeric film, such as one composed of polyvinyl acetate and shellac. In another embodiment, the composition may contain a combination of polymers in a matrix that is swellable. Exemplary swellable matrices are described in U.S. Patent Nos. 6,723,340, 6,340,475, and 6,635,280, the disclosures of which are herein incorporated by reference in their entirety.

[000255] In still another embodiment, the physical property of the composition that imparts gastric retention may be the shape of the composition. For example, the composition may have a ring, tetrahedron, spiral, coil, planar disc, planar multilobe, continuous stick, sheet, oval, parallelogram, or string geometric configuration, wherein the composition is unable to pass through the pyloric sphincter. In some iterations, the composition may be folded into a pharmaceutical carrier (e.g., a gelatin capsule) or secured by readily dissolvable (e.g., gelatin) strips such that, upon dissolution of the carrier or strips, the composition unfolds in the stomach. In general, unfoldable compositions comprise biodegradable polymers such that the composition is degraded and/or reduced in size over a specified period of time (e.g., the dosing interval). In another embodiment, the composition has a diameter of greater than or equal to 7.5 mm. Exemplary shaped dosage forms are described in U.S. Patent No. 6,488,962, the entirety of which is herein incorporated by reference.

[000256] In yet another embodiment, the physical property of the composition that imparts gastric retention may be the adhesivity of the composition. Bio-mucoadhesive compositions bind to the gastric epithelial cell surface, or mucin, and increase gastric retention time by increasing the intimacy and duration of contact between the composition and the biological membrane. Bio-mucoadhesive compositions generally comprise polycarbophil, carbopol, cholestyramine, chitosan, polymeric acids, or a natural or

synthetic polymer that is capable of adhering to a biological membrane (e.g., a bioadhesive polymer) or the mucus lining of the stomach or intestinal tract (e.g., a mucoadhesive polymer). Exemplary adhesive polymers include anionic (e.g., carboxymethylcellulose, chondroitin sulfate, polyacrylic acid, pectin, carageenan, chitosan, and alginic acid), cationic (e.g., polylysine and polybrene), and neutral (e.g., polyethylene glycol, polyvinyl pyrrolidone, and dextran) polymers. Certain hydrophilic polymers tend to imbibe large amounts of water and become sticky, thereby acquiring bioadhesive properties. The adhesion of polymers to a mucus or epithelial cell surface may involve various bonding mechanisms, including physical-mechanical bonding and chemical bonding. Physical-mechanical bonding may result from the insertion of the adhesive material into the crevices or folds of the mucosa. Chemical bonds may be either covalent or non-covalent (e.g., ionic bonds, hydrogen bonds, van der Waals interactions, etc). Moreover, certain polymers may bind to specific receptor sites on the surface of cells, thereby enhancing the gastric retention. For example, certain plant lectins interact specifically with the sugar groups present in mucus or on the glycocalyx.

[000257] In still another embodiment, the physical property of the composition that imparts gastric retention may be the density of the composition. In one iteration, the composition may have a low density with sufficient buoyancy such that the composition floats over the gastric contents and remains in the stomach for a prolonged period. Floating compositions may be effervescent or noneffervescent. Effervescent compositions generally comprise matrices prepared with swellable polymers and an effervescent component. For example, the effervescent component can be either a carbonate or bicarbonate salt (e.g., sodium bicarbonate, calcium bicarbonate), an organic acid (e.g., citric acid, tartaric acid), or any combination thereof. The effervescent component can also be a floating chamber filled with vacuum, air, an inert gas, or a liquid that gasifies at body temperature. Floatability is generally achieved by generation of gas bubbles. Gas may be introduced into the floating chamber by the volatilization of an organic solvent, or by an effervescent reaction between a carbonate-bicarbonate salt and an organic acid. The matrices may be fabricated so that upon arrival in the stomach, carbon dioxide is liberated by the acidity of the gastric contents and is entrapped in the gellified matrix. This maintains the buoyancy of the composition, causing it to float. In

another embodiment, the composition may also contain a polymer which exhibits floating characteristics, such as hydroxypropyl cellulose, hydroxypropyl methylcellulose, crospovidone, sodium carboxymethyl cellulose, or ethyl cellulose. In a further embodiment, the composition may comprise a device having a hollow deformable unit that converts from a collapsed to expanded form and vice versa. The unit is supported by a housing that is internally divided into two chambers separated by a pressure-sensitive movable bladder. The first chamber contains the therapeutic agent and the second contains a volatile liquid (e.g., cyclopentane, ether) that vaporizes at body temperature and imparts buoyancy to the system. The system also contains a bioerodible plug to aid in the exit from the body. Further embodiments of this two chamber system are disclosed in U.S. Patent Nos. 3,901,232 and 3,786,813, which are hereby incorporated by reference. In still a further embodiment, the composition may contain hollow microspheres or microballoons, which cause the composition to float. The composition may also comprise floating microparticles such as polypropylene foam, Eudragit, ethyl cellulose, or polymethyl methacrylate (PMMA).

[000258] Noneffervescent compositions incorporate a high level of one or more gel-forming, highly swellable, cellulosic hydrocolloids. Upon contact with the gastric contents, these hydrocolloids hydrate and forms a colloidal gel barrier, wherein air trapped by the swollen hydrocolloid confers buoyancy to this composition. In another iteration, the composition may have a density that exceeds the density of normal gastric contents such the composition sinks to the bottom of the stomach (i.e., the antrum) where it is entrapped in the folds of the antrum and withstands the peristaltic waves of the gastric wall. In yet another iteration, the composition has a density that is greater than or equal to 1.3 g/mL.

[000259] In one embodiment, the composition is retained in the stomach due to the presence of an extended release polymer that absorbs water from the gastric contents and swells or expands to a size that cannot pass through the pyloric sphincter. As a consequence, the opioid and the other API are slowly released from the composition in the stomach and absorbed in the upper gastrointestinal tract.

[000260] In still another embodiment, the physical property of the composition that results in gastric retention may be the physical size of the composition. That is, the

composition may have a size that is small enough to be orally ingested and enter the stomach, but large enough to prevent passage through the pyloric sphincter into the small intestine. In some embodiments in which the composition is designed for humans, the composition may have a length (or diameter) of more than about 7 mm, 8 mm, 9 mm, or 10 mm. In other embodiments in which the composition is designed for humans, the composition may have a length (or diameter) of more than about 11 mm, 12 mm, or 13 mm, 14 mm, 15 mm, 16 mm, 17 mm, 18 mm, 19 mm, 20 mm or longer. In still other embodiments, the composition may have (i) a length of approximately 19 mm, 19.1 mm, 19.2 mm, 19.3 mm, 19.4 mm, 19.5 mm, 19.6 mm, 19.7 mm, 19.8 mm, 19.9 mm, or 20 mm as measured on the major axis, (ii) a width of approximately 12 mm, 12.1 mm, 12.2 mm, 12.3 mm, 12.4 mm, 12.5 mm, 12.6 mm, 12.7 mm, 12.8 mm, 12.9 mm, or 13 mm as measured on the minor axis, and (iii) a height or thickness of approximately 5 mm, 5.1 mm, 5.2 mm, 5.3 mm, 5.4 mm, 5.5 mm, 5.6 mm, 5.7 mm, 5.8 mm, 5.9 mm, or 6 mm. In yet another embodiment, the composition may have (i) a length of approximately 19.1 mm, 19.11 mm, 19.12 mm, 19.13 mm, 19.14 mm, 19.15 mm, 19.16 mm, 19.17 mm, 19.18 mm, 19.19 mm, 19.2 mm, 19.21 mm, 19.22 mm, 19.23 mm, 19.24 mm, 19.25 mm, 19.26 mm, 19.27 mm, 19.28 mm, 19.29 mm, or 19.3 mm as measured on the major axis, (ii) a width of approximately 12.4 mm, 12.41 mm, 12.42 mm, 12.43 mm, 12.44 mm, 12.45 mm, 12.46 mm, 12.47 mm, 12.48 mm, 12.49 mm, or 12.5 mm as measured on the minor axis, and (iii) a height or thickness of approximately 5.6 mm, 5.61 mm, 5.62 mm, 5.63 mm, 5.64 mm, 5.65 mm, 5.66 mm, 5.67 mm, 5.68 mm, 5.69 mm, 5.7 mm, 5.71 mm, 5.72 mm, 5.73 mm, 5.74 mm, 5.75 mm, 5.76 mm, 5.77 mm, 5.78 mm, 5.79 mm, or 5.8 mm. In general, such compositions are designed to degrade, disintegrate, decrease in size, or collapse in a specified time interval (e.g., dosing interval) such that they may pass through the pyloric valve or be evacuated from the stomach by a housekeeper wave of gastric contractions.

[000261] In still another embodiment, the composition may contain an agent which delays the passage of the composition through the pyloric sphincter. For example, the composition may include triethanol amine myristate or propantheline.

(ii) opioid release

[000262] Because opioids, such as oxycodone, reduce gastric motility, the erosion time of the dosage form can be increased (thus, hindering drug release) if the

opioid is not properly dosed. The gastric retentive extended release composition disclosed herein is engineered to release the opioid(s) at a rate that is sufficient to delay gastric emptying such that the composition is retained in the stomach for a longer period of time than a comparable composition that is not gastric retentive. For example, the composition may be designed to release the opioid(s) at a rate that delays gastric emptying by about 15 minutes, 30 minutes, 60 minutes, 90 minutes, 2.0 hours, 2.5 hours, 3.0 hours, 3.5 hours, 4.0 hours, 4.5 hours, or 5.0 hours. The rate of release of the opioid(s) may be manipulated by selecting a suitable extended release component for inclusion in an extended release portion of the composition. For example, in embodiments in which the extended release component is an extended release polymer, the extended release polymer generally is selected such that the composition releases the opioid(s) at a rate that delays gastric emptying by the desired amount. Additionally, the rate of release of the opioid(s) from the composition may be adjusted by selecting the proper ratio of opioid present in the at least one immediate release and the at least one extended release portions of the composition. For instance, the proportion of the opioid(s) in the at least one immediate release portion and the at least one extended release portion may be about 20:80, 21:79, 22:78, 23:77; 24:76, 25:75, 26:74, 27:73, 28:72, 29:71, 30:70, 31:69, 32:68, 33:67, 34:66, 35:65, 34:66, 35:65, 36:64, 37:63, 38:62, 39:61, or 40:60.

[000263] Additionally, the gastric retentive extended release composition is engineered to release the opioid(s) at a rate that is insufficient to cause any serious adverse gastrointestinal effects. Adverse gastrointestinal effects include, but are not limited to, intestinal hypomotility, intestinal blockage, intestinal pseudo-obstruction, abdominal distention, bloating, constipation, intestinal distress, severe intestinal contractions, colon spasms, hypoactive bowel, and increased anal sphincter tone.

(iii) overall composition

[000264] With the knowledge of the preferred dissolution and pharmacokinetic profiles for the opioid and the additional API, and the pharmacodynamics effects of the opioid and the additional API, as discovered by the applicants and first described herein, a composition exhibiting the same or similar dissolution and pharmacokinetic profiles and pharmacodynamics effects can be developed using any of the dosage forms discussed

above. Moreover, a composition under the present invention can be developed using another dosage form that achieves the same or similar dissolution, pharmacokinetic, and pharmacodynamic profiles as the compositions disclosed herein. For example, in one embodiment, a controlled-release dosage form can be developed that exhibits pharmacokinetic and pharmacodynamic parameters (e.g., C_{max}, AUC) which are within 80% to 125% at a confidence interval of 90% of those parameters for the compositions described herein. In another embodiment, a sustained release dosage form can be developed that exhibits pharmacokinetic and pharmacodynamic parameters which are within 80% to 125% at a confidence interval of 90% of those parameters for the compositions described herein. A composition could also be developed that lacks one of the specific gastric retentive dosage forms discussed above, yet, achieves the same dissolution and pharmacokinetic profiles, and exhibits the pharmacodynamic effects.

[000265] For example, a gastric retentive extended release composition as described herein may comprise an opioid, such as oxycodone, an additional API, such as acetaminophen, an immediate release portion, and a gastric retentive portion, wherein the immediate release and gastric retentive portions comprise a filler and a lubricant. In one embodiment, the immediate release and gastric retentive portions may each comprise a filler in an amount of about 5 mg to about 500 mg. In another embodiment, the immediate release and gastric retentive portions may each comprise a filler in an amount of about 20 mg to about 400 mg. In yet another embodiment, the immediate release and gastric retentive portions may each comprise a filler in an amount of about 40 mg to about 300 mg.

[000266] In one embodiment, the immediate release and gastric retentive portions may each comprise a lubricant in an amount of about 0.1 mg to about 25 mg. In another embodiment, the immediate release and gastric retentive portions may each comprise a lubricant in an amount of about 0.4 mg to about 15 mg. In still another embodiment, the immediate release and gastric retentive portions may each comprise a lubricant in an amount of about 0.7 mg to about 5 mg. In another aspect, the gastric retentive portion may further comprise between about 0 mg to about 50 mg of an effervescent agent, such as a bicarbonate salt.

[000267] As discussed above, an extended release composition without gastric retention is also described herein. In one embodiment, an extended release composition as described herein may comprise an opioid, such as oxycodone, an additional API, such as acetaminophen, an immediate release portion, and an extended release portion, wherein the immediate release and extended release portions comprise a filler in an amount of about 5 mg to about 500 mg and a lubricant in an amount of about 0.1 mg to about 25 mg. The extended release portion may comprise any suitable extended release polymer. In one embodiment, the extended release polymer is present in an amount of about 5 mg to about 500 mg. In another embodiment, the extended release polymer is present in an amount of about 20 mg to about 400 mg. In a further embodiment, the extended release polymer is present in an amount of about 40 mg to about 300 mg

[000268] For example, some exemplary formulations of the gastric retentive (Examples A-I) or sustained release (Examples J-R) dosage forms described above are as follows:

Chart A: Exemplary Gastric Retentive and Sustained Release Dosage Forms.

	A	B	C
Immediate Release Portion	Oxycodone HCl (0-15 mg) APAP (0-325 mg) Filler (5-100 mg) Lubricant (0.1-5 mg)	Oxycodone HCl (0-7.5 mg) APAP (0-175 mg) Filler (5-250 mg) Stearate salt (0.1-10 mg)	Oxycodone HCl (0-15 mg) APAP (200-325 mg) Filler (50-75 mg) Lubricant (2-3 mg)
Gastric Retentive Portion	Oxycodone HCl (0-15 mg) APAP (0-325 mg) Polymer (5-500 mg) Filler (5-100 mg) Lubricant (0.1-5 mg)	Oxycodone HCL (0-7.5 mg) APAP (0-175 mg) Polymer (50-750 mg) Filler (5-250 mg) Stearate Salt (0.1-10 mg)	Oxycodone HCl (0-15 mg) APAP (100-325 mg) Polymer (100-250 mg) Filler (25-50 mg) Lubricant (1-3 mg)
	D	E	F
Immediate Release Portion	Oxycodone HCl (5-10 mg) APAP (100-400 mg) Filler (25-50 mg) Lubricant (3-5 mg)	Oxycodone HCl (5-10 mg) APAP (100-400 mg) Filler (25-50 mg) Lubricant (3-5 mg)	Oxycodone HCl (2-5 mg) APAP (300-450 mg) Filler (25-75 mg) Lubricant (2-5 mg)
Gastric Retentive Portion	Oxycodone HCl (5-10 mg)	Oxycodone HCl (5-10 mg)	Oxycodone HCl (3-10 mg)

	APAP (50-250 mg) Filler (50-75 mg) Polycarbophil (5-500 mg) Lubricant (3-5 mg)	APAP (50-250 mg) Filler (50-75 mg) Polymer (5-500 mg) Bicarbonate salt (0-10 mg) Lubricant (3-5 mg)	APAP (50-300 mg) Filler (50-75 mg) Polymer (100-450 mg) Bicarbonate salt (0-10 mg) Lubricant (3-5 mg)
	G	H	I
Immediate Release Portion	Oxycodone HCl (1-10 mg) APAP (100-325 mg) Filler (25-75 mg) Lubricant (2-5 mg)	Oxycodone HCl (0-15 mg) APAP (0-325 mg) Filler (5-100 mg) Lubricant (0.1-5 mg)	Oxycodone HCl (0-15 mg) APAP (0-325 mg) Filler (5-100 mg) Lubricant (0.1-5 mg)
Gastric Retentive Portion	Oxycodone HCl (3-10 mg) APAP (100-450 mg) Filler (5-100 mg) Carbopol (5-500 mg) Lubricant (3-5 mg)	Oxycodone HCl (0-15 mg) APAP (0-325 mg) Polyacrylate (100-300 mg) Filler (5-100 mg)	Oxycodone HCl (0-15 mg) APAP (0-325 mg) Cholestyramine (100-300 mg) Filler (5-100 mg)
	J	K	L
Immediate Release Portion	Oxycodone HCl (0-15 mg) APAP (0-325 mg) Filler (5-100 mg) Lubricant (0.1-5 mg)	Oxycodone HCl (0-7.5 mg) APAP (0-175 mg) Filler (5-250 mg) Stearate salt (0.1-10 mg)	Oxycodone HCl (0-15 mg) APAP (200-325 mg) Filler (50-75 mg) Lubricant (2-3 mg)
Extended Release Portion	Oxycodone HCl (0-15 mg) APAP (0-325 mg) Polymer (5-500 mg) Filler (5-100 mg) Lubricant (0.1-5 mg)	Oxycodone HCl (0-7.5 mg) APAP (0-175 mg) Polymer (50-750 mg) Filler (5-250 mg) Stearate Salt (0.1-10 mg)	Oxycodone HCl (0-15 mg) APAP (100-325 mg) Polymer (100-250 mg) Filler (25-50 mg) Lubricant (1-3 mg)
	M	N	O
Immediate Release Portion	Oxycodone HCl (5-10 mg) APAP (100-400 mg) Filler (25-50 mg) Lubricant (3-5 mg)	Oxycodone HCl (5-10 mg) APAP (100-400 mg) Filler (25-50 mg) Lubricant (3-5 mg)	Oxycodone HCl (2-5 mg) APAP (300-450 mg) Filler (25-75 mg) Lubricant (2-5 mg)
Extended Release Portion	Oxycodone HCl (5-10 mg)	Oxycodone HCl (5-10 mg)	Oxycodone HCl (3-10 mg)

	APAP (50-250 mg) Filler (50-75 mg) Methacrylate copolymer (5-500 mg) Lubricant (0.1-10 mg)	APAP (50-250 mg) Filler (50-75 mg) Hydroxy propylmethyl cellulose (5-500 mg) Lubricant (0.1-10 mg)	APAP (50-300 mg) Filler (50-75 mg) Propylmethyl cellulose (100-450 mg) Lubricant (0.1-10 mg)
	P	Q	R
Immediate Release Portion	Oxycodone HCl (1-10 mg) APAP (100-325 mg) Filler (25-75 mg) Lubricant (2-5 mg)	Oxycodone HCl (0-15 mg) APAP (0-325 mg) Filler (5-100 mg) Lubricant (0.1-5 mg)	Oxycodone HCl (0-15 mg) APAP (0-325 mg) Filler (5-100 mg) Lubricant (0.1-5 mg)
Extended Release Portion	Oxycodone HCl (3-10 mg) APAP (100-450 mg) Filler (5-100 mg) Alginate (5-500 mg) Lubricant (3-5 mg)	Oxycodone HCl (0-15 mg) APAP (0-325 mg) Ethylcellulose (5-500 mg) Filler (5-100 mg)	Oxycodone HCl (0-15 mg) APAP (0-325 mg) Polyacrylate (5-500 mg) Filler (5-100 mg)
	S	T	U
Sustained Release Formulation	Oxycodone HCl (1-15 mg) APAP (50-650 mg) Filler (0-100 mg) Methacrylate copolymer (5-500 mg) Lubricant (0.1-10 mg)	Oxycodone HCl (1-15 mg) APAP (50-650 mg) Filler (0-100 mg) Hydroxy propylmethyl cellulose (5-500 mg) Lubricant (0.1-10 mg)	Oxycodone HCl (1-15 mg) APAP (50-650 mg) Filler (0-100 mg) Propylmethyl cellulose (5-550 mg) Lubricant (0.1-10 mg)
	V	W	X
Sustained Release Formulation	Oxycodone HCl (1-15 mg) APAP (50-650 mg) Filler (0-100 mg) Alginate (5-500 mg) Lubricant (0.1-10 mg)	Oxycodone HCl (1-15 mg) APAP (50-650 mg) Filler (0-100 mg) Polysorbate (5-500 mg) Lubricant (0.1-10 mg)	Oxycodone HCl (1-15 mg) APAP (50-650 mg) Filler (0-100 mg) Polyacrylate (5-550 mg) Lubricant (0.1-10 mg)

(e) **Abuse and tamper resistant properties of the composition**

[000269] Extended release pain medications have provided many benefits to patients in the management of their chronic pain by providing a sustained release over time of a larger quantity of drug than is typically contained in an immediate release formulation. Consequently, these dosage forms (especially if they contain opioids) are attractive targets for drug abusers looking to defeat the extended release formulation to allow immediate bolus administration or “dose-dumping” of the entire drug contents of the dosage form.

[000270] Dosage forms of the pharmaceutical composition disclosed herein may be more resistant to crushing, grinding, pulverizing, or other common means used to produce a powder than an immediate release product. Accordingly, some embodiment forms are tamper resistant and less prone to abuse or misuse. For example, certain embodiments may not be crushed into a powder and snorted. Additionally, some embodiments comprising an extended release polymer may not be crushed, mixed with an aqueous solution, and injected (i.e., the resultant mixture becomes extremely viscous and cannot be effectively drawn into a syringe.)

[000271] For example, dosage forms of the pharmaceutical composition disclosed herein form a pasty semi-solid mixture when dissolved. Thus, the pharmaceutical composition is difficult to draw into a syringe and inject intravenously. The yield of active pharmaceutical ingredient(s) obtained from the pharmaceutical composition is also low (less than 20%).

[000272] Further, dosage forms of the pharmaceutical composition disclosed herein cannot easily be snorted. In order for a drug abuser to successfully snort a drug obtained from a dosage form, he must prepare a crushed, finely divided powder form of the dosage form for insufflating the powder into the nasal cavity. However, the pharmaceutical compositions disclosed herein form a clumpy, solid mass upon insufflation and do not allow acceptable absorption through the nasal tissue.

[000273] Dosage forms of the pharmaceutical composition disclosed herein also do not allow “dose dumping” caused by the deliberate introduction of alcohol into a drug abuser’s stomach which accelerates the release of active ingredient(s) from the

time-release formulation. The pharmaceutical compositions disclosed herein are resistant to the accelerated release of active ingredient(s).

[000274] In addition, dosage forms of the pharmaceutical composition disclosed herein do not allow for “free basing.” Successful free basing by a drug abuser requires the generation of a salt free form of the active pharmaceutical ingredient(s). This requires physical and chemical manipulation to release the active pharmaceutical ingredient(s) from its salt(s) and selective extraction from other matrix excipients. The pharmaceutical composition disclosed herein cannot be easily manipulated to generate a free base preparation.

[000275] Moreover, the tamper resistance properties of the pharmaceutical compositions disclosed herein may be increased by increasing the average molecular weight of the extended release polymer used in the pharmaceutical composition. In another embodiment, the tamper resistance properties of the pharmaceutical compositions disclosed herein may be increased by increasing the amount of the extended release polymer used in the pharmaceutical composition.

[000276] In further embodiments, the solid oral dosage forms of the pharmaceutical compositions disclosed herein exhibit substantial differences in the release profiles of oxycodone and acetaminophen when the dosage forms are crushed or ground. Indeed, the intact solid oral dosage forms surprisingly exhibit a higher release rate of both active ingredients than one that is crushed or ground. This suggests that upon grinding or crushing the solid oral dosage forms disclosed herein, the immediate release portion and extended release portion of the dosage form combine, and the hydration and swelling of the polymer(s) in the extended release portion of the dosage form retards the release of the oxycodone and acetaminophen in the immediate release portion, and may also retard the release of the oxycodone and acetaminophen in the extended release portion. Hence the incorporation of the ground or crushed components from the immediate release portion into a mixture with the ground or crushed components of the extended release portion causes the pharmaceutical composition to lose its immediate release characteristics. This feature may effectively negate a drug abuser's purpose for crushing the solid oral dosage form in the first place—to obtain an early onset of analgesia. Indeed, when the dosage forms disclosed herein are crushed or ground,

the absorption of oxycodone and acetaminophen is delayed, thereby delaying the onset of euphoria as compared to when the dosage forms are ingested in an intact state. Thus, this is an unexpected tamper resistant property of the pharmaceutical compositions disclosed herein.

[000277] It was also surprisingly discovered that when an extended release dosage form disclosed herein (such as a bilayer tablet comprising an immediate release layer and an extended release layer), containing oxycodone and acetaminophen was administered to a subject, all the AUC measurements for oxycodone and acetaminophen were higher when the tablet was administered in an intact state versus when the tablet was administered in a crushed or ground state. For example, in one embodiment, the AUC measurements for either oxycodone and/or acetaminophen were about 5% to about 60% higher when a subject ingested the tablet in an intact state versus a crushed or ground state. In another embodiment, the AUC measurements for either oxycodone and/or acetaminophen were about 10% to about 50% higher when a subject ingested the tablet in an intact state versus a crushed or ground. In yet another embodiment, the AUC measurements for either oxycodone and/or acetaminophen were about 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29% or 30% higher when a subject ingested the tablet in an intact state versus in a crushed or ground state.

[000278] In a further embodiment, the $AUC_{(0-1hr)}$ for either oxycodone and/or acetaminophen was about 50%, 100%, 150%, 200%, 250%, 300%, 350%, 400%, 450%, 500%, 550%, 600%, 650%, 700%, 750%, 800%, 850%, 900%, 950%, or 1000% higher when a subject ingested the tablet in an intact state versus in a crushed or ground state. In another embodiment, the $AUC_{(0-1hr)}$ for either oxycodone and/or acetaminophen will be about 50% to about 1000% higher when a subject ingested the tablet in an intact state versus in a crushed or ground state. In a further embodiment, the $AUC_{(0-1hr)}$ for either oxycocodone and/or acetaminophen will be about 100% to about 900% higher when a subject ingested the tablet in an intact state versus in a crushed or ground state. In still a further embodiment, the $AUC_{(0-1hr)}$ for either oxycodone and/or acetaminophen will be about 200% to about 800% higher when a subject ingested the tablet in an intact state versus in a crushed or ground state. In yet another embodiment, the $AUC_{(0-1hr)}$ for either

oxycodone and/or acetaminophen was about 300% to about 700% higher when a subject ingested the tablet in an intact state versus in a crushed or ground state.

[000279] In another embodiment, the $AUC_{(0-2hr)}$ for either oxycodone and/or acetaminophen was about 50%, 100%, 150%, 200%, 250%, 300%, 350%, 400%, 450%, or 500% higher when a subject ingested the tablet in an intact state versus in a crushed or ground state. In another embodiment, the $AUC_{(0-2hr)}$ for either oxycodone and/or acetaminophen will be about 50% to about 500% higher when a subject ingested the tablet in an intact state versus in a crushed or ground state. In a further embodiment, the $AUC_{(0-2hr)}$ for either oxycodone and/or acetaminophen will be about 100% to about 400% higher when a subject ingested the tablet in an intact state versus in a crushed or ground state. In still a further embodiment, the $AUC_{(0-2hr)}$ for either oxycodone and/or acetaminophen will be about 150% to about 300% higher when a subject ingested the tablet in an intact state versus in a crushed or ground state. In an additional embodiment, the $AUC_{(0-2hr)}$ for either oxycodone and/or acetaminophen was about 50% to about 250% higher when a subject ingested the tablet in an intact state versus in a crushed or ground state.

[000280] In another embodiment, the $AUC_{(0-4hr)}$ for either oxycodone and/or acetaminophen will be about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% higher when a subject ingested the tablet in an intact state versus in a crushed or ground state. In a further embodiment, the $AUC_{(0-4hr)}$ for either oxycodone and/or acetaminophen will be about 25% to about 75% higher when a subject ingested the tablet in an intact state versus in a crushed or ground state. In still another embodiment, the $AUC_{(0-8hr)}$ for either oxycodone and/or acetaminophen will be about 10%, 20%, 30%, 40%, 50%, 60%, 70% or 80% higher when a subject ingested the tablet in an intact state versus in a crushed or ground state. In an additional embodiment, the $AUC_{(0-8hr)}$ for either oxycodone and/or acetaminophen will be about 10% to about 45% higher when a subject ingested the tablet in an intact state versus in a crushed or ground state.

[000281] In still another embodiment, the $AUC_{(0-8hr)}$ for either oxycodone and/or acetaminophen was about 10%, 20%, 30%, 40%, 50%, 60%, 70% or 80% higher when a subject ingested the tablet in an intact state versus in a crushed or ground state. In an

additional embodiment, the $AUC_{(0-8hr)}$ for either oxycodone and/or acetaminophen was about 10% to about 45% higher when a subject ingested the tablet in an intact state versus in a crushed or ground state.

[000282] In another embodiment, the $AUC_{(0-inf)}$ for either oxycodone and/or acetaminophen will be about 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, or 50% higher when a subject ingested the tablet in an intact state versus in a crushed or ground state. In still another embodiment, the $AUC_{(0-inf)}$ for either oxycodone and/or acetaminophen will be from about 5% to about 40% higher when a subject ingested the tablet in an intact state versus in a crushed or ground state. In still another embodiment, the $AUC_{(0-inf)}$ for either oxycodone and/or acetaminophen will be from about 7% to about 30% higher when a subject ingested the tablet in an intact state versus in a crushed or ground state. In a further embodiment, the $AUC_{(0-inf)}$ for either oxycodone and/or acetaminophen will be from about 10% to about 30% higher when a subject ingested the tablet in an intact state versus in a crushed or ground state.

[000283] In another embodiment, the $AUC_{(0-t)}$ for either oxycodone and/or acetaminophen will be about 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, or 50% higher when a subject ingested the tablet in an intact state versus in a crushed or ground state. In another embodiment, the $AUC_{(0-t)}$ for either oxycodone and/or acetaminophen will be from about 2% to about 40% higher when a subject ingested the tablet in an intact state versus in a crushed or ground state. In still another embodiment, the $AUC_{(0-t)}$ for either oxycodone and/or acetaminophen will be from about 3% to about 30% higher when a subject ingested the tablet in an intact state versus in a crushed or ground state. In a further embodiment, the $AUC_{(0-t)}$ for either oxycodone and/or acetaminophen will be from about 4% to about 30% higher when a subject ingested the tablet in an intact state versus in a crushed or ground state. In another embodiment, the $AUC_{(0-t)}$ for either oxycodone and/or acetaminophen will be

from about 5% to about 20% higher when a subject ingested the tablet in an intact state versus in a crushed or ground state.

[000284] Unexpectedly, the $T_{\max}$ for both oxycodone and/or acetaminophen was lower when the tablet was administered in an intact state versus when the tablet was administered in a crushed or ground state. For instance, in one embodiment, the $T_{\max}$ for either oxycodone and/or acetaminophen was lower by about 5% to about 70% when the tablet was administered in an intact state versus when the tablet was administered in a crushed or ground state. In an additional embodiment, the $T_{\max}$ for either oxycodone and/or acetaminophen was lower by about 10% to about 40% when the tablet was administered in an intact state versus when the tablet was administered in a crushed or ground state. In another embodiment, the $T_{\max}$ for either hydrocodone and/or acetaminophen will be about 20% to about 60%. In still another embodiment, the $T_{\max}$ for either oxycodone and/or acetaminophen was about 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 46%, 48%, 49% or 50% higher when a subject ingested the tablet in a crushed or ground state versus in an intact state. In yet another embodiment, the $T_{\max}$ for either oxycodone and/or acetaminophen was about 25%, 50%, 75%, 100%, 125%, 150%, 175%, 200%, 225%, 250%, 300% or 325% higher when a subject ingested the tablet in a crushed or ground state versus in an intact state. In an additional embodiment, administration of the tablet to a subject produces a mean $T_{\max}$ for either oxycodone or acetaminophen that is at least about 30 minutes greater when the tablet is administered in a crushed or ground state as compared to an intact state. In a further embodiment, administration of the tablet to a subject produces a mean $T_{\max}$ for either oxycodone or acetaminophen that is at least about 30 minutes, 45 minutes, 60 minutes, 75 minutes, 90 minutes, 105 minutes, 120 minutes, 135 minutes, or 150 minutes greater when the tablet is administered in a crushed or ground state as compared to an intact state.

[000285] And the $C_{\max}$ for acetaminophen was higher when the tablet was administered in an intact state versus when the tablet was administered in a crushed or ground state. For example, in one embodiment, the $C_{\max}$ for acetaminophen was about

5% to about 50% higher when the tablet was administered in an intact state versus when the tablet was administered in a crushed or ground state. In yet another embodiment, the C_{max} for acetaminophen was about 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 46%, 48%, 49% or 50% higher when the tablet was administered in an intact state versus when the tablet was administered in a crushed or ground state.

[000286] In one embodiment, the abuse quotient of the tablet will be higher when the tablet is administered in an intact state versus when the tablet is administered in a crushed or ground state. For example, in another embodiment, the abuse quotient may decrease in an amount of from about 5% to about 90% when the tablet is administered in a crushed or ground state versus in an intact state. In a further embodiment, the abuse quotient may decrease in an amount from about 10% to about 80% when the tablet is administered in a crushed or ground state versus in an intact state. In yet another embodiment, the abuse quotient may decrease in an amount from about 15% to about 80% when the tablet is administered in a crushed or ground state versus in an intact state. In still another embodiment, the abuse quotient may decrease in an amount of from about 20% to about 70% when the tablet is administered in a crushed or ground state versus in an intact state. In another embodiment, the abuse quotient may decrease in an amount of about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, or 90% when the tablet is administered in a crushed or ground state versus in an intact state.

[000287] As a result of these pharmacokinetic parameters, a drug abuser is more likely to take the extended release dosage forms disclosed herein that comprise an immediate release portion and an extended release portion in an intact form rather than in a crushed form. Moreover, drug abusers "like" the dosage forms disclosed herein better when the dosage forms are taken in an intact state rather than in a crushed or ground state. See FDA's Guidance for Industry Document titled, "Assessment of Abuse Potential of Drug," dated January 2010. Both overall and "at the moment" drug liking may be assessed on a bipolar visual analog scale (VAS) anchored by "strong disliking" (0), "neutral" (50), and "strong liking" (100).

[000288] In another embodiment, as the amount of oxycodone in the pharmaceutical composition increases, so does the duration of gastric retention after administration to a subject. Consequently, if a subject either intentionally or accidentally ingests a larger dose of the pharmaceutical composition than prescribed, the pharmaceutical composition will be retained in the stomach for a longer time period than an IR or traditional ER pharmaceutical composition, thereby giving a medical provider additional time to perform gastric lavage, induce vomiting, or administer activated charcoal to prevent the body from absorbing the oxycodone. In a further embodiment, the pharmaceutical composition provides a medical provider with about an additional 15 minutes, 30 minutes, 45 minutes, 60 minutes, 75 minutes, 90 minutes, 105 minutes, 2.0 hours, 2.25 hours, 2.5 hours, 2.75 hours, 3.0 hours, 3.25 hours, 3.5 hours, 3.75 hours, or 4 hours in which to prevent the absorption of oxycodone in the subject. In another embodiment, the pharmaceutical composition provides a medical provider with sufficient time to treat a subject who has overdosed on oxycodone so that death, difficulty breathing, cardiac arrest, and limp muscles do not occur in the subject.

[000289] In yet another embodiment, if vomiting is induced or naturally occurs as a result of an increased dose of oxycodone, the entire pharmaceutical composition is expelled from the subject. Thus, toxic concentrations of the oxycodone due to absorption into the subject's blood are prevented by removing the further release of oxycodone. In still another embodiment, if vomiting is induced or naturally occurs as a result of the increased dose of oxycodone about 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% of the pharmaceutical composition is expelled from the subject. In yet another embodiment, if vomiting is induced or naturally occurs within about 30 minutes to about 60 minutes after ingestion of the increased dose of oxycodone about 50% to about 65% of the oxycodone dose is expelled from the subject.

(f) **In vitro release properties of the composition**

[000290] The in vitro release rates of oxycodone and acetaminophen from the pharmaceutical compositions disclosed herein may be measured in 900 mL of 0.1 N HCl using a USP type II paddle apparatus and at a paddle speed of either about 100 rpm or 150 rpm and a constant temperature of 37°C.

[000291] In one embodiment, the at least one immediate release portion of the composition may have in vitro release rates of oxycodone and acetaminophen as follows: more than about 90% of the oxycodone and/or the acetaminophen present in the at least one immediate release portion may be released within about 15 minutes, or essentially 100% of the oxycodone and/or the acetaminophen present in the at least one immediate release portion may be released within about 15 minutes. In another embodiment, more than about 90% of the oxycodone and/or the acetaminophen present in the at least one immediate release portion may be released within about 5 minutes. In yet another embodiment, essentially 100% of the oxycodone and / or acetaminophen present in the at least one immediate release portion may be released within about 5 minutes.

[000292] In one embodiment, the at least one extended release portion of the composition may have in vitro release rates of oxycodone as follows: from about 1% to about 20% of the oxycodone present in the at least one extended release portion may be released within about 15 minutes, from about 35% to about 55% of the oxycodone present in the at least one extended release portion may be released within about 2 hours, from about 65% to about 85% of the oxycodone present in the at least one extended release portion may be released within about 4 hours, and at least about 90% of the oxycodone present in the at least one extended release portion may be released within about 8 hours.

[000293] In yet another embodiment, the at least one extended release portion may have in vitro release rates of oxycodone as follows: from about 1% to about 10% of the oxycodone present in the at least one extended release portion may be released within about 15 minutes, from about 40% to about 50% of the oxycodone present in the at least one extended release portion may be released within about 2 hours, from about 70% to about 80% of the oxycodone present in the at least one extended release portion may be released within about 4 hours, and from about 90% to about 100% of the oxycodone present in the at least one extended release portion may be released within about 8 hours.

[000294] In one embodiment, the at least one extended release portion may have in vitro release rates of acetaminophen as follows: from about 1% to about 15% of the acetaminophen present in the at least one extended release portion may be released

within about 15 minutes, from about 25% to about 40% of the acetaminophen present in the at least one extended release portion may be released within about 2 hours, from about 50% to about 65% of the acetaminophen present in the at least one extended release portion may be released within about 4 hours, and from about 80% to about 95% of the acetaminophen present in the at least one extended release portion may be released within about 8 hours.

[000295] In another embodiment, the at least one extended release portion of the composition may have in vitro release rates of acetaminophen as follows: from about 1% to about 10% of the acetaminophen present in the at least one extended release portion may be released within about 15 minutes, from about 25% to about 35% of the acetaminophen present in the at least one extended release portion may be released within about 2 hours, from about 55% to about 65% of the acetaminophen present in the at least one extended release portion may be released within about 4 hours, and from about 80% to about 90% of the acetaminophen present in the at least one extended release portion may be released within about 8 hours.

[000296] In another embodiment, the at least one extended release portion of the composition may have in vitro release rates of acetaminophen as follows: from about 1% to about 10% of the acetaminophen present in the at least one extended release portion may be released within about 15 minutes, from about 20% to about 50% of the acetaminophen present in the at least one extended release portion may be released within about 2 hours, from about 35% to about 75% of the acetaminophen present in the at least one extended release portion may be released within about 4 hours, and from about 65% to about 100% of the acetaminophen present in the at least one extended release portion may be released within about 8 hours.

[000297] In one embodiment, the in vitro release rates of oxycodone from the composition may be as follows: about 20% to about 45% of oxycodone may be released from the composition within about 15 minutes, from about 50% to about 75% of oxycodone may be released from the composition in about 2 hours, from about 70% to about 95% of oxycodone may be released from the composition within about 4 hours, and from about 90% to about 100% of oxycodone may be released from the composition within about 8 hours.

[000298] In one embodiment, the in vitro release rates of oxycodone from the composition may be as follows: about 25% to about 35% of oxycodone may be released from the composition within about 15 minutes, from about 40% to about 80% of oxycodone may be released from the composition in about 2 hours, from about 70% to about 85% of oxycodone may be released from the composition within about 4 hours, and from about 90% to about 100% of oxycodone may be released from the composition within about 8 hours.

[000299] In another embodiment, the pharmaceutical composition disclosed herein may have in vitro release rates of oxycodone as follows: about 25% to about 30% of oxycodone may be released from the pharmaceutical composition within about 15 minutes, from about 50% to about 60% of oxycodone may be released from the pharmaceutical composition within about 2 hours, from about 70% to about 80% of oxycodone may be released from the pharmaceutical composition within about 4 hours, and from about 90% to about 95% of oxycodone may be released from the pharmaceutical composition within about 8 hours.

[000300] In one embodiment, the in vitro release rates of acetaminophen from the composition may be as follows: from about 40% to about 65% of acetaminophen may be released from the composition in about 15 minutes, from about 55% to about 80% of acetaminophen may be released from the composition in about 2 hours, from about 65% to about 95% of acetaminophen may be released from the composition in about 4 hours, and from about 80% to about 100% of acetaminophen may be released from the composition in about 8 hours.

[000301] In one embodiment, the in vitro release rates of acetaminophen from the composition may be as follows: from about 30% to about 70% of acetaminophen may be released from the composition in about 15 minutes, from about 50% to about 90% of acetaminophen may be released from the composition in about 2 hours, from about 60% to about 95% of acetaminophen may be released from the composition in about 4 hours, and from about 90% to about 100% of acetaminophen may be released from the composition in about 8 hours.

[000302] In another embodiment, the in vitro release rates of acetaminophen from the pharmaceutical composition disclosed herein may be as follows: from about 50% to

about 55% of acetaminophen may be released from the pharmaceutical composition within about 15 minutes, from about 60% to about 70% of acetaminophen may be released from the pharmaceutical composition within about 2 hours, from about 75% to about 85% of acetaminophen may be released from the pharmaceutical composition within about 4 hours, and from about 90% to about 100% of acetaminophen may be released from the pharmaceutical composition within about 8 hours.

[000303] In another embodiment, about 90% to about 100% of the IR dose of acetaminophen is released within about 15 minutes, 30 minutes, 45 minutes or 60 minutes after oral administration. In one embodiment, the pharmaceutical composition provides a dissolution profile wherein about 20% to about 65%, about 35% to about 55% or about 40% to about 50% of the ER dose of acetaminophen remains in the ER layer between about 1 and 2 hours after administration.

[000304] In yet another embodiment, the pharmaceutical composition provides a dissolution profile wherein about 50% to about 95% of the ER dose of acetaminophen remains in the ER layer between about 1 and 2 hours after administration. In another embodiment, the dosage form provides a dissolution profile wherein about 15% to about 40% of the ER dose of acetaminophen is released from the ER layer between about 1 and 2 hours after administration. In one embodiment, not more than 50% of the ER dose of acetaminophen is released within about the first hour. In a further embodiment, not more than 45% or not more than 40% of the ER dose of acetaminophen is released within about the first hour.

[000305] In another embodiment, not more than 85% of the ER dose of acetaminophen is released within about 4 hours. In yet another embodiment, not less than 50% is released after about 6 hours. In yet another embodiment, not less than 55% is released after about 6 hours. In one embodiment, the ER dose of acetaminophen is released over a time period of about 6 to 12, about 8 to 10, or about 9 to 10 hours in vitro. In another embodiment, the ER dose of acetaminophen is released over a time period of about 7 hours, 8 hours, 9 hours, 10 hours, 11 hours or 12 hours in vitro. In one embodiment, at least 80% or 85% of the ER dose of acetaminophen is released over a time period of about 7 hours, 8 hours, 9 hours, 10 hours, 11 hours or 12 hours in vitro. In another embodiment, at least 90% or 95% of the ER dose of acetaminophen is released

over a time period of about 7 hours, 8 hours, 9 hours, 10 hours, 11 hours or 12 hours in vitro.

[000306] Additionally, the in vitro release rates of oxycodone and acetaminophen from the pharmaceutical composition generally are not affected by low concentrations of ethanol (i.e., from about 5% v/v to about 20% v/v) when measured in 900 mL of 0.1 N HCl containing the desired percentage of ethanol using a USP type II paddle apparatus and at a paddle speed of about 150 rpm and a constant temperature of 37°C. For example, from about 25% to about 35% of oxycodone and about 50% to about 55% of acetaminophen may be released from the pharmaceutical composition within about 15 minutes when measured in the presence of 5% to 20% ethanol, and from about 50% to about 65% of oxycodone and from about 60% to about 70% of acetaminophen may be released from the pharmaceutical composition within about 2 hour when measured in the presence of 5% to 20% ethanol.

[000307] The in vitro release rates of oxycodone and acetaminophen from the pharmaceutical compositions disclosed herein generally are reduced, however, in the presence of 40% ethanol. For example, from about 5% to about 15% of the oxycodone and from about 15% to about 25% of the acetaminophen may be released from the pharmaceutical composition within about 15 minutes when measured in the presence of 40% ethanol, and from about 35% to about 45% of oxycodone and from about 45% to about 55% of acetaminophen may be released from the pharmaceutical composition within about 2 hours when measured in the presence of 40% ethanol.

[000308] Stated another way, less oxycodone is extracted from the pharmaceutical composition by a solution of 0.1 N HCl and 40% ethanol than is extracted by a solution of 0.1 N HCl. In some embodiments, less than about 75% of the oxycodone that is released in the presence of 0.1N HCl may be released in the presence of 0.1N HCl containing 40% ethanol. In additional embodiments, less than about 70%, 65%, 60%, 55%, 50%, 45%, or 40% of the oxycodone that may be released in the presence of 0.1N HCl may be released in the presence of 0.1N HCl and 40% ethanol. For example, less than about 40% of the oxycodone that may be released in the presence of 0.1N HCl in about 15 minutes may be released in the presence of 0.1N HCl and 40% ethanol within about 15 minutes. In other embodiments, less than about 60% of the oxycodone that may

be released in the presence of 0.1N HCl in about 30 minutes may be released in the presence of 0.1N HCl and 40% ethanol within about 30 minutes. In additional embodiments, less than about 75% of the oxycodone that may be released in the presence of 0.1N HCl in about 2 hours may be released in the presence of 0.1N HCl and 40% ethanol within about 2 hours.

(g) Stability data for the pharmaceutical composition

[000309] In one embodiment, p-aminophenol may be present in the pharmaceutical composition as a degradation product of acetaminophen in any amount up to and including, but no more than, about 100 ppm. In other embodiments, p-aminophenol may be present in the pharmaceutical composition as a degradation product of acetaminophen in an amount of about 0.2 ppm to about 6.0 ppm after storage for about 1, 2, or 3 months at a temperature of about 25 °C to about 40°C and at about 60% to about 75% relative humidity. In yet another embodiment, p-aminophenol may be present in the pharmaceutical composition as a degradation product of acetaminophen in an amount of about 0.6 ppm to about 6.0 ppm after storage for about 1, 2, or 3 months at a temperature of about 25 °C to about 40°C and at about 60% to about 75% relative humidity. In still another embodiment, p-aminophenol may be present in the pharmaceutical composition as a degradation product of acetaminophen in an amount of about 0.2 ppm, 0.3 ppm, 0.4 ppm, 0.5 ppm, 0.6 ppm, 0.7 ppm, 0.8 ppm, 0.9 ppm, 1.0 ppm, 1.1 ppm, 1.2 ppm, 1.3 ppm, 1.4 ppm, 1.5 ppm, 1.6 ppm, 1.7 ppm, 1.8 ppm, 1.9 ppm, 2.0 ppm, 2.1 ppm, 2.2 ppm, 2.3 ppm, 2.4 ppm, 2.5 ppm, 2.6 ppm, 2.7 ppm, 2.8 ppm, 2.9 ppm, 3.0 ppm, 3.1 ppm, 3.2 ppm, 3.3 ppm, 3.4 ppm, 3.5 ppm, 3.6 ppm, 3.7 ppm, 3.8 ppm, 3.9 ppm, 4.0 ppm, 4.1 ppm, 4.2 ppm, 4.3 ppm, 4.4 ppm, 4.5 ppm, 4.6 ppm, 4.7 ppm, 4.8 ppm, 4.9 ppm, 5.0 ppm, 5.1 ppm, 5.2 ppm, 5.3 ppm, 5.4 ppm, 5.5 ppm, 5.6 ppm, 5.7 ppm, 5.8 ppm, 5.9 ppm, and 6.0 ppm after storage for about 1, 2, or 3 months at a temperature of 25 °C to about 40°C and at about 60% to about 75% relative humidity

[000310] In one embodiment, oxycodone N-oxide may be present in the pharmaceutical composition as a degradation product of oxycodone in any amount up to and including about 0.5% by weight of the oxycodone. In other embodiments, oxycodone N-oxide may be present in the pharmaceutical composition as a degradation product of oxycodone in an amount of about 0.01% to about 0.5% by weight of the oxycodone after

storage for about 1, 2, or 3 months at a constant temperature of about 25°C to 40°C and at about 60% to 75% relative humidity. In yet another embodiment, oxycodone N-oxide may be present in the pharmaceutical composition as a degradation product of oxycodone in an amount of about 0.05% to about 0.5% by weight of the oxycodone after storage for about 1, 2, or 3 months at a constant temperature of about 25°C to 40°C and at about 60% to 75% relative humidity. In additional embodiments, oxycodone N-oxide may be present in the pharmaceutical composition as a degradation product of oxycodone in an amount of about 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1%, 0.11%, 0.12%, 0.13%, 0.14%, 0.15%, 0.16%, 0.17%, 0.18%, 0.19%, 0.2%, 0.21%, 0.22%, 0.23%, 0.24%, 0.25%, 0.26%, 0.27%, 0.28%, 0.29%, 0.3%, 0.31%, 0.32%, 0.33%, 0.34%, 0.35%, 0.36%, 0.37%, 0.38%, 0.39%, 0.4%, 0.41%, 0.42%, 0.43%, 0.44%, 0.45%, 0.46%, 0.47%, 0.48%, 0.49%, and 0.5% by weight of the oxycodone after storage for about 1, 2, or 3 months at a constant temperature of about 25°C to about 40°C and at about 60% to about 75% relative humidity.

[000311] In one embodiment, Related Substance A (i.e., C-Normorphinan-6-carboxylic acid, 4,5-epoxy-6,14-dihydroxy-3-methoxy-17-methyl-, (5 α ,6 α)-) may be present in the pharmaceutical composition as a degradation product of oxycodone in a maximum amount of about 0.5% by weight of the oxycodone. In other embodiments, Related Substance A may be present in the pharmaceutical composition as a degradation product of oxycodone in an amount of about 0.01% to about 0.5% by weight of the oxycodone after storage for about 1, 2, or 3 months at a temperature of about 25°C to about 40°C and at about 60% to about 75% relative humidity. In yet another embodiment, Related Substance A may be present in the pharmaceutical composition as a degradation product of oxycodone in an amount of about 0.05% to about 0.5% by weight of the oxycodone after storage for about 1, 2, or 3 months at a temperature of about 25°C to about 40°C and at about 60% to about 75% relative humidity. In other embodiments, Related Substance A may be present in the pharmaceutical composition as a degradation product of oxycodone in an amount of about 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1%, 0.11%, 0.12%, 0.13%, 0.14%, 0.15%, 0.16%, 0.17%, 0.18%, 0.19%, 0.2%, 0.21%, 0.22%, 0.23%, 0.24%, 0.25%, 0.26%, 0.27%, 0.28%, 0.29%, 0.3%, 0.31%, 0.32%, 0.33%,

0.34%, 0.35%, 0.36%, 0.37%, 0.38%, 0.39%, 0.4%, 0.41%, 0.42%, 0.43%, 0.44%, 0.45%, 0.46%, 0.47%, 0.48%, 0.49%, and 0.5% by weight of the oxycodone after storage for about 1, 2, or 3 months at a temperature of about 25°C to about 40°C and at about 60% to about 75% relative humidity.

[000312] In one embodiment, each unspecified acetaminophen degradation product may be present in the pharmaceutical composition in any amount up to about 0.15% by weight of the acetaminophen. In another embodiment, each unspecified acetaminophen degradation product may be present in the pharmaceutical composition as a degradation product of acetaminophen in an amount of about 0.01% and about 0.15% by weight of the acetaminophen after storage for about 1, 2, or 3 months at a temperature of about 25°C to about 40°C and at about 60% to about 75% relative humidity. In still another embodiment, each unspecified acetaminophen degradation product may be present in the pharmaceutical composition as a degradation product of acetaminophen in an amount of about 0.05% and about 0.15% by weight of the acetaminophen after storage for about 1, 2, or 3 months at a temperature of about 25°C to about 40°C and at about 60% to about 75% relative humidity. In other embodiments, each unspecified acetaminophen degradation product may be present in the pharmaceutical composition as a degradation product of acetaminophen in an amount of about 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1%, 0.11%, 0.12%, 0.13%, 0.14%, and 0.15% by weight of the acetaminophen after storage for about 1, 2, or 3 months at a temperature of about 25°C to about 40°C and at about 60% to about 75% relative humidity.

[000313] In one embodiment, each unspecified oxycodone HCl degradation product may be present in the pharmaceutical composition in a maximum amount of about 0.2% by weight of the oxycodone. In other embodiments, each unspecified oxycodone HCl degradation product may be present in the pharmaceutical composition in an amount of about 0.01% to about 0.2% by weight of the oxycodone after storage for about 1, 2, or 3 months at a temperature of about 25°C to about 40°C and at about 60% to about 75% relative humidity. In yet another embodiment, each unspecified oxycodone HCl degradation product may be present in the pharmaceutical composition in an amount of about 0.05% to about 0.2% by weight of the oxycodone after storage for about 1, 2, or

3 months at a temperature of about 25°C to about 40°C and at about 60% to about 75% relative humidity. In further embodiments, each unspecified oxycodone HCl degradation product may be present in the pharmaceutical composition in an amount of about 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.10%, 0.11%, 0.12%, 0.13%, 0.14%, 0.15%, 0.16%, 0.17%, 0.18%, 0.19%, and 0.2% by weight of the oxycodone after storage for about 1, 2, or 3 months at a temperature of about 25°C to about 40°C and at about 60% to about 75% relative humidity.

[000314] In one embodiment, the total acetaminophen degradation products may be present in the pharmaceutical composition in a maximum amount of about 1.0% by weight of the acetaminophen. In other embodiments, the total acetaminophen degradation products may be present in the pharmaceutical composition in an amount of about 0.05% to about 1.0% by weight of the acetaminophen after storage for about 1, 2, or 3 months at a temperature of about 25°C to about 40°C and at about 60% to about 75% relative humidity. In further embodiments, the total acetaminophen degradation products may be present in the pharmaceutical composition in an amount of about 0.05%, 0.1%, 0.15%, 0.2%, 0.25%, 0.3%, 0.35%, 0.4%, 0.45%, 0.5%, 0.55%, 0.6%, 0.65%, 0.7%, 0.75%, 0.8%, 0.85%, 0.9%, 0.95%, and 1.0% by weight of the acetaminophen after storage for about 1, 2, or 3 months at a temperature of about 25°C to about 40°C and at about 60% to about 75% relative humidity.

[000315] In one embodiment, the total oxycodone degradation products may be present in the pharmaceutical composition in a maximum amount of about 1.0% by weight of the oxycodone. In further embodiments, the total oxycodone degradation products may be present in the pharmaceutical composition in an amount of about 0.05% to about 1.0% by weight of the oxycodone after storage for about 1, 2, or 3 months at a temperature of about 25°C to about 40°C and at about 60% to about 75% relative humidity. In yet other embodiments, the total oxycodone degradation products may be present in the pharmaceutical composition in an amount of about 0.05%, 0.1%, 0.15%, 0.2%, 0.25%, 0.3%, 0.35%, 0.4%, 0.45%, 0.5%, 0.55%, 0.6%, 0.65%, 0.7%, 0.75%, 0.8%, 0.85%, 0.9%, 0.95%, and 1.0% by weight of the oxycodone after storage for about 1, 2, or 3 months at a temperature of about 25°C to about 40°C and at about 60% to about 75% relative humidity.

(h) *In vivo* and pharmacokinetic properties of the pharmaceutical composition

[000316] The pharmaceutical composition disclosed herein comprises at least one immediate release portion for immediate release of oxycodone and acetaminophen such that therapeutic plasma concentrations are quickly attained (e.g., within one hour) and the initial onset of action is achieved within about 5 minutes, 10 minutes, 15 minutes, 20 minutes, 25 minutes, 30 minutes, 35 minutes, 40 minutes, 45 minutes, 50 minutes, 55 minutes, or 60 minutes after administration of the composition upon oral administration to a subject. The pharmaceutical composition disclosed herein also comprises at least one extended release portion for sustained release of oxycodone and acetaminophen over an extended period of time, e.g., about 3 to about 12 hours, or about 4 to about 9 hours, or at least about 6 hours, or at least about 8 hours, to the upper gastrointestinal tract where acetaminophen, and potentially oxycodone, is best absorbed.

[000317] The pharmaceutical composition may be orally administered to a subject once in a 24 hour period (q.d. or once-daily), two times in a 24 hour period (b.i.d. or twice-daily), or three times in a 24 hour period (t.i.d. or three times daily). In one embodiment, the pharmaceutical composition may be orally administered to the subject twice a day (i.e., every 12 hours). In another embodiment, the pharmaceutical composition may be orally administered to the subject at time zero ($t=0$), and then the subject may be administered a subsequent dose of the pharmaceutical composition either after eight hours ($t=8$) or twelve hours ($t=12$). The subject may be a mammal, and in certain embodiments, the subject may be a human.

[000318] In another embodiment, the subject may be administered a first or loading dose of the pharmaceutical composition. This first or loading dose may assist the subject in more quickly attaining steady state blood levels of the active drugs. In a further embodiment, the subject may be administered a first or loading dose of the pharmaceutical composition comprising about 22.5 mg of oxycodone and about 975 mg of acetaminophen. In yet another embodiment, the subject may be administered a first or loading dose of the pharmaceutical composition comprising 2 tablets, each tablet comprising about 11.25 mg of oxycodone and about 462.5 mg of acetaminophen. In yet another embodiment, the subject may be administered a first or loading dose of the pharmaceutical composition comprising 3 tablets, each tablet comprising about 7.5 mg of

oxycodone and about 325 mg of acetaminophen. In still another embodiment, the subject may be administered a first or loading dose of the pharmaceutical composition comprising 4 tablets, each tablet comprising about 5.625 mg of oxycodone and about 231.25 mg of acetaminophen. In yet another embodiment, the subject may be administered a first or loading dose of the pharmaceutical composition comprising 2 capsules, each capsule comprising about 11.25 mg of oxycodone and about 462.5 mg of acetaminophen. In yet another embodiment, the subject may be administered a first or loading dose of the pharmaceutical composition comprising 3 capsules, each capsules comprising about 7.5 mg of oxycodone and about 325 mg of acetaminophen. In still another embodiment, the subject may be administered a first or loading dose of the pharmaceutical composition comprising 4 capsules, each capsules comprising about 5.625 mg of oxycodone and about 231.25 mg of acetaminophen.

[000319] Upon oral administration to a subject, the pharmaceutical composition disclosed herein may maintain a therapeutic blood plasma concentration of oxycodone of at least about 5 ng/mL from about 0.75 hours to about 12 hours after administration of the composition. In another embodiment, the plasma concentration of oxycodone may be maintained at a concentration of at least about 7.5 ng/mL from about 1 hour to about 12 hours after administration of the composition. In a further embodiment, the plasma concentration of oxycodone may be maintained at a concentration of at least about 7.5 ng/mL from about 0.75 hour to about 10 hours after administration of the composition. In a further embodiment, the plasma concentration of oxycodone may be maintained at a concentration of at least about 10 ng/mL from about 2 hour to about 10 hours after administration of the composition. In yet another embodiment, the plasma concentration of oxycodone may be maintained at a concentration of at least about 10 ng/mL from about 1 hour to about 10 hours after administration of the composition. In still another embodiment, the plasma concentration of oxycodone may be maintained at a concentration of at least about 10 ng/mL from about 0.75 hour to about 10 hours after administration of the composition.

[000320] In another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by a mean C_{max} (peak plasma concentration) for oxycodone from about 0.9 ng/mL/mg to about 1.6

ng/mL/mg. In another embodiment, the mean C_{max} for oxycodone may range from about 1.0 ng/mL/mg to about 1.5 ng/mL/mg. In an additional embodiment, the mean C_{max} for oxycodone may be about 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, or 1.6 ng/mL/mg. Moreover, the mean C_{max} for oxycodone at steady state may range from about 1.5 ng/mL/mg to about 2.0 ng/mL/mg, from about 1.6 ng/mL/mg to about 1.95 ng/mL/mg, or from about 1.7 ng/mL/mg to about 1.85 ng/mL/mg.

[000321] In a further embodiment, the pharmaceutical composition, when orally administered to a subject, surprisingly may produce a blood plasma concentration profile characterized by a biphasic increase in blood plasma concentrations of oxycodone. Deconvolution of the pharmaceutical composition and the target plasma profiles can be done in WinNonLin (version 5.2, Pharsight Corp., Mountain View, Calif.). The results of such a deconvolution analysis for oxycodone is depicted in FIG. 23. The biphasic absorption of oxycodone may be characterized by an initial rapid absorption resulting in a first peak in plasma concentration between about 1 hour and 2 hours, which contributes to the early onset of action, and a second peak in plasma concentrations between about 3 hours and 7 hours as a result of slower absorption taking place from the at least one extended release portion after administration of the composition, which contributes to the duration or maintenance of analgesia. In some instances, the second peak may correspond to the overall C_{max} of the composition. The biphasic increase in blood plasma concentrations of oxycodone may be characterized by a plasma concentration-time profile for oxycodone in which the slope of a line drawn between 0 hour and about 2 hours is greater than the slope of a line drawn between about 2 hours and about 5 hours. See FIG. 23.

[000322] This biphasic increase in oxycodone levels resulting from the composition has several benefits. For example, providing rapid but not too high concentrations of oxycodone for quick onset of analgesia followed by maintenance of oxycodone levels over an extended time period could prevent a human subject from developing liking or dependence (abuse) for oxycodone. Further fluctuations in the oxycodone plasma levels could also prevent development of tolerance at the active site. Thus, the biphasic increase in oxycodone levels helps to prevent this acute tolerance.

[000323] In an additional embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by a mean AUC for oxycodone from about 9.0 ng·hr/mL/mg to about 18.5 ng·hr/mL/mg. In a further embodiment, the mean AUC for oxycodone may be from about 12.0 ng·hr/mL/mg to about 16.0 ng·hr/mL/mg. In another embodiment, the mean AUC for oxycodone may be about 9.0, 9.5, 10.0, 10.5, 11.0, 11.5, 12.0, 12.5, 13.0, 13.5, 14.0, 14.5, 15.0, 15.5, or 16.0 ng·hr/mL/mg. Additionally, the mean AUC for oxycodone at steady state may range from about 11.0 ng·hr/mL/mg to about 17.0 ng·hr/mL/mg, from about 12.0 ng·hr/mL/mg to about 16.0 ng·hr/mL/mg, or from about 13.0 ng·hr/mL/mg to about 15.0 ng·hr/mL/mg.

[000324] In a further embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by a median T_{max} (time to peak plasma concentration) for oxycodone from about 2.0 hours to about 7.0 hours. In an alternate embodiment, the median T_{max} for oxycodone may be from about 3.0 hours to about 6.0 hours. In another embodiment, the median T_{max} for oxycodone may be about 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5 or 6.0 hours. Moreover, the median T_{max} for oxycodone at steady state may range from about 1.5 hours to about 3.5 hours, or from about 2 hours to about 3 hours.

[000325] In still another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by a median tlag for oxycodone from about 0 hours to about 0.5 hours. In an alternate embodiment, the median tlag for oxycodone may be from about 0 hours to about 0.25 hours.

[000326] Rates of absorption are often assessed by comparing standard pharmacokinetic parameters such as T_{max} and C_{max} . The extent of absorption is assessed by the AUC. A short T_{max} has been used to indicate rapid absorption. The U.S. FDA, Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations (March 2003) and related publications (Chen et al, Clin. Pharmacokinet. 40(8):565-72, 2001) also recommends the use of partial AUC for some modified-release drugs ("MR drugs"), such as the pharmaceutical compositions disclosed herein. A partial AUC calculation may be used to measure early exposure to a drug, which may signify an initial onset of pain relief and/or to measure prolonged exposure of a drug in achieving sustained relief. Partial AUC

calculations can also demonstrate whether two MR drugs are truly bioequivalent by comparing, for example, an early partial AUC, which will be associated with a drug's response onset, and a late partial AUC, which will be associated with a drug's sustained response. The parameters for compositions vary greatly between subjects. The parameters also vary depending on aspects of the study protocol such as the sampling scheduling, subject posture and general subject health. Values quoted in this specification are given as mean $\pm$ standard deviation unless otherwise noted.

[000327] For partial AUC calculations, the standard linear trapezoidal summation over each time interval is used. The partial AUCs are calculated from the mean pharmacokinetic profile. For time 0 to 1 hour the partial AUC is AUC(0-1hr); for time 0 to 2 hours the partial AUC is AUC_(0-2hr); for time 0-4 hours the partial AUC is AUC_(0-4hr); for time 0 to 6 hour the partial AUC is AUC_(0-6hr); for time 0 to 8 hours the partial AUC is AUC_(0-8hr); and for time 0 to the last measurable time point ("x") the partial AUC is AUC(0-(x)hr) where each partial AUC is calculated according to standard pharmaceutical industry pharmacokinetic calculation methodologies as given by:

[000328] AUC_(0-1hr) –Area under the drug concentration-time curve calculated using linear trapezoidal summation from time zero to time 1 hour.

[000329] AUC_(0-2hr) – Area under the drug concentration-time curve calculated using linear trapezoidal summation from time zero to time 2 hours.

[000330] AUC_(0-4hr) –Area under the drug concentration-time curve calculated using linear trapezoidal summation from time zero to time 4 hours.

[000331] AUC_(0-6hr) –Area under the drug concentration-time curve calculated using linear trapezoidal summation from time zero to time 6 hours.

[000332] AUC_(0-8hr) –Area under the drug concentration-time curve calculated using linear trapezoidal summation from time zero to time 8 hours.

[000333] AUC_{(0-(t)hr)} –Area under the drug concentration-time curve calculated using linear trapezoidal summation from time zero to the last measurable time point.

[000334] AUC_{(0-(T_{max} of IR product + 2SD))} – Area under the drug concentration-time curve calculated using linear trapezoidal summation from time zero to the time of the mean peak (T_{max}) for the immediate release version of the drug plus two standard deviations ("2SD") for the immediate release drug. The FDA has identified this calculation

in association with an early onset of response for certain modified-release dosage forms, which show complex pharmacokinetic characteristics. (See supra March 2003 Guidance; Draft Guidance on Dexmethylphenidate Hydrochloride (March 2012); Draft Guidance on Methylphenidate Hydrochloride (Nov. 2011)).

[000335] $AUC_{((T_{max} \text{ of IR product} + 2SD)-t)}$ — Area under the drug concentration-time curve calculated using linear trapezoidal summation from the time of the mean peak (T_{max}) for the immediate release version of the drug plus two standard deviations (“2SD”) for the immediate release drug to the last measurable time point. The FDA has identified this parameter in association with sustaining the response for modified-release dosage forms, which shows complex pharmacokinetic characteristics. (See March 2003 Guidance supra; Draft Guidance on Dexmethylphenidate Hydrochloride (March 2012); Draft Guidance on Methylphenidate Hydrochloride (Nov. 2011)).

[000336] $AUC_{(x-(y)hr)}$ — Area under the drug concentration-time curve calculated using linear trapezoidal summation from time “x” (e.g., any measurable time point, such as 8 hours) to time “y” (e.g., any other measurable time point later than “x”, such as 12 hours).

[000337] $AUC_{(0-\infty)}$ — Area under the drug concentration-time curve calculated using linear trapezoidal summation from time 0 to infinity.

[000338] Further, partial AUC may be calculated using trapezoidal summation from time T_{max} to time t (the last measured time point of plasma concentration profile).

[000339] In one embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-1hr} for oxycodone from about 0.10 ng·hr/mL/mg to about 0.45 ng·hr/mL/mg, from about 0.15 ng·hr/mL/mg to about 0.25 ng·hr/mL/mg, or from about 0.25 ng·hr/mL/mg to about 0.35 ng·hr/mL/mg. In another embodiment, the AUC_{0-1hr} for oxycodone may be about 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, or 0.45 ng·hr/mL/mg.

[000340] In an additional embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-2hr} for oxycodone from about 0.65 ng·hr/mL/mg to about 1.50 ng·hr/mL/mg, from about 0.80 ng·hr/mL/mg to about 1.0 ng·hr/mL/mg, or from about 1.0 ng·hr/mL/mg to about 1.2 ng·hr/mL/mg. In another embodiment, the AUC_{0-2hr} for oxycodone may be

about 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, 1.0, 1.05, 1.10, 1.15, 1.20, 1.25, 1.30, 1.35, 1.40, 1.45, or 1.50 ng·hr/mL/mg.

[000341] In an additional embodiment, the pharmaceutical composition, when orally administered to a subject under fasted conditions, may produce a plasma profile characterized by an AUC_{0-2hr} for oxycodone from about 0.8 ng·hr/mL/mg to about 1.50 ng·hr/mL/mg, from about 0.80 ng·hr/mL/mg to about 1.0 ng·hr/mL/mg, or from about 1.0 ng·hr/mL/mg to about 1.2 ng·hr/mL/mg. In another embodiment, the AUC_{0-2hr} for oxycodone may be about 0.80, 0.85, 0.90, 0.95, 1.0, 1.05, 1.10, 1.15, 1.20, 1.25, 1.30, 1.35, 1.40, 1.45, or 1.50 ng·hr/mL/mg.

[000342] In a further embodiment, the pharmaceutical composition, when orally administered to a subject under fed conditions (high fat meal), may produce a plasma profile characterized by an AUC_{0-2hr} for oxycodone from about 0.65 ng·hr/mL/mg to about 1.30 ng·hr/mL/mg, from about 0.80 ng·hr/mL/mg to about 1.0 ng·hr/mL/mg, or from about 1.0 ng·hr/mL/mg to about 1.2 ng·hr/mL/mg. In another embodiment, the AUC_{0-2hr} for oxycodone may be about 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, 1.0, 1.05, 1.10, 1.15, 1.20, 1.25, or 1.30 ng·hr/mL/mg.

[000343] In a further embodiment, the pharmaceutical composition, when orally administered to a subject under fed conditions (low fat meal), may produce a plasma profile characterized by an AUC_{0-2hr} for oxycodone from about 0.65 ng·hr/mL/mg to about 1.30 ng·hr/mL/mg, from about 0.80 ng·hr/mL/mg to about 1.0 ng·hr/mL/mg, or from about 1.0 ng·hr/mL/mg to about 1.2 ng·hr/mL/mg. In another embodiment, the AUC_{0-2hr} for oxycodone may be about 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, 1.0, 1.05, 1.10, 1.15, 1.20, 1.25, or 1.30 ng·hr/mL/mg.

[000344] In an additional embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{2-48hr} for oxycodone from about 8.0 ng·hr/mL/mg to about 17.8 ng·hr/mL/mg, from about 10.0 ng·hr/mL/mg to about 11.0 ng·hr/mL/mg, or from about 11.0 ng·hr/mL/mg to about 12.0 ng·hr/mL/mg, or from about 12.0 ng·hr/mL/mg to about 13.0 ng·hr/mL/mg, or from about 13.0 ng·hr/mL/mg to about 14.0 ng·hr/mL/mg, or from about 14.0 ng·hr/mL/mg to about 15.0 ng·hr/mL/mg. In another embodiment, the AUC_{2-48hr} for oxycodone may be about 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3,

9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, 12.0, 12.1, 12.2, 12.3, 12.4, 12.5, 12.6, 12.7, 12.8, 12.9, 13.0, 13.1, 13.2, 13.3, 13.4, 13.5, 13.6, 13.7, 13.8, 13.9, 14.0, 14.1, 14.2, 14.3, 14.4, 14.5, 14.6, 14.7, 14.8, 14.9, 15.0, 15.1, 15.2, 15.3, 15.4, 15.5, 15.6, 15.7, 15.8, 15.9, 16.0, 16.1, 16.2, 16.3, 16.4, 16.5, 16.6, 16.7, 16.8, 16.9, 17.0, 17.1, 17.2, 17.3, 17.4, 17.5, 17.6, 17.7, or 17.8 ng·hr/mL/mg.

[000345] In an additional embodiment, the pharmaceutical composition, when orally administered to a subject under fasted conditions, may produce a plasma profile characterized by an AUC_{2-48hr} for oxycodone from about 8.0 ng·hr/mL/mg to about 15.1 ng·hr/mL/mg, from about 10.0 ng·hr/mL/mg to about 11.0 ng·hr/mL/mg, or from about 11.0 ng·hr/mL/mg to about 12.0 ng·hr/mL/mg, or from about 12.0 ng·hr/mL/mg to about 13.0 ng·hr/mL/mg, or from about 13.0 ng·hr/mL/mg to about 14.0 ng·hr/mL/mg, or from about 14.0 ng·hr/mL/mg to about 15.0 ng·hr/mL/mg. In another embodiment, the AUC_{2-48hr} for oxycodone may be about 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, 12.0, 12.1, 12.2, 12.3, 12.4, 12.5, 12.6, 12.7, 12.8, 12.9, 13.0, 13.1, 13.2, 13.3, 13.4, 13.5, 13.6, 13.7, 13.8, 13.9, 14.0, 14.1, 14.2, 14.3, 14.4, 14.5, 14.6, 14.7, 14.8, 14.9, 15.0, or 15.1 ng·hr/mL/mg.

[000346] In an additional embodiment, the pharmaceutical composition, when orally administered to a subject under fed conditions (high fat meal), may produce a plasma profile characterized by an AUC_{2-48hr} for oxycodone from about 9.5 ng·hr/mL/mg to about 17.8 ng·hr/mL/mg, from about 10.0 ng·hr/mL/mg to about 11.0 ng·hr/mL/mg, or from about 11.0 ng·hr/mL/mg to about 12.0 ng·hr/mL/mg, or from about 12.0 ng·hr/mL/mg to about 13.0 ng·hr/mL/mg, or from about 13.0 ng·hr/mL/mg to about 14.0 ng·hr/mL/mg, or from about 14.0 ng·hr/mL/mg to about 15.0 ng·hr/mL/mg, or from about 14.0 ng·hr/mL/mg to about 15.0 ng·hr/mL/mg. In another embodiment, the AUC_{2-48hr} for oxycodone may be about 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, 12.0, 12.1, 12.2, 12.3, 12.4, 12.5, 12.6, 12.7, 12.8, 12.9, 13.0, 13.1, 13.2, 13.3, 13.4, 13.5, 13.6, 13.7, 13.8, 13.9, 14.0, 14.1, 14.2, 14.3, 14.4, 14.5, 14.6, 14.7, 14.8, 14.9, 15.0, 15.1, 15.2, 15.3, 15.4,

15.5, 15.6, 15.7, 15.8, 15.9, 16.0, 16.1, 16.2, 16.3, 16.4, 16.5, 16.6, 16.7, 16.8, 16.9, 17.0, 17.1, 17.2, 17.3, 17.4, 17.5, 17.6, 17.7, or 17.8 ng·hr/mL/mg.

[000347] In an additional embodiment, the pharmaceutical composition, when orally administered to a subject under fed conditions (low fat meal), may produce a plasma profile characterized by an AUC_{2-48hr} for oxycodone from about 9.5 ng·hr/mL/mg to about 17.8 ng·hr/mL/mg, from about 10.0 ng·hr/mL/mg to about 11.0 ng·hr/mL/mg, or from about 11.0 ng·hr/mL/mg to about 12.0 ng·hr/mL/mg, or from about 12.0 ng·hr/mL/mg to about 13.0 ng·hr/mL/mg, or from about 13.0 ng·hr/mL/mg to about 14.0 ng·hr/mL/mg, or from about 14.0 ng·hr/mL/mg to about 15.0 ng·hr/mL/mg, or from about 14.0 ng·hr/mL/mg to about 15.0 ng·hr/mL/mg. In another embodiment, the AUC_{2-48hr} for oxycodone may be about 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, 12.0, 12.1, 12.2, 12.3, 12.4, 12.5, 12.6, 12.7, 12.8, 12.9, 13.0, 13.1, 13.2, 13.3, 13.4, 13.5, 13.6, 13.7, 13.8, 13.9, 14.0, 14.1, 14.2, 14.3, 14.4, 14.5, 14.6, 14.7, 14.8, 14.9, 15.0, 15.1, 15.2, 15.3, 15.4, 15.5, 15.6, 15.7, 15.8, 15.9, 16.0, 16.1, 16.2, 16.3, 16.4, 16.5, 16.6, 16.7, 16.8, 16.9, 17.0, 17.1, 17.2, 17.3, 17.4, 17.5, 17.6, 17.7, or 17.8 ng·hr/mL/mg.

[000348] In an additional embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{8-10hr} for oxycodone from about 0.90 ng·hr/mL/mg to about 2.30 ng·hr/mL/mg, from about 0.80 ng·hr/mL/mg to about 1.0 ng·hr/mL/mg, or from about 1.0 ng·hr/mL/mg to about 1.2 ng·hr/mL/mg, or from about 1.2 ng·hr/mL/mg to about 1.4 ng·hr/mL/mg, or from about 1.4 ng·hr/mL/mg to about 1.6 ng·hr/mL/mg, or from about 1.6 ng·hr/mL/mg to about 1.8 ng·hr/mL/mg, or from about 1.6 ng·hr/mL/mg to about 1.8 ng·hr/mL/mg, or from about 1.8 ng·hr/mL/mg to about 2.0 ng·hr/mL/mg. In another embodiment, the AUC_{8-10hr} for oxycodone may be about 0.90, 0.95, 1.0, 1.05, 1.10, 1.15, 1.20, 1.25, 1.30, 1.35, 1.40, 1.45, 1.50, 1.55, 1.60, 1.65, 1.70, 1.75, 1.80, 1.85, 1.90, 1.95, 2.0, 2.05, 2.10, 2.15, 2.20, 2.25, or 2.30 ng·hr/mL/mg.

[000349] In an additional embodiment, the pharmaceutical composition, when orally administered to a subject under fasted conditions, may produce a plasma profile characterized by an AUC_{8-10hr} for oxycodone from about 0.90 ng·hr/mL/mg to about 1.70 ng·hr/mL/mg, from about 0.90 ng·hr/mL/mg to about 1.0 ng·hr/mL/mg, or from about 1.0

ng·hr/mL/mg to about 1.2 ng·hr/mL/mg, or from about 1.2 ng·hr/mL/mg to about 1.4 ng·hr/mL/mg, or from about 1.4 ng·hr/mL/mg to about 1.6 ng·hr/mL/mg. In another embodiment, the AUC_{8-10hr} for oxycodone may be about 0.90, 0.95, 1.0, 1.05, 1.10, 1.15, 1.20, 1.25, 1.30, 1.35, 1.40, 1.45, 1.50, 1.55, 1.60, 1.65, or 1.70 ng·hr/mL/mg.

[000350] In an additional embodiment, the pharmaceutical composition, when orally administered to a subject under fed conditions (high fat meal), may produce a plasma profile characterized by an AUC_{8-10hr} for oxycodone from about 1.15 ng·hr/mL/mg to about 2.30 ng·hr/mL/mg, or from about 1.2 ng·hr/mL/mg to about 1.4 ng·hr/mL/mg, or from about 1.4 ng·hr/mL/mg to about 1.6 ng·hr/mL/mg, or from about 1.6 ng·hr/mL/mg to about 1.8 ng·hr/mL/mg, or from about 1.8 ng·hr/mL/mg to about 2.0 ng·hr/mL/mg. In another embodiment, the AUC_{8-10hr} for oxycodone may be about 1.15, 1.20, 1.25, 1.30, 1.35, 1.40, 1.45, 1.50, 1.55, 1.60, 1.65, 1.70, 1.75, 1.80, 1.85, 1.90, 1.95, 2.0, 2.05, 2.10, 2.15, 2.20, 2.25, or 2.30 ng·hr/mL/mg.

[000351] In an additional embodiment, the pharmaceutical composition, when orally administered to a subject under fed conditions (low fat meal), may produce a plasma profile characterized by an AUC_{8-10hr} for oxycodone from about 1.20 ng·hr/mL/mg to about 2.30 ng·hr/mL/mg, or from about 1.2 ng·hr/mL/mg to about 1.4 ng·hr/mL/mg, or from about 1.4 ng·hr/mL/mg to about 1.6 ng·hr/mL/mg, or from about 1.6 ng·hr/mL/mg to about 1.8 ng·hr/mL/mg, or from about 1.8 ng·hr/mL/mg to about 2.0 ng·hr/mL/mg. In another embodiment, the AUC_{8-10hr} for oxycodone may be about 1.20, 1.25, 1.30, 1.35, 1.40, 1.45, 1.50, 1.55, 1.60, 1.65, 1.70, 1.75, 1.80, 1.85, 1.90, 1.95, 2.0, 2.05, 2.10, 2.15, 2.20, 2.25, or 2.30 ng·hr/mL/mg.

[000352] In an additional embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{10-12hr}$ for oxycodone from about 0.70 ng·hr/mL/mg to about 2.0 ng·hr/mL/mg, from about 0.80 ng·hr/mL/mg to about 1.0 ng·hr/mL/mg, or from about 1.0 ng·hr/mL/mg to about 1.2 ng·hr/mL/mg, or from about 1.2 ng·hr/mL/mg to about 1.4 ng·hr/mL/mg, or from about 1.4 ng·hr/mL/mg to about 1.6 ng·hr/mL/mg, or from about 1.6 ng·hr/mL/mg to about 1.8 ng·hr/mL/mg, or from about 1.6 ng·hr/mL/mg to about 1.8 ng·hr/mL/mg. In another embodiment, the $AUC_{10-12hr}$ for oxycodone may be about 0.70, 0.75, 0.80, 0.85, 0.90,

0.95, 1.0, 1.05, 1.10, 1.15, 1.20, 1.25, 1.30, 1.35, 1.40, 1.45, 1.50, 1.55, 1.60, 1.65, 1.70, 1.75, 1.80, 1.85, 1.90, 1.95, or 2.0 ng·hr/mL/mg.

[000353] In an additional embodiment, the pharmaceutical composition, when orally administered to a subject under fasted conditions, may produce a plasma profile characterized by an $AUC_{10-12hr}$ for oxycodone from about 0.70 ng·hr/mL/mg to about 1.4 ng·hr/mL/mg, from about 0.80 ng·hr/mL/mg to about 1.0 ng·hr/mL/mg, or from about 1.0 ng·hr/mL/mg to about 1.2 ng·hr/mL/mg, or from about 1.2 ng·hr/mL/mg to about 1.4 ng·hr/mL/mg. In another embodiment, the $AUC_{10-12hr}$ for oxycodone may be about 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, 1.0, 1.05, 1.10, 1.15, 1.20, 1.25, 1.30, 1.35, or 1.40 ng·hr/mL/mg.

[000354] In an additional embodiment, the pharmaceutical composition, when orally administered to a subject under fed conditions (high fat meal), may produce a plasma profile characterized by an $AUC_{10-12hr}$ for oxycodone from about 1.0 ng·hr/mL/mg to about 1.95 ng·hr/mL/mg, or from about 1.0 ng·hr/mL/mg to about 1.2 ng·hr/mL/mg, or from about 1.2 ng·hr/mL/mg to about 1.4 ng·hr/mL/mg, or from about 1.4 ng·hr/mL/mg to about 1.6 ng·hr/mL/mg, or from about 1.6 ng·hr/mL/mg to about 1.8 ng·hr/mL/mg. In another embodiment, the $AUC_{10-12hr}$ for oxycodone may be about 1.0, 1.05, 1.10, 1.15, 1.20, 1.25, 1.30, 1.35, 1.40, 1.45, 1.50, 1.55, 1.60, 1.65, 1.70, 1.75, 1.80, 1.85, 1.90, or 1.95 ng·hr/mL/mg.

[000355] In an additional embodiment, the pharmaceutical composition, when orally administered to a subject under fed conditions (low fat meal), may produce a plasma profile characterized by an $AUC_{10-12hr}$ for oxycodone from about 0.95 ng·hr/mL/mg to about 1.85 ng·hr/mL/mg, or from about 1.0 ng·hr/mL/mg to about 1.2 ng·hr/mL/mg, or from about 1.2 ng·hr/mL/mg to about 1.4 ng·hr/mL/mg, or from about 1.4 ng·hr/mL/mg to about 1.6 ng·hr/mL/mg, or from about 1.6 ng·hr/mL/mg to about 1.8 ng·hr/mL/mg. In another embodiment, the $AUC_{10-12hr}$ for oxycodone may be about 0.95, 1.0, 1.05, 1.10, 1.15, 1.20, 1.25, 1.30, 1.35, 1.40, 1.45, 1.50, 1.55, 1.60, 1.65, 1.70, 1.75, 1.80, or 1.85 ng·hr/mL/mg.

[000356] In a further embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-4hr} for oxycodone from about 2.0 ng·hr/mL/mg to about 4.0 ng·hr/mL/mg, from about 2.5

ng·hr/mL/mg to about 3.0 ng·hr/mL/mg, or from about 3.0 ng·hr/mL/mg to about 3.5 ng·hr/mL/mg. In another embodiment, the AUC_{0-4hr} for oxycodone may be about 2.0, 2.5, 3.0, 3.5, or 4.0 ng·hr/mL/mg.

[000357] In yet another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{Tmax-t} for oxycodone from about 5.0 ng·hr/mL/mg to about 16.0 ng·hr/mL/mg, from about 8.0 ng·hr/mL/mg to about 10.5 ng·hr/mL/mg, or from about 10.5 ng·hr/mL/mg to about 14.0 ng·hr/mL/mg. In another embodiment, the AUC_{Tmax-t} for oxycodone may be about 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 11.0, 12.0, 12.5, 13.0, 13.5, 14.0, 14.5, 15.0 or 16.0 ng·hr/mL/mg.

[000358] In still another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(0-(Tmax\ of\ IR\ product+2SD))}$ for oxycodone after a single dose from about 1.0 ng·hr/mL/mg to about 3.0 ng·hr/mL/mg, from about 1.50 ng·hr/mL/mg to about 2.5 ng·hr/mL/mg, or from about 1.75 ng·hr/mL/mg to about 2.25 ng·hr/mL/mg. In another embodiment, the $AUC_{(0-(Tmax\ of\ IR\ product+2SD))}$ for oxycodone may be about 1.25, 1.3, 1.35, 1.4, 1.45, 1.5, 1.55, 1.6, 1.65, 1.7, 1.75, 1.8, 1.85, 1.9, 1.95, 2.0, 2.05, 2.1, 2.15, 2.2, 2.25, 2.3, 2.35, 2.4, 2.45, 2.5, 2.55, 2.6, 2.65, 2.7, or 2.75 ng·hr/mL/mg.

[000359] In one embodiment, the immediate release product referenced for the Partial AUC calculations is Percocet in the fasted state and the following calculation was used to determine $AUC_{(0-(Tmax\ of\ IR\ product+2SD))}$:

$$\text{oxycodone mean} \pm \text{SD} = 1.0h \pm 0.89h; T_{max} + 2SD = 2.8 \text{ hours}$$

In such embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(0-2.8)}$ for oxycodone after a single dose from about 1.0 ng·hr/mL/mg to about 3.0 ng·hr/mL/mg, from about 1.50 ng·hr/mL/mg to about 2.5 ng·hr/mL/mg, or from about 1.75 ng·hr/mL/mg to about 2.25 ng·hr/mL/mg. In another embodiment, the $AUC_{(0-2.8)}$ for oxycodone may be about 1.25, 1.3, 1.35, 1.4, 1.45, 1.5, 1.55, 1.6, 1.65, 1.7, 1.75, 1.8, 1.85, 1.9, 1.95, 2.0, 2.05, 2.1, 2.15, 2.2, 2.25, 2.3, 2.35, 2.4, 2.45, 2.5, 2.55, 2.6, 2.65, 2.7, or 2.75 ng·hr/mL/mg.

[000360] In yet another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an

$AUC_{(2.8-48)}$ for oxycodone after a single dose from about 7.5 ng•hr/mL/mg to about 15.0 ng•hr/mL/mg, from about 8.45 ng•hr/mL/mg to about 13.7 ng•hr/mL/mg, or from about 9.5 ng•hr/mL/mg to about 11.5 ng•hr/mL/mg. In another embodiment, the $AUC_{(2.8-48)}$ for oxycodone may be about 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, 12.0, 12.1, 12.2, 12.3, 12.4, or 12.5 ng•hr/mL/mg.

[000361] In one embodiment, the immediate release product referenced for the Partial AUC calculations is Percocet in the fed state and the following calculation was used to determine $AUC_{(0-(T_{max} \text{ of IR product} + 2SD))}$:

$$\text{oxycodone mean} \pm \text{SD} = 1.9\text{h} \pm 1.2\text{h}; T_{max} + 2SD = 4.3 \text{ hours}$$

In such embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(0-4.3)}$ for oxycodone after a single dose from about 1.5 ng•hr/mL/mg to about 5.5 ng•hr/mL/mg, from about 2.0 ng•hr/mL/mg to about 5.0 ng•hr/mL/mg, from about 2.5 ng•hr/mL/mg to about 4.5 ng•hr/mL/mg, or from about 3.0 ng•hr/mL/mg to about 4.0 ng•hr/mL/mg. In another embodiment, the $AUC_{(0-4.3)}$ for oxycodone may be about 1.5, 1.55, 1.6, 1.65, 1.7, 1.75, 1.8, 1.85, 1.9, 1.95, 2.0, 2.05, 2.1, 2.15, 2.2, 2.25, 2.3, 2.35, 2.4, 2.45, 2.5, 2.55, 2.6, 2.65, 2.7, 2.75, 2.8, 2.85, 2.9, 2.95, 3.0, 3.05, 3.1, 3.15, 3.2, 3.25, 3.3, 3.35, 3.4, 3.45, 3.5, 3.55, 3.6, 3.65, 3.7, 3.75, 3.8, 3.85, 3.9, 3.95, 4.0, 4.05, 4.1, 4.15, 4.2, 4.25, 4.3, 4.35, 4.4, 4.45, 4.5, 4.55, 4.6, 4.65, 4.7, 4.75, 4.8, 4.85, 4.9, 4.95, 5.0, 5.05, 5.1, 5.15, 5.2, 5.25, 5.3, 5.35, 5.4, 5.45, or 5.5 ng•hr/mL/mg.

[000362] In yet another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{(4.3-48)}$ for oxycodone after a single dose from about 5.0 ng•hr/mL/mg to about 15.0 ng•hr/mL/mg, from about 7.5 ng•hr/mL/mg to about 13.5 ng•hr/mL/mg, from about 9.0 ng•hr/mL/mg to about 12.0 ng•hr/mL/mg, or from about 9.5 ng•hr/mL/mg to about 11.5 ng•hr/mL/mg. In another embodiment, the $AUC_{(4.3-48)}$ for oxycodone may be about 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8,

10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, 12.0, 12.1, 12.2, 12.3, 12.4, 12.5, 12.6, 12.7, 12.8, 12.9, 13.0, 13.1, 13.2, 13.3, 13.4, 13.5, 13.6, 13.7, 13.8, 13.9, 14.0, 14.1, 14.2, 14.3, 14.4, 14.5, 14.6, 14.7, 14.8, 14.9, or 15.0 ng•hr/mL/mg.

[000363] In one embodiment, the pharmaceutical composition, when orally administered to a subject in a fasted state, may produce a plasma profile characterized by an AUC_{8-12hr} for oxycodone from about 3% to about 33% of the AUC_{0-t}, from about 10% to about 27% of the AUC_{0-t}, or from about 15% to about 22% of the AUC_{0-t}. In another embodiment, the pharmaceutical composition, when orally administered to a subject in a fed state, may produce a plasma profile characterized by an AUC_{8-12hr} for oxycodone from about 5% to about 35% of the AUC_{0-t}, from about 12% to about 30% of the AUC_{0-t}, or from about 15% to about 25% of the AUC_{0-t}.

[000364] In an alternate embodiment, the pharmaceutical composition, when orally administered to a subject, may provide a mean half-life of oxycodone that ranges from about 3.5 hours to about 5.5 hours, or from about 4 hours to about 5 hours. In various embodiments, the mean half-life of oxycodone may be about 3.8, 4.0, 4.2, 4.4, 4.6, 4.8, 5.0, or 5.2 hours.

[000365] In yet another embodiment, the pharmaceutical composition, when orally administered to a subject, produces a plasma profile characterized by an abuse quotient for oxycodone from about 3 to about 5. In other embodiments, the abuse quotient for oxycodone may be about 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, or 5.0.

[000366] Moreover, upon oral administration, the pharmaceutical composition disclosed herein may maintain a therapeutic plasma concentration of acetaminophen of at least about 2 mg/mL from about 1 hour to about 6 hours after administration. In another embodiment, the pharmaceutical composition may maintain a therapeutic plasma concentration of acetaminophen of at least about 2 mg/mL from about 0.75 hour to about 6.5 hours after administration. In yet another embodiment, the composition may maintain a plasma concentration of acetaminophen of at least about 1 mg/mL from about 0.5 hour to about 12 hours after administration.

[000367] In another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by a mean C_{max} for

acetaminophen from about 4.0 ng/mL/mg to about 11.0 ng/mL/mg. In other embodiments, the mean $C_{\max}$ for acetaminophen may be from about 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10.0, 10.5, or 11.0 ng/mL/mg. Moreover, the mean $C_{\max}$ for acetaminophen at steady state may range from about 6.0 ng/mL/mg to about 9.0 ng/mL/mg, from about 6.5 ng/mL/mg to about 8.5 ng/mL/mg, or from about 7.0 ng/mL/mg to about 8.0 ng/mL/mg.

[000368] In a further embodiment, the pharmaceutical composition, when orally administered to a subject, surprisingly may produce a blood plasma concentration profile characterized by a biphasic increase in blood plasma concentrations of acetaminophen. The biphasic absorption of acetaminophen may be characterized by an initial rapid absorption resulting in first peak in plasma concentrations between about 0.5 hour and 2 hours, which contributes to the early onset of action, and a second peak in plasma concentrations between about 3 hours and 7 hours after administration of the composition, which contributes to the duration or maintenance of analgesia. In some instances, the second peak may correspond to the overall $C_{\max}$ of the composition. The biphasic increase in blood plasma concentrations of acetaminophen is characterized by a plasma concentration-time profile for acetaminophen in which the slope of a line drawn between 0 hour and 2 hours is greater than the slope of a line drawn between about 2 hours and 5 hours. See FIG. 24.

[000369] This biphasic increase in acetaminophen levels resulting from the composition has several benefits. For example, the initial rapid rise in plasma levels produce quick onset of analgesia and the slower absorption provides maintenance of analgesia for an extended period of time.

[000370] In a further embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by a mean AUC for acetaminophen from about 35.0 ng·hr/mL/mg to about 80.0 ng·hr/mL/mg. In a further embodiment, the mean AUC for acetaminophen may range from about 35.0 ng·hr/mL/mg to about 60.0 ng·hr/mL/mg. In other embodiments, the mean AUC for acetaminophen may be about 35.0, 40.0, 45.0, 50.0, 55.0, 60.0, 65.0, 70.0, 75.0, or 80.0 ng·hr/mL/mg. Additionally, the mean AUC for acetaminophen at steady state may range from about

40.0 ng·hr/mL/mg to about 50.0 ng·hr/mL/mg, from about 35.0 ng·hr/mL/mg to about 45.0 ng·hr/mL/mg, or from about 37.0 ng·hr/mL/mg to about 42.0 ng·hr/mL/mg.

[000371] In yet another embodiment, the pharmaceutical composition when orally administered to a subject, may produce a plasma profile characterized by a median T_{max} for acetaminophen from about 0.5 hours to about 6.0 hours. In another embodiment, the median T_{max} for acetaminophen may be from about 1.0 hour to about 5.0 hours. In a further embodiment, the median T_{max} for acetaminophen may range from about 0.5 hour to about 4.0 hours. In still another embodiment, the median T_{max} for acetaminophen may range from about 0.75 to about 1.5 hours. In other embodiments, the median T_{max} may be about 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.2, 2.4, 2.6, 2.8, 3.0, 3.2, 3.4, 3.6, 3.8, 4.0, 4.2, 4.4, 4.6, 4.8, or 5.0 hours. Moreover, the median T_{max} for acetaminophen at steady state may range from about 0.5 hour to about 1.0 hour, or from about 0.5 hour to about 0.75 hour.

[000372] In a further embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by a median tlag for acetaminophen from about 0 hour to about 0.5 hour. In an alternate embodiment, the median tlag for acetaminophen may be from about 0 hour to about 0.25 hour. In one embodiment, the median tlag for acetaminophen may be 0 hour. In another embodiment, the median tlag for acetaminophen may be 0.25 hour.

[000373] In one embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by various partial AUCs for acetaminophen. The partial AUCs for acetaminophen are calculated as described above for oxycodone. The pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-1hr} for acetaminophen from about 1.25 ng·hr/mL/mg to about 3.25 ng·hr/mL/mg, from about 1.60 ng·hr/mL/mg to about 2.0 ng·hr/mL/mg, or from about 2.0 ng·hr/mL/mg to about 2.75 ng·hr/mL/mg. In another embodiment, the AUC_{0-1hr} for acetaminophen may be about 1.25, 1.30, 1.40, 1.50, 1.55, 1.60, 1.65, 1.70, 1.75, 1.80, 1.85, 1.90, 1.95, 2.0, 2.05, 2.10, 2.15, 2.20, 2.25, 2.30, 2.35, 2.40, 2.45, 2.50, 2.55, 2.60, 2.65, 2.70, 2.75, 2.80, 2.85, or 2.90 or ng·hr/mL/mg.

[000374] In an additional embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-2hr} for acetaminophen from about 4.25 ng·hr/mL/mg to about 14.0 ng·hr/mL/mg, or from about 5.50 ng·hr/mL/mg to about 6.0 ng·hr/mL/mg, or from about 6.0 ng·hr/mL/mg to about 7.25 ng·hr/mL/mg, or from about 7.25 ng·hr/mL/mg to about 8.5 ng·hr/mL/mg, or from about 8.5 ng·hr/mL/mg to about 9.75 ng·hr/mL/mg, or from about 9.75 ng·hr/mL/mg to about 11.0 ng·hr/mL/mg, or from about 11.0 ng·hr/mL/mg to about 12.25 ng·hr/mL/mg. In another embodiment, the AUC_{0-2hr} for acetaminophen may be about 4.25, 4.5, 4.75, 5.0, 5.25, 5.5, 5.75, 6.0, 6.25, 6.5, 6.75, 7.0, 7.25, 7.50, 7.75, 8.0, 8.25, 8.5, 8.75, 9.0, 9.25, 9.5, 9.75, 10.0, 10.25, 10.5, 10.75, 11.0, 11.25, 11.5, 11.75, 12.0, 12.25, 12.5, 12.75, 13.0, 13.25, 13.5, 13.75, or 14.0 ng·hr/mL/mg.

[000375] In an additional embodiment, the pharmaceutical composition, when orally administered to a subject under fasted conditions, may produce a plasma profile characterized by an AUC_{0-2hr} for acetaminophen from about 7.25 ng·hr/mL/mg to about 14.0 ng·hr/mL/mg, or from about 7.25 ng·hr/mL/mg to about 8.5 ng·hr/mL/mg, or from about 8.5 ng·hr/mL/mg to about 9.75 ng·hr/mL/mg, or from about 9.75 ng·hr/mL/mg to about 11.0 ng·hr/mL/mg, or from about 11.0 ng·hr/mL/mg to about 12.25 ng·hr/mL/mg. In another embodiment, the AUC_{0-2hr} for acetaminophen may be about 7.25, 7.50, 7.75, 8.0, 8.25, 8.5, 8.75, 9.0, 9.25, 9.5, 9.75, 10.0, 10.25, 10.5, 10.75, 11.0, 11.25, 11.5, 11.75, 12.0, 12.25, 12.5, 12.75, 13.0, 13.25, 13.5, 13.75, or 14.0 ng·hr/mL/mg.

[000376] In an additional embodiment, the pharmaceutical composition, when orally administered to a subject under fed conditions (high fat meal), may produce a plasma profile characterized by an AUC_{0-2hr} for acetaminophen from about 4.5 ng·hr/mL/mg to about 8.75 ng·hr/mL/mg, or from about 5.0 ng·hr/mL/mg to about 6.0 ng·hr/mL/mg, or from about 6.0 ng·hr/mL/mg to about 7.0 ng·hr/mL/mg, or from about 7.0 ng·hr/mL/mg to about 8.0 ng·hr/mL/mg. In another embodiment, the AUC_{0-2hr} for acetaminophen may be about 4.5, 4.75, 5.0, 5.25, 5.5, 5.75, 6.0, 6.25, 6.5, 6.75, 7.0, 7.25, 7.50, 7.75, 8.0, 8.25, 8.5, or 8.75 ng·hr/mL/mg.

[000377] In an additional embodiment, the pharmaceutical composition, when orally administered to a subject under fed conditions (low fat meal), may produce a plasma profile characterized by an AUC_{0-2hr} for acetaminophen from about 4.5

ng·hr/mL/mg to about 8.75 ng·hr/mL/mg, or from about 5.0 ng·hr/mL/mg to about 6.0 ng·hr/mL/mg, or from about 6.0 ng·hr/mL/mg to about 7.0 ng·hr/mL/mg, or from about 7.0 ng·hr/mL/mg to about 8.0 ng·hr/mL/mg. In another embodiment, the AUC_{0-2hr} for acetaminophen may be about 4.5, 4.75, 5.0, 5.25, 5.5, 5.75, 6.0, 6.25, 6.5, 6.75, 7.0, 7.25, 7.50, 7.75, 8.0, 8.25, 8.5, or 8.75 ng·hr/mL/mg.

[000378] In an additional embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{2-48hr} for acetaminophen from about 26.0 ng·hr/mL/mg to about 53.5 ng·hr/mL/mg, or from about 32.0 ng·hr/mL/mg to about 35.0 ng·hr/mL/mg, or from about 35.0 ng·hr/mL/mg to about 38.0 ng·hr/mL/mg, or from about 38.0 ng·hr/mL/mg to about 41.0 ng·hr/mL/mg, or from about 41.0 ng·hr/mL/mg to about 44.0 ng·hr/mL/mg, or from about 44.0 ng·hr/mL/mg to about 47.0 ng·hr/mL/mg, or from about 47.0 ng·hr/mL/mg to about 50.0 ng·hr/mL/mg. In another embodiment, the AUC_{2-48hr} for acetaminophen may be about 26.0, 26.5, 27.0, 27.5, 28.0, 28.5, 29.0, 29.5, 30.0, 30.5, 31.0, 31.5, 32.0, 32.5, 33.0, 33.5, 34.0, 34.5, 35.0, 35.5, 36.0, 36.5, 37.0, 37.5, 38.0, 38.5, 39.0, 39.5, 40.0, 40.5, 41.0, 41.5, 42.0, 42.5, 43.0, 43.5, 44.0, 44.5, 45.0, 45.5, 46.0, 46.5, 47.0, 47.5, 48.0, 48.5, 49.0, 49.5, 50.0, 50.5, 51.0, 51.5, 52.0, 52.5, 53.0, or 53.5 ng·hr/mL/mg.

[000379] In an additional embodiment, the pharmaceutical composition, when orally administered to a subject under fasted conditions, may produce a plasma profile characterized by an AUC_{2-48hr} for acetaminophen from about 26.0 ng·hr/mL/mg to about 49.0 ng·hr/mL/mg, or from about 32.0 ng·hr/mL/mg to about 35.0 ng·hr/mL/mg, or from about 35.0 ng·hr/mL/mg to about 38.0 ng·hr/mL/mg, or from about 38.0 ng·hr/mL/mg to about 41.0 ng·hr/mL/mg, or from about 41.0 ng·hr/mL/mg to about 44.0 ng·hr/mL/mg, or from about 44.0 ng·hr/mL/mg to about 47.0 ng·hr/mL/mg. In another embodiment, the AUC_{2-48hr} for acetaminophen may be about 26.0, 26.5, 27.0, 27.5, 28.0, 28.5, 29.0, 29.5, 30.0, 30.5, 31.0, 31.5, 32.0, 32.5, 33.0, 33.5, 34.0, 34.5, 35.0, 35.5, 36.0, 36.5, 37.0, 37.5, 38.0, 38.5, 39.0, 39.5, 40.0, 40.5, 41.0, 41.5, 42.0, 42.5, 43.0, 43.5, 44.0, 44.5, 45.0, 45.5, 46.0, 46.5, 47.0, 47.5, 48.0, 48.5, or 49.0.

[000380] In an additional embodiment, the pharmaceutical composition, when orally administered to a subject under fed conditions (high fat meal), may produce a plasma profile characterized by an AUC_{2-48hr} for acetaminophen from about 28.5

ng·hr/mL/mg to about 53.5 ng·hr/mL/mg, or from about 32.0 ng·hr/mL/mg to about 35.0 ng·hr/mL/mg, or from about 35.0 ng·hr/mL/mg to about 38.0 ng·hr/mL/mg, or from about 38.0 ng·hr/mL/mg to about 41.0 ng·hr/mL/mg, or from about 41.0 ng·hr/mL/mg to about 44.0 ng·hr/mL/mg, or from about 44.0 ng·hr/mL/mg to about 47.0 ng·hr/mL/mg, or from about 47.0 ng·hr/mL/mg to about 50.0 ng·hr/mL/mg. In another embodiment, the AUC_{2-48hr} for acetaminophen may be about 28.5, 29.0, 29.5, 30.0, 30.5, 31.0, 31.5, 32.0, 32.5, 33.0, 33.5, 34.0, 34.5, 35.0, 35.5, 36.0, 36.5, 37.0, 37.5, 38.0, 38.5, 39.0, 39.5, 40.0, 40.5, 41.0, 41.5, 42.0, 42.5, 43.0, 43.5, 44.0, 44.5, 45.0, 45.5, 46.0, 46.5, 47.0, 47.5, 48.0, 48.5, 49.0, 49.5, 50.0, 50.5, 51.0, 51.5, 52.0, 52.5, 53.0, or 53.5 ng·hr/mL/mg.

[000381] In an additional embodiment, the pharmaceutical composition, when orally administered to a subject under fed conditions (low fat meal), may produce a plasma profile characterized by an AUC_{2-48hr} for acetaminophen from about 28.0 ng·hr/mL/mg to about 52.5 ng·hr/mL/mg, or from about 32.0 ng·hr/mL/mg to about 35.0 ng·hr/mL/mg, or from about 35.0 ng·hr/mL/mg to about 38.0 ng·hr/mL/mg, or from about 38.0 ng·hr/mL/mg to about 41.0 ng·hr/mL/mg, or from about 41.0 ng·hr/mL/mg to about 44.0 ng·hr/mL/mg, or from about 44.0 ng·hr/mL/mg to about 47.0 ng·hr/mL/mg, or from about 47.0 ng·hr/mL/mg to about 50.0 ng·hr/mL/mg. In another embodiment, the AUC_{2-48hr} for acetaminophen may be about 28.0, 28.5, 29.0, 29.5, 30.0, 30.5, 31.0, 31.5, 32.0, 32.5, 33.0, 33.5, 34.0, 34.5, 35.0, 35.5, 36.0, 36.5, 37.0, 37.5, 38.0, 38.5, 39.0, 39.5, 40.0, 40.5, 41.0, 41.5, 42.0, 42.5, 43.0, 43.5, 44.0, 44.5, 45.0, 45.5, 46.0, 46.5, 47.0, 47.5, 48.0, 48.5, 49.0, 49.5, 50.0, 50.5, 51.0, 51.5, 52.0, or 52.5 ng·hr/mL/mg.

[000382] In an additional embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{8-10hr} for acetaminophen from about 2.3 ng·hr/mL/mg to about 6.0 ng·hr/mL/mg, or from about 2.50 ng·hr/mL/mg to about 3.0 ng·hr/mL/mg, or from about 3.0 ng·hr/mL/mg to about 3.5 ng·hr/mL/mg, or from about 3.5 ng·hr/mL/mg to about 4.0 ng·hr/mL/mg, or from about 4.0 ng·hr/mL/mg to about 4.5 ng·hr/mL/mg, or from about 4.5 ng·hr/mL/mg to about 5.0 ng·hr/mL/mg, or from about 5.0 ng·hr/mL/mg to about 5.5 ng·hr/mL/mg. In another embodiment, the AUC_{8-10hr} for acetaminophen may be about 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, or 6.0 ng·hr/mL/mg.

[000383] In an additional embodiment, the pharmaceutical composition, when orally administered to a subject under fasted conditions, may produce a plasma profile characterized by an AUC_{8-10hr} for acetaminophen from about 2.3 ng·hr/mL/mg to about 4.5 ng·hr/mL/mg, or from about 2.50 ng·hr/mL/mg to about 3.0 ng·hr/mL/mg, or from about 3.0 ng·hr/mL/mg to about 3.5 ng·hr/mL/mg, or from about 3.5 ng·hr/mL/mg to about 4.0 ng·hr/mL/mg. In another embodiment, the AUC_{8-10hr} for acetaminophen may be about 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, or 4.5 ng·hr/mL/mg.

[000384] In an additional embodiment, the pharmaceutical composition, when orally administered to a subject under fed conditions (high fat meal), may produce a plasma profile characterized by an AUC_{8-10hr} for acetaminophen from about 3.0 ng·hr/mL/mg to about 5.8 ng·hr/mL/mg, or from about 3.5 ng·hr/mL/mg to about 4.0 ng·hr/mL/mg, or from about 4.0 ng·hr/mL/mg to about 4.5 ng·hr/mL/mg, or from about 4.5 ng·hr/mL/mg to about 5.0 ng·hr/mL/mg, or from about 5.0 ng·hr/mL/mg to about 5.5 ng·hr/mL/mg. In another embodiment, the AUC_{8-10hr} for acetaminophen may be about 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, or 5.8 ng·hr/mL/mg.

[000385] In an additional embodiment, the pharmaceutical composition, when orally administered to a subject under fed conditions (low fat meal), may produce a plasma profile characterized by an AUC_{8-10hr} for acetaminophen from about 3.0 ng·hr/mL/mg to about 6.0 ng·hr/mL/mg, or from about 3.5 ng·hr/mL/mg to about 4.0 ng·hr/mL/mg, or from about 4.0 ng·hr/mL/mg to about 4.5 ng·hr/mL/mg, or from about 4.5 ng·hr/mL/mg to about 5.0 ng·hr/mL/mg, or from about 5.0 ng·hr/mL/mg to about 5.5 ng·hr/mL/mg. In another embodiment, the AUC_{8-10hr} for acetaminophen may be about 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, or 6.0 ng·hr/mL/mg.

[000386] In an additional embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC_{10-12hr}$ for acetaminophen from about 1.8 ng·hr/mL/mg to about 5.0 ng·hr/mL/mg, or from about 2.0 ng·hr/mL/mg to about 2.5 ng·hr/mL/mg, or from about 2.5 ng·hr/mL/mg to about 3.0 ng·hr/mL/mg, or from about 3.0 ng·hr/mL/mg to about 3.5 ng·hr/mL/mg, or from

about 3.5 ng·hr/mL/mg to about 4.0 ng·hr/mL/mg, or from about 4.0 ng·hr/mL/mg to about 4.5 ng·hr/mL/mg. In another embodiment, the $AUC_{10-12hr}$ for acetaminophen may be about 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, or 5.0 ng·hr/mL/mg.

[000387] In an additional embodiment, the pharmaceutical composition, when orally administered to a subject under fasted conditions, may produce a plasma profile characterized by an $AUC_{10-12hr}$ for acetaminophen from about 1.8 ng·hr/mL/mg to about 3.5 ng·hr/mL/mg, or from about 2.0 ng·hr/mL/mg to about 2.5 ng·hr/mL/mg, or from about 2.5 ng·hr/mL/mg to about 3.0 ng·hr/mL/mg, or from about 3.0 ng·hr/mL/mg to about 3.5 ng·hr/mL/mg. In another embodiment, the $AUC_{10-12hr}$ for acetaminophen may be about 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, or 3.5 ng·hr/mL/mg.

[000388] In an additional embodiment, the pharmaceutical composition, when orally administered to a subject under fed conditions (high fat meal), may produce a plasma profile characterized by an $AUC_{10-12hr}$ for acetaminophen from about 2.7 ng·hr/mL/mg to about 5.0 ng·hr/mL/mg, or from about 3.0 ng·hr/mL/mg to about 3.5 ng·hr/mL/mg, or from about 3.5 ng·hr/mL/mg to about 4.0 ng·hr/mL/mg, or from about 4.0 ng·hr/mL/mg to about 4.5 ng·hr/mL/mg. In another embodiment, the $AUC_{10-12hr}$ for acetaminophen may be about 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, or 5.0 ng·hr/mL/mg.

[000389] In an additional embodiment, the pharmaceutical composition, when orally administered to a subject under fed conditions (low fat meal), may produce a plasma profile characterized by an $AUC_{10-12hr}$ for acetaminophen from about 2.4 ng·hr/mL/mg to about 4.5 ng·hr/mL/mg, or from about 2.5 ng·hr/mL/mg to about 3.0, or from about 3.0 ng·hr/mL/mg to about 3.5 ng·hr/mL/mg, or from about 3.5 ng·hr/mL/mg to about 4.0 ng·hr/mL/mg, or from about 4.0 ng·hr/mL/mg to about 4.5 ng·hr/mL/mg. In another embodiment, the $AUC_{10-12hr}$ for acetaminophen may be about 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, or 4.5 ng·hr/mL/mg.

[000390] In a further embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-4hr} for

acetaminophen from about 10.0 ng·hr/mL/mg to about 20.0 ng·hr/mL/mg, from about 13.0 ng·hr/mL/mg to about 14.5 ng·hr/mL/mg, or from about 14.5 ng·hr/mL/mg to about 16.5 ng·hr/mL/mg. In another embodiment, the AUC_{0-4hr} for acetaminophen may be about 10.0, 11.0, 12.0, 13.0, 13.5, 14.0, 14.5, 15.0, 15.5, 16.0, 16.5, or 17.0 ng·hr/mL/mg.

[000391] In yet another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{Tmax-t} for acetaminophen from about 20.0 ng·hr/mL/mg to about 40.0 ng·hr/mL/mg, from about 23.5 ng·hr/mL/mg to about 36.0 ng·hr/mL/mg, or from about 29.0 ng·hr/mL/mg to about 31.0 ng·hr/mL/mg. In another embodiment, the AUC_{Tmax-t} for acetaminophen may be about 20.0, 21.0, 22.0, 23.0, 23.5, 24.0, 24.5, 25.0, 25.5, 26.0, 26.5, 27.0, 27.5, 28.0, 28.5, 29.0, 29.5, 30.0, 30.5, 31.0, 31.5, 32.0, 32.5, 33.0, 33.5, 34.0, 34.5, 35.0, 35.5 or 36.0 ng·hr/mL/mg.

[000392] In yet another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC(0-(Tmax\ of\ IR\ product + 2SD))$ for acetaminophen after a single dose from about 5.0 ng·hr/mL/mg to about 13.0 ng·hr/mL/mg, from about 7.2 ng·hr/mL/mg to about 11.6 ng·hr/mL/mg, or from about 8.5 ng·hr/mL/mg to about 10.0 ng·hr/mL/mg. In another embodiment, the $AUC(0-(Tmax\ of\ IR\ product + 2SD))$ for acetaminophen may be about 5.0, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, or 12.0 ng·hr/mL/mg.

[000393] In one embodiment, the immediate release product referenced for the Partial AUC calculations is Percocet in the fasted state and the following calculation was used to determine $AUC(0-(Tmax\ of\ IR\ product + 2SD))$:

$$\text{acetaminophen mean} \pm SD = 0.596h \pm 0.529h; Tmax + 2SD = 1.65\ \text{hour}$$

In such embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an $AUC(0-1.7)$ for acetaminophen after a single dose from about 5.0 ng·hr/mL/mg to about 13.0 ng·hr/mL/mg, from about 7.2 ng·hr/mL/mg to about 11.6 ng·hr/mL/mg, or from about 8.5 ng·hr/mL/mg to about 10.0 ng·hr/mL/mg. In another embodiment, the $AUC(0-1.7)$ for

acetaminophen may be about 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, or 12.0 ng•hr/mL/mg.

[000394] In still a further embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC(1.7-48) for acetaminophen after a single dose from about 25.0 ng•hr/mL/mg to about 75.0 ng•hr/mL/mg, from about 31.5 ng•hr/mL/mg to about 55.0 ng•hr/mL/mg, or from about 35.0 ng•hr/mL/mg to about 50.0 ng•hr/mL/mg. In another embodiment, the AUC(1.7-48) for acetaminophen may be about 25.0, 25.5, 26.0, 26.5, 27.0, 27.5, 28.0, 28.5, 29.0, 29.5, 30.0, 30.5, 31.0, 31.5, 32.0, 32.5, 33.0, 33.5, 34.0, 34.5, 35.0, 35.5, 36.0, 36.5, 37.0, 37.5, 38.0, 38.5, 39.0, 39.5, 40.0, 40.5, 41.0, 41.5, 42.0, 42.5, 43.0, 43.5, 44.0, 44.5, 45.0, 45.5, 46.0, 46.5, 47.0, 47.5, 48.0, 48.5, 49.0, 49.5, 50.0, 50.5, 51.0, 51.5, 52.0, 52.5, 53.0, 53.5, 54.0, 54.5, or 55.0 ng•hr/mL/mg.

[000395] In one embodiment, the immediate release product referenced for the Partial AUC calculations is Percocet in the fed state and the following calculation was used to determine AUC(0-(Tmax of IR product+ 2SD)):

$$\text{acetaminophen mean} \pm \text{SD} = 1.48\text{h} \pm 0.875\text{h}; \text{Tmax} + 2\text{SD} = 3.2 \text{ hour}$$

In such embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC(0-3.2) for acetaminophen after a single dose from about 7.0 ng•hr/mL/mg to about 21.0 ng•hr/mL/mg, from about 9.0 ng•hr/mL/mg to about 18.0 ng•hr/mL/mg, from about 10.0 ng•hr/mL/mg to about 16.0 ng•hr/mL/mg, or from about 12.0 ng•hr/mL/mg to about 15.0 ng•hr/mL/mg. In another embodiment, the AUC(0-3.2) for acetaminophen may be about 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, 12.0, 12.1, 12.2, 12.3, 12.4, 12.5, 12.6, 12.7, 12.8, 12.9, 13.0, 13.1, 13.2, 13.3, 13.4, 13.5, 13.6, 13.7, 13.8, 13.9, 14.0, 14.1, 14.2, 14.3, 14.4, 14.5, 14.6, 14.7, 14.8, 14.9, 15.0, 15.1, 15.2, 15.3, 15.4, 15.5, 15.6, 15.7, 15.8, 15.9, 16.0, 16.1, 16.2, 16.3, 16.4, 16.5, 16.6, 16.7, 16.8, 16.9, 17.0,

17.1, 17.2, 17.3, 17.4, 17.5, 17.6, 17.7, 17.8, 17.9, 18.0, 18.1, 18.2, 18.3, 18.4, 18.5, 18.6, 18.7, 18.8, 18.9, 19.0, 19.1, 19.2, 19.3, 19.4, 19.5, 19.6, 19.7, 19.8, 19.9, 20.0, 20.1, 20.2, 20.3, 20.4, 20.5, 20.6, 20.7, 20.8, 20.9, or 21.0 ng•hr/mL/mg.

[000396] In still a further embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC(3.2-48) for acetaminophen after a single dose from about 15.0 ng•hr/mL/mg to about 75.0 ng•hr/mL/mg, from about 25.0 ng•hr/mL/mg to about 55.0 ng•hr/mL/mg, from about 27.5 ng•hr/mL/mg to about 45.0 ng•hr/mL/mg, or from about 30.0 ng•hr/mL/mg to about 40.0 ng•hr/mL/mg. In another embodiment, the AUC(3.2-48) for acetaminophen may be about 15.0, 15.5, 16.0, 16.5, 17.0, 17.5, 18.0, 18.5, 19.0, 19.5, 20.0, 20.5, 21.0, 21.5, 22.0, 22.5, 23.0, 23.5, 24.0, 24.5, 25.0, 25.5, 26.0, 26.5, 27.0, 27.5, 28.0, 28.5, 29.0, 29.5, 30.0, 30.5, 31.0, 31.5, 32.0, 32.5, 33.0, 33.5, 34.0, 34.5, 35.0, 35.5, 36.0, 36.5, 37.0, 37.5, 38.0, 38.5, 39.0, 39.5, 40.0, 40.5, 41.0, 41.5, 42.0, 42.5, 43.0, 43.5, 44.0, 44.5, 45.0, 45.5, 46.0, 46.5, 47.0, 47.5, 48.0, 48.5, 49.0, 49.5, 50.0, 50.5, 51.0, 51.5, 52.0, 52.5, 53.0, 53.5, 54.0, 54.5, 55.0, 55.5, 56.0, 56.5, 57.0, 57.5, 58.0, 58.5, 59.0, 59.5, 60.0, 60.5, 61.0, 61.5, 62.0, 62.5, 63.0, 63.5, 64.0, 64.5, 65.0, 65.5, 66.0, 66.5, 67.0, 67.5, 68.0, 68.5, 69.0, 69.5, 70.0, 70.5, 71.0, 71.5, 72.0, 72.5, 73.0, 73.5, 74.0, 74.5, or 75.0 ng•hr/mL/mg.

[000397] In one embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-12hr} for acetaminophen from about 20.0 ng•hr/mL/mg to about 60.0 ng•hr/mL/mg, from about 30 ng•hr/mL/mg to about 50 ng•hr/mL/mg, from about 35 to about 45 ng•hr/mL/mg, or from about 37.5 ng•hr/mL/mg to about 42.5 ng•hr/mL/mg. In another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{0-12hr} for acetaminophen from about 20.0, 20.5, 21.0, 21.5, 22.0, 22.5, 23.0, 23.5, 24.0, 24.5, 25.0, 25.5, 26.0, 26.5, 27.0, 27.5, 28.0, 28.5, 29.0, 29.5, 30.0, 30.5, 31.0, 31.5, 32.0, 32.5, 33.0, 33.5, 34.0, 34.5, 35.0, 35.5, 36.0, 36.5, 37.0, 37.5, 38.0, 38.5, 39.0, 39.5, 40.0, 40.5, 41.0, 41.5, 42.0, 42.5, 43.0, 43.5, 44.0, 44.5, 45.0, 45.5, 46.0, 46.5, 47.0, 47.5, 48.0, 48.5, 49.0, 49.5, 50.0, 50.5, 51.0, 51.5, 52.0, 52.5, 53.0, 53.5, 54.0, 54.5, or 55.0. In a further embodiment, at AUC_{0-12hr} between about 70%-95%, about 75%-92%, or about 77%-90% of the acetaminophen has been cleared. In still another embodiment, about 80% of the acetaminophen has been cleared.

[000398] In another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{1-12hr} for acetaminophen from about 15.0 ng•hr/mL/mg to about 55.0 ng•hr/mL/mg, from about 25.0 ng•hr/mL/mg to about 45.0 ng•hr/mL/mg, or from about 30.0 to about 40.0 ng•hr/mL/mg. In another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{1-12hr} for acetaminophen from about 15, 16, 17, 18, 19, 20.0, 20.5, 21.0, 21.5, 22.0, 22.5, 23.0, 23.5, 24.0, 24.5, 25.0, 25.5, 26.0, 26.5, 27.0, 27.5, 28.0, 28.5, 29.0, 29.5, 30.0, 30.5, 31.0, 31.5, 32.0, 32.5, 33.0, 33.5, 34.0, 34.5, 35.0, 35.5, 36.0, 36.5, 37.0, 37.5, 38.0, 38.5, 39.0, 39.5, 40.0, 40.5, 41.0, 41.5, 42.0, 42.5, 43.0, 43.5, 44.0, 44.5, 45.0, 45.5, 46.0, 46.5, 47.0, 47.5, 48.0, 48.5, 49.0, 49.5, or 50.0 ng•hr/mL/mg.

[000399] In yet another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{12-36hr} for acetaminophen from about 5.0 ng•hr/mL/mg to about 25.0 ng•hr/mL/mg, from about 7.5 ng•hr/mL/mg to about 20.0 ng•hr/mL/mg, or from about 10.0 ng•hr/mL/mg to about 15.0. In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{12-36hr} for acetaminophen from about 5.0, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, 12.0, 12.1, 12.2, 12.3, 12.4, 12.5, 12.6, 12.7, 12.8, 12.9, 13.0, 13.1, 13.2, 13.3, 13.4, 13.5, 13.6, 13.7, 13.8, 13.9, 14.0, 14.1, 14.2, 14.3, 14.4, 14.5, 14.6, 14.7, 14.8, 14.9, or 15.0 ng•hr/mL/mg.

[000400] In another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{8-12hr} for acetaminophen from about 1.5 ng•hr/mL/mg to about 15.5 ng•hr/mL/mg, from about 2 ng•hr/mL/mg to about 12.25 ng•hr/mL/mg, from about 3.5 ng•hr/mL/mg to about 10 ng•hr/mL/mg, or from about 4.5 ng•hr/mL/mg to about 6.5 ng•hr/mL/mg. In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC_{8-12hr} for acetaminophen from about 1.5, 1.75, 2.0, 2.25, 2.5, 2.75, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1,

4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, or 12.0 ng•hr/mL/mg.

[000401] In one embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC(0-3hr) for acetaminophen from about 5 ng•hr/mL/mg to about 30 ng•hr/mL/mg, from about 10 ng•hr/mL/mg to about 20 ng•hr/mL/mg, or from about 13 ng•hr/mL/mg to about 17 ng•hr/mL/mg. In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC(0-3hr) for acetaminophen from about 5.0, 6.0, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, 12.0, 12.1, 12.2, 12.3, 12.4, 12.5, 12.6, 12.7, 12.8, 12.9, 13.0, 13.1, 13.2, 13.3, 13.4, 13.5, 13.6, 13.7, 13.8, 13.9, 14.0, 14.1, 14.2, 14.3, 14.4, 14.5, 14.6, 14.7, 14.8, 14.9, 15.0, 15.1, 15.2, 15.3, 15.4, 15.5, 15.6, 15.7, 15.8, 15.9, 16.0, 16.1, 16.2, 16.3, 16.4, 16.5, 16.6, 16.7, 16.8, 16.9, 17.0, 17.1, 17.2, 17.3, 17.4, 17.5, 17.6, 17.7, 17.8, 17.9, 18.0, 18.1, 18.2, 18.3, 18.4, 18.5, 18.6, 18.7, 18.8, 18.9, 19.0, 19.1, 19.2, 19.3, 19.4, 19.5, 19.6, 19.7, 19.8, 19.9, or 20.0 ng•hr/mL/mg.

[000402] In another embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC(3-36hr) for acetaminophen from about 20 ng•hr/mL/mg to about 50 ng•hr/mL/mg, from about 20 ng•hr/mL/mg to about 40 ng•hr/mL/mg, or from about 25 ng•hr/mL/mg to about 35 ng•hr/mL/mg. In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC(3-36hr) for acetaminophen from about 20, 20.5, 21, 21.5, 22, 22.5, 23, 23.5, 24, 24.5, 25, 25.5, 26, 26.5, 27, 27.5, 28, 28.5, 29, 29.5, 30, 30.5, 31, 31.5, 32, 32.5, 33, 33.5, 34, 34.5, 35, 35.5, 36, 36.5, 37, 37.5, 38, 38.5, 39, 39.5, 40, 40.5, 41, 41.5, 42, 42.5, 43, 43.5, 44, 44.5, 45, 45.5, 46, 46.5, 47, 47.5, 48, 48.5, 49, 49.5, or 50 ng•hr/mL/mg.

[000403] In one embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC0-12hr for acetaminophen from about 50% to about 90% of the AUC0-t, from about 55% to about 85% of the AUC0-t, or from about 75% to about 85% of the AUC0-t. In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC0-12hr for acetaminophen that is about 50%, 55%, 60%, 65%, 70%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84% or 85% of the AUC0-t.

[000404] In one embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC1-12hr for acetaminophen from about 40% to about 90% of the AUC0-t, from about 55% to about 85% of the AUC0-t, or from about 60% to about 75% of the AUC0-t. In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC1-12hr for acetaminophen of about 40%, 45%, 50%, 55%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, or 80% of the AUC0-t.

[000405] In one embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC12-36hr for acetaminophen from about 10% to about 40% of the AUC0-t, from about 15% to about 35% of the AUC0-t, or from about 20% to about 30% of the AUC0-t. In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC12-36hr for acetaminophen of about 10%, 12%, 14%, 16%, 18%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, or 30% of the AUC0-t.

[000406] In one embodiment, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC8-12hr for acetaminophen from about 5% to about 30% of the AUC0-t, from about 7% to about 25% of the AUC0-t, or from about 10% to about 20% of the AUC0-t. In other embodiments, the pharmaceutical composition, when orally administered to a subject, may produce a plasma profile characterized by an AUC8-12hr for acetaminophen of

about 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, or 25% of the AUC_{0-t}.

[000407] In an alternate embodiment, the pharmaceutical composition, when orally administered to a subject, may have a mean half-life of acetaminophen that ranges from about 2 hours to about 10 hours, or from about 3 hours to about 6 hours. In another embodiment, the pharmaceutical composition, when orally administered to a subject, may have a mean half-life of acetaminophen that ranges from about 3 hours to about 5 hours. In still another embodiment, the pharmaceutical composition, when orally administered to a subject, may have a mean half-life of acetaminophen that ranges from about 4 hours to about 5 hours. In various embodiments, the mean half-life of acetaminophen may be about 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 6.0, 7.0, 7.5, or 8 hours. In additional embodiments, the pharmaceutical composition, when orally administered to a subject, has a mean observed half-life of acetaminophen that is more than the mean half-life of commercially available immediate release acetaminophen products.

[000408] In another embodiment, upon administration of the pharmaceutical composition to a subject, the composition may provide at least about 4 hours to about 12 hours of drug delivery to the upper gastrointestinal tract, which includes the duodenum, jejunum, and ileum of the small intestine. In another embodiment, the composition may provide at least about 6 hours of drug delivery to the upper gastrointestinal tract. In yet a further embodiment, the composition may provide at least about 8 hours of drug delivery to the upper gastrointestinal tract. In yet a further embodiment, the composition may provide at least about 9 hours, or at least about 10 hours of drug delivery to the upper gastrointestinal tract.

[000409] In yet another embodiment, upon administration of the pharmaceutical composition to a subject, APAP undergoes presystemic metabolism in the gut and/or liver allowing only a fraction of the drug to reach the systemic circulation. The fraction of drug that is originally absorbed prior to pre-systemic metabolism is referred to as the fraction absorbed and denoted "F_{ab}." This is different from the fraction bioavailable "F," which is the fraction that reaches the systemic circulation after the metabolism in the gut and liver.

[000410] In another embodiment, 60-90% of the acetaminophen in the pharmaceutical composition, which is available for absorption into the systemic circulation, is absorbed in the upper gastrointestinal tract. In still another embodiment, 60-85% of acetaminophen in the pharmaceutical composition, which is available for absorption into the systemic circulation, is absorbed in the duodenum and jejunum. See Figure 27. Greater than 50% absorption of acetaminophen in the upper gastrointestinal tract is beneficial to a human subject because acetaminophen is poorly absorbed in the stomach and well absorbed in the small intestine and particularly, the upper segment of the gastrointestinal tract. It is therefore critical that acetaminophen is available in upper small intestine for its absorption. In one embodiment acetaminophen is released in stomach and reaches quickly into upper part of the small intestine for the absorption to take place.

[000411] In another embodiment, when about 60% to about 75% of the acetaminophen is released from the dosage form in the stomach within 2 hours following oral administration, about 10% to about 25% of the total amount of the acetaminophen in the dosage form, which is available for absorption into the systemic circulation, is absorbed in the duodenum, about 25% to about 40% is absorbed in the proximal jejunum (noted as "jejunum 1" in Figure 27), about 15% to about 20% is absorbed in the distal jejunum (noted as "jejunum 2" in Figure 27), and about 5% to about 15% is absorbed in the ileum.

[000412] In another embodiment, when about 70% to about 90% of the acetaminophen is released from the dosage form in the stomach within 4 hours following oral administration, about 10% to about 25% of the total amount of the acetaminophen in the dosage form, which is available for absorption into the systemic circulation, is absorbed in the duodenum, about 25% to about 40% is absorbed in the proximal jejunum (noted as "jejunum 1" in Figure 27), about 15% to about 20% is absorbed in the distal jejunum (noted as "jejunum 2" in Figure 27), and about 5% to about 15% is absorbed in the ileum.

[000413] In yet another embodiment, when at least about 55% of the total amount of the acetaminophen is released from the dosage form in the stomach within 1 hour after oral administration and when at least about 60% of the acetaminophen is released in the

stomach after 2 hours, about 15% to about 20% of the total amount of the acetaminophen in the dosage form, which is available for absorption into the systemic circulation, is absorbed in the duodenum, about 30% to about 37% is absorbed in the proximal jejunum, about 15% to about 18% is absorbed in the distal jejunum, and about 8% to about 10% is absorbed in the ileum.

[000414] In still another embodiment, upon administration of the pharmaceutical composition to a subject, the opioid undergoes presystemic metabolism in the gut and/or liver allowing only a fraction of the drug to reach the systemic circulation. The fraction of drug that is originally absorbed prior to pre-systemic metabolism is referred to as the fraction absorbed and denoted "Fab." In one embodiment, the opioid is oxycodone. This is different from the fraction bioavailable "F," which is the fraction that reaches the systemic circulation after metabolism in the gut and liver.

[000415] In a further embodiment, 70-95% of the oxycodone in the pharmaceutical composition, which is available for absorption into the systemic circulation, is absorbed in the upper gastrointestinal tract. In still another embodiment, 80-95% of oxycodone in the pharmaceutical composition, which is available for absorption into the systemic circulation, is absorbed in the duodenum and jejunum. See Figure 28.

[000416] In one embodiment, the composition releases the opioid and other API in the stomach to optimize drug absorption in the duodenum and jejunum. For example, when about 25% to about 50% of oxycodone is released from the dosage form in the stomach within 1 hour following oral administration, about 10% to about 45% of the total amount of the oxycodone in the dosage form, which is available for absorption into the systemic circulation, is absorbed in the duodenum, about 25% to about 50% is absorbed in the proximal jejunum (noted as "jejunum 1" in Figure 28), about 7% to about 20% is absorbed in the distal jejunum (noted as "jejunum 2" in Figure 28), and about 2% to about 15% is absorbed in the ileum.

[000417] In another embodiment, when about 45% to about 65% of oxycodone is released from the dosage form in the stomach within 2 hours following oral administration, about 10% to about 50% of the total amount of the oxycodone in the dosage form, which is available for absorption into the systemic circulation, is absorbed in the duodenum,

about 25% to about 55% is absorbed in the proximal jejunum (noted as "jejunum 1" in Figure 28), about 5% to about 25% is absorbed in the distal jejunum (noted as "jejunum 2" in Figure 28), and about 2% to about 15% is absorbed in the ileum.

[000418] In another embodiment, when about 60% to about 85% of oxycodone is released from the dosage form in the stomach within 4 hours following oral administration, about 10% to about 55% of the total amount of the oxycodone in the dosage form, which is available for absorption into the systemic circulation, is absorbed in the duodenum, about 30% to about 60% is absorbed in the proximal jejunum (noted as "jejunum 1" in Figure 28), about 10% to about 30% is absorbed in the distal jejunum (noted as "jejunum 2" in Figure 28), and about 2% to about 20% is absorbed in the ileum.

[000419] In yet another embodiment, when at least 25% of the total amount of the oxycodone is released from the dosage form in the stomach within 1 hour after oral administration and when at least 45% of the oxycodone is released in the stomach after 2 hours, about 30% to about 45% of the total amount of oxycodone in the dosage form, which is available for absorption into the systemic circulation, is absorbed in the duodenum, about 37% to about 43% is absorbed in the proximal jejunum (noted as "jejunum 1" in Figure 28), about 10% to about 15% is absorbed in the distal jejunum (noted as "jejunum 2" in Figure 28), and about 2% to about 8% is absorbed in the ileum.

[000420] In another embodiment, about 90% to about 100% of the IR dose of acetaminophen is released within about 15 minutes, 30 minutes, 45 minutes or 60 minutes after oral administration. In one embodiment, the dosage form provides a dissolution profile wherein about 20% to about 65%, about 35% to about 55% or about 40% to about 50% of the ER dose of acetaminophen remains in the ER layer between about 1 and 2 hours after administration. In one embodiment, not more than 50% of the ER dose of acetaminophen is released within about the first hour. In a further embodiment, not more than 45% or not more than 40% of the ER dose of acetaminophen is released within about the first hour. In another embodiment, not more than 85% of the ER dose of acetaminophen is released within about 4 hours. In yet another embodiment, not less than 50% is released after about 6 hours. In yet another embodiment, not less than 60% is released after about 6 hours. In one embodiment, the ER dose of acetaminophen is released over a time period of about 6 to 12, about 8 to 10, or about 9 to

10 hours in vitro. In another embodiment, the ER dose of acetaminophen is released over a time period of about 7 hours, 8 hours, 9 hours, 10 hours, 11 hours or 12 hours in vitro. In another embodiment, at least 90% or 95% of the ER dose of acetaminophen is released over a time period of about 7 hours, 8 hours, 9 hours, 10 hours, 11 hours or 12 hours in vitro.

[000421] In one embodiment, the pharmaceutical compositions disclosed herein rapidly achieve therapeutic plasma drug levels of oxycodone and acetaminophen similar to an immediate release product, which provides an early onset of action within about the first 5 minutes, 10 minutes, 15 minutes, 20 minutes, 25 minutes, 30 minutes, 35 minutes, 40 minutes, 45 minutes, 50 minutes, 55 minutes or 60 minutes after administration of the composition, but unlike an immediate release product, the pharmaceutical composition is able to maintain those therapeutic plasma drug levels of oxycodone and acetaminophen over an extended period of time (e.g., up to 12 hours). Currently, there is no pharmaceutical composition available comprising oxycodone and acetaminophen which is able to provide a patient with quick onset of analgesia and maintenance of analgesia for an extended period of time.

[000422] In yet another embodiment, upon average, within one hour of administration to a subject, the pharmaceutical composition achieves a C_{max} for acetaminophen. The C_{max} achieved by the pharmaceutical composition disclosed herein is comparable to the C_{max} obtained from a commercially-available immediate release product containing acetaminophen formulated at half the strength of the commercially-available immediate release product. The acetaminophen continues to be released from the pharmaceutical composition at a rate less than the clearance rate for the acetaminophen, so that the acetaminophen levels fall smoothly until all of the acetaminophen is absorbed. Stated another way, the acetaminophen released by the pharmaceutical composition is eliminated by the body faster than it is being absorbed. The absorption of the acetaminophen released from the pharmaceutical composition is complete in about 8 to about 10 hours so that for one half life of acetaminophen the blood supply reaching the subject's liver via the portal vein contains no additional amounts of acetaminophen beyond the amounts present in the subject's general circulation.

[000423] These additional amounts of acetaminophen delivered to the liver from the subject's portal vein are frequently caused by the absorption of acetaminophen in the subject's gastrointestinal tract. Indeed, blood from the subject's intestines passes through the liver and then on to the general circulation. When acetaminophen is undergoing absorption, blood containing acetaminophen from the absorption process passes through the subject's liver prior to entering the general circulation where the acetaminophen is diluted by the distribution and clearance processes. The metabolism of these higher acetaminophen concentrations in blood coming into the subject's liver is termed the "first pass effect." Hence, the absorption process for acetaminophen taxes a subject's metabolic systems in the liver due to these higher "first pass" concentrations. Once the absorption process is complete, the concentration of acetaminophen in the blood reaching the subject's liver through the portal vein will be the same concentration of acetaminophen as found in blood throughout the rest of the subject's body. Thus, the pharmaceutical compositions disclosed herein provide a C_{max} comparable to a commercially-available immediate-release acetaminophen product (dosed at half strength) while providing a less taxing burden on the subject's metabolic systems in the liver because the acetaminophen released by the pharmaceutical composition is eliminated by the subject's body faster than it is being absorbed. This results in decreased levels of acetaminophen in a subject's liver as compared to an immediate release dosage form of acetaminophen dosed every 6 hours.

(i) The Pharmacokinetic Profiles of the Pharmaceutical Compositions of the Invention are not Affected by the Fed or Fasted State of the Subject

[000424] Food can play a significant role in both the rate and extent of absorption of a drug. As is known, the primary function of the small intestine is to absorb food. During and after a meal, the intestine normally shows very irregular or unsynchronized contractions that move the food content back and forth and mix it with the digestive enzymes that are secreted into the intestine. However, these contractions are not entirely unsynchronized; they move the contents of the intestine slowly towards the large intestine. It normally takes about 90-120 minutes for the first part of a meal to reach the large intestine, and the last portion of the meal may not reach the large intestine for five (5) hours. Between meals, the intestine shows cycles of activity that repeat about every

90-120 minutes. The cycle consists of a short period of very few contractions (Phase I), followed by a long period of unsynchronized contractions that appear similar to the fed pattern (pre-burst, Phase II), and then a burst of strong, regular contractions that move down the intestine in a peristaltic fashion (Phase III). Phase III represents a continuation of the "housekeeper waves" that start in the stomach; its function is to sweep undigested food particles and bacteria out of the small intestine and ultimately into the large intestine.

[000425] Because non-opioid GR dosage forms of the prior art, as well as prior art extended release opioid formulations, demonstrate food effects, Applicants expected to likewise see a food effect with the pharmaceutical compositions of the present invention. Here, however, Applicants have surprisingly discovered that the pharmacokinetic profiles of a pharmaceutical composition that comprises oxycodone and acetaminophen are not substantially affected by the fed or fasted state of a human subject ingesting the composition.

[000426] In general, a fed state is defined as having consumed food within about 30 min prior to administration of the composition. The food may be a high fat meal, a low fat meal, a high calorie meal, or a low calorie meal. A fasted state may be defined as not having ingested food for at least 10 hours prior to administration of the composition. In some embodiments, the subject may have fasted for at least 10 hours prior to the first dose and refrains from ingesting food for at least one hour prior to administration of subsequent doses. In other embodiments, the fasted subject may not have ingested food for at least 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, or 10 hours prior to administration of each dose of the composition.

[000427] As the pharmacokinetic profiles of a pharmaceutical composition that comprises oxycodone and acetaminophen are not substantially affected by the fed or fasted state of a human subject, there is no substantial difference in the quantity of drug absorbed or the rate of drug absorption when the oxycodone/acetaminophen compositions are administered in the fed versus the fasted state. Without being bound to theory, Applicants believe that in a fasted state the opioid acts to reduce gastric motility in an amount sufficient to retain the dosage form in the stomach thereby mitigating the "housekeeper waves" described above.

[000428] As shown in Examples 6 and 9, the pharmacokinetic parameters of the compositions of the invention are similar when the composition is administered in the fed and fasted states. Benefits of a dosage form, which substantially eliminates the effect of food, include an increase in convenience, thereby increasing patient compliance, as the patient does not need to ensure that they are taking a dose either with or without food. This is significant because poor patient compliance can lead to adverse therapeutic outcomes.

[000429] The invention also encompasses an oxycodone/APAP pharmaceutical composition in which administration of the composition to a human subject in a fasted state is bioequivalent to administration of the composition to a human subject in a fed state wherein bioequivalence is established by: (1) a 90% Confidence Interval (CI) for AUC which is between 80% and 125%, and (2) a 90% CI for C_{max}, which is 80% and 125%. In a further embodiment, the compositions disclosed herein may be administered to a subject in need thereof without regard to food.

[000430] In other embodiments, the difference in absorption of either the opioids and/or the APIs of the invention, when administered in the fed versus the fasted state, is less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, or less than about 3%. The pharmacokinetic parameter of the other API(s) that is independent of food may be, but is not limited to, C_{max}, C_{1hr}, C_{2hr}, AUC, partial AUC, T_{max}, and T_{lag}. Additionally, the opioid(s) in the composition produce a plasma profile characterized by at least one pharmacokinetic parameter that differs by less than about 30% under fed and fasted conditions. In various embodiments, the pharmacokinetic parameter may vary by less than about 25%, 20%, 15%, 10%, or 5% under fed and fasted conditions. In one embodiment, the pharmacokinetic parameter of the opioid that is independent of food may be, but is not limited to, C_{max}, C_{1hr}, C_{2hr}, AUC, partial AUC, T_{max}, and T_{lag}.

(i) **Exemplary compositions**

[000431] In one embodiment, the pharmaceutical composition for extended release of oxycodone and acetaminophen comprises at least one extended release portion comprising acetaminophen, oxycodone or a combination thereof, and the at least one extended release portion of the composition comprises an extended release

component and oxycodone, acetaminophen, or a combination thereof. In yet another embodiment, the composition comprises an immediate release portion comprising oxycodone and acetaminophen and an extended release portion comprising oxycodone, acetaminophen and an extended release component. In still yet another embodiment, the compositions comprises two extended release portions, each comprising an extended release component and one of oxycodone or acetaminophen, and an immediate release portion comprising oxycodone and acetaminophen. In another embodiment, the composition comprises two extended release portions, each comprising an extended release component and one of oxycodone or acetaminophen, and two immediate release portions, each comprising one of oxycodone or acetaminophen. In one embodiment, the extended release component comprise at least one extended release polymer. In one exemplary embodiment, the at least one extended release polymer comprises a polyethylene oxide. The molecular weight of the polyethylene oxide may be from about 500,000 Daltons to about 10,000,000 Daltons.

[000432] In another embodiment, the pharmaceutical composition may comprise from about 5 mg to about 30 mg of oxycodone and from about 250 mg to about 1300 mg of acetaminophen. In one embodiment, the composition may comprise about 15 mg of oxycodone and about 650 mg of acetaminophen. In another exemplary embodiment, the composition may comprise about 15 mg of oxycodone and about 500 mg of acetaminophen. In still another embodiment, the composition may comprise about 15 mg of oxycodone and about 325 mg of acetaminophen. In yet another exemplary embodiment, the composition may comprise about 7.5 mg of oxycodone and about 325 mg of acetaminophen. In yet another exemplary embodiment, the composition may comprise about 5 mg of oxycodone and about 325 mg of acetaminophen. In still another exemplary embodiment, the pharmaceutical composition may comprise about 10 mg of oxycodone and about 325 mg of acetaminophen. In a further exemplary embodiment, the pharmaceutical composition may comprise about 20 mg of oxycodone and about 650 mg of acetaminophen. In another exemplary embodiment, the composition may comprise about 30 mg of oxycodone and about 650 mg of acetaminophen.

[000433] In another embodiment, the composition may comprise from about 5 mg to about 30 mg of opioid and from about 250 mg to about 1300 mg of at least one other

API. In one embodiment, the composition may comprise about 15 mg of opioid and about 650 mg of at least one other API. In another embodiment, the composition may comprise about 15 mg of opioid and about 500 mg of at least one other API. In a further embodiment, the composition may comprise about 30 mg of opioid and about 500 mg of at least one other API. In still another embodiment, the composition may comprise about 15 mg of opioid and about 325 mg of at least one other API. In yet another exemplary embodiment, the composition may comprise about 7.5 mg of opioid and about 325 mg of at least one other API. In yet another exemplary embodiment, the composition may comprise about 5 mg of opioid and about 325 mg of at least one other API. In still another exemplary embodiment, the pharmaceutical composition may comprise about 10 mg of opioid and about 325 mg of at least one other API. In a further exemplary embodiment, the pharmaceutical composition may comprise about 20 mg of opioid and about 650 mg of at least one other API. In another exemplary embodiment, the composition may comprise about 30 mg of opioid and about 650 mg of at least one other API. In yet another exemplary embodiment, the composition may comprise about 22.5 mg of opioid and about 925 mg of at least one other API.

[000434] In a further embodiment, a single dosage form of the pharmaceutical composition disclosed herein (e.g., one tablet) will provide a subject with approximately the same therapeutic benefit and pharmacokinetic profile as either two dosage forms (e.g., two tablets) of the composition formulated at half the strength, or three dosage forms (e.g., three tablets) of the composition formulated at a third of the strength. In yet another exemplary embodiment, the pharmaceutical composition comprising 15 mg of oxycodone and 650 mg of acetaminophen in a single dosage form (e.g., one tablet) will provide a subject with approximately the same therapeutic benefit and pharmacokinetic profile as two dosage forms of the pharmaceutical composition formulated at half the strength (e.g., each tablet comprising 7.5 mg of oxycodone and 325 mg of acetaminophen). In still another exemplary embodiment, the pharmaceutical composition comprising 15 mg of oxycodone and 650 mg of acetaminophen in a single dosage form (e.g., one tablet) will provide a subject with approximately the same therapeutic benefit and pharmacokinetic profile as three dosage forms of the pharmaceutical composition formulated at a third of the strength (e.g., each tablet

comprising 5 mg of oxycodone and about 216.7 mg of acetaminophen). In yet another embodiment, the pharmaceutical composition comprising 15 mg of oxycodone and 325 mg of acetaminophen in a single dosage form (e.g., one tablet) taken together with another tablet comprising 7.5 mg of oxycodone and 325 mg of acetaminophen in a single dosage form will provide a subject with approximately the same therapeutic benefit and pharmacokinetic profile as a single tablet comprising 22.5 mg of oxycodone and 650 mg of acetaminophen. In still another exemplary embodiment, the pharmaceutical composition comprising 15 mg of oxycodone and 325 mg of acetaminophen in a single dosage form (e.g., one tablet) taken together with another tablet comprising 15 mg of oxycodone and 325 mg of acetaminophen in a single dosage form will provide a subject with approximately the same therapeutic benefit and pharmacokinetic profile as a single tablet configuration totaling 30 mg of oxycodone and 650 mg of acetaminophen. In yet a further exemplary embodiment, a pharmaceutical composition comprising 21 mg of oxycodone and 650 mg of acetaminophen in a single dosage form (e.g., one tablet) will provide a subject with approximately the same therapeutic benefit and pharmacokinetic profile as two dosage forms of the pharmaceutical composition formulated at half the strength (e.g., each tablet comprising 10.5 mg of oxycodone and 325 mg of acetaminophen). In yet another exemplary embodiment, a pharmaceutical composition comprising 22.5 mg of oxycodone and 925 mg of acetaminophen in a single dosage form (e.g., one tablet) will provide a subject with approximately the same therapeutic benefit and pharmacokinetic profile as three dosage forms of the pharmaceutical composition formulated at a third of the strength (e.g., each tablet comprising 7.5 mg of oxycodone and 325 mg of acetaminophen).

[000435] In yet another embodiment, the at least one extended release portion of the composition may comprise from about 40% to about 60% (w/w) of the total amount of acetaminophen in the composition and from about 70% to about 80% (w/w) of the total amount of oxycodone in the composition, whereas the at least one immediate release portion may comprise from about 40% to about 60% (w/w) of the total amount of acetaminophen in the composition and from about 20% to about 30% (w/w) of the total amount of oxycodone in the composition. In still another embodiment, the at least one extended release portion may comprise about 50% (w/w) of the total amount of

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CLAIMS

What is claimed:

1. A solid oral dosage form comprising:
 - (a) at least one immediate release portion comprising acetaminophen and oxycodone or a pharmaceutically acceptable salt thereof; and
 - (b) at least one extended release portion comprising acetaminophen, oxycodone or a pharmaceutically acceptable salt thereof, and an extended release component;wherein the total amount of acetaminophen in the dosage form is about 325 mg to about 650 mg, and the total amount of oxycodone or its pharmaceutically acceptable salt in the dosage form is about 5 mg to about 15 mg; and
wherein upon oral administration of the dosage form to a subject, the dosage form provides a higher AUC for oxycodone when the dosage form is administered to the subject in an intact state versus when the dosage form is administered to the subject in a crushed or ground state.
2. The solid oral dosage form of claim 1, wherein the extended release component is an extended release polymer.
3. The solid oral dosage form of claim 2, wherein the extended release portion comprises, by weight of the extended release portion, from about 30% to about 50% of the extended release polymer.
4. The solid oral dosage form of claim 2, wherein the extended release polymer is polyethylene oxide.
5. The solid oral dosage form of claim 4, wherein the polyethylene oxide has a molecular weight of about 900,000 Daltons to about 7,000,000 Daltons.
6. The solid oral dosage form of claim 1, wherein upon oral administration of the dosage form to a subject, the dosage form provides a longer T_{max} for oxycodone when the dosage form is administered to the subject in a

crushed or ground state versus when the dosage form is administered to the subject in an intact state.

7. The solid oral dosage form of claim 6, wherein administration of the dosage form to a subject produces a mean $T_{\max}$ for oxycodone that is at least about 30 minutes greater when the dosage form is administered in a crushed or ground state versus when the dosage form is administered in an intact state.

8. The solid oral dosage form of claim 6, wherein administration of the dosage form to a subject produces a mean $T_{\max}$ for oxycodone that is at least about 45 minutes greater when the dosage form is administered in a crushed or ground state versus when the dosage form is administered in an intact state.

9. The solid oral dosage form of claim 6, wherein administration of the dosage form to a subject produces a mean $T_{\max}$ for oxycodone that is at least about 60 minutes greater when the dosage form is administered in a crushed or ground state versus when the dosage form is administered in an intact state.

10. The solid oral dosage form of claim 6, wherein administration of the dosage form to a subject produces a mean $T_{\max}$ for oxycodone that is at least about 75 minutes greater when the dosage form is administered in a crushed or ground state versus when the dosage form is administered in an intact state.

11. The solid oral dosage form of claim 6, wherein administration of the dosage form to a subject produces a mean $T_{\max}$ for oxycodone that is at least about 90 minutes greater when the dosage form is administered in a crushed or ground state versus when the dosage form is administered in an intact state.

12. The solid oral dosage form of claim 6, wherein administration of the dosage form to a subject produces a mean $T_{\max}$ for oxycodone that is at least about 105 minutes greater when the dosage form is administered in a crushed or ground state versus when the dosage form is administered in an intact state.

13. The solid oral dosage form of claim 6, wherein administration of the dosage form to a subject produces a mean T_{max} for oxycodone that is at least about 120 minutes greater when the dosage form is administered in a crushed or ground state versus when the dosage form is administered in an intact state.

14. The solid oral dosage form of claim 1, wherein upon oral administration of the dosage form to a subject, the dosage form provides a AUC(0-1hr) for oxycodone that is about 50% to about 1000% higher when the dosage form is administered to the subject in an intact state versus when the dosage form is administered to the subject in a crushed or ground state.

15. The solid oral dosage form of claim 14, wherein upon oral administration of the dosage form to a subject, the dosage form provides a AUC(0-1hr) for oxycodone that is about 100% to about 900% higher when the dosage form is administered to the subject in an intact state versus when the dosage form is administered to the subject in a crushed or ground state.

16. The solid oral dosage form of claim 14, wherein upon oral administration of the dosage form to a subject, the dosage form provides a AUC(0-1hr) for oxycodone that is about 200% to about 800% higher when the dosage form is administered to the subject in an intact state versus when the dosage form is administered to the subject in a crushed or ground state.

17. The solid oral dosage form of claim 14, wherein upon oral administration of the dosage form to a subject, the dosage form provides a AUC(0-1hr) for oxycodone that is about 300% to about 700% higher when the dosage form is administered to the subject in an intact state versus when the dosage form is administered to the subject in a crushed or ground state.

18. The solid oral dosage form of claim 1, wherein upon oral administration of the dosage form to a subject, the dosage form provides a AUC(0-2hr) for oxycodone that is about 50% to about 500% higher when the

dosage form is administered to the subject in an intact state versus when the dosage form is administered to the subject in a crushed or ground state.

19. The solid oral dosage form of claim 18, wherein upon oral administration of the dosage form to a subject, the dosage form provides a AUC(0-2hr) for oxycodone that is about 100% to about 400% higher when the dosage form is administered to the subject in an intact state versus when the dosage form is administered to the subject in a crushed or ground state.

20. The solid oral dosage form of claim 18, wherein upon oral administration of the dosage form to a subject, the dosage form provides a AUC(0-2hr) for oxycodone that is about 150% to about 300% higher when the dosage form is administered to the subject in an intact state versus when the dosage form is administered to the subject in a crushed or ground state.

21. The solid oral dosage form of claim 18, wherein upon oral administration of the dosage form to a subject, the dosage form provides a AUC(0-2hr) for oxycodone that is about 50% to about 250% higher when the dosage form is administered to the subject in an intact state versus when the dosage form is administered to the subject in a crushed or ground state.

22. The solid dosage form of claim 1, wherein upon oral administration of the dosage form to a subject, the dosage form provides a Tmax for oxycodone that decreases by about 5% to about 70% when the dosage form is administered in an intact state versus when the dosage form is administered in a crushed or ground state.

23. The solid dosage form of claim 22, wherein the Tmax for oxycodone is decreased by about 5% to about 50% when the dosage form is administered in an intact state versus when the dosage form is administered in a crushed or ground state.

24. The solid dosage form of claim 22, wherein the Tmax for oxycodone is decreased by about 5% to about 40% when the dosage form is administered in an intact state versus when the dosage form is administered in a crushed or ground state.

25. The solid dosage form of claim 22, wherein the Tmax for oxycodone is decreased by about 5% to about 30% when the dosage form is administered in an intact state versus when the dosage form is administered in a crushed or ground state.

26. The solid dosage form of claim 22, wherein the Tmax for oxycodone is decreased by about 5% to about 20% when the dosage form is administered in an intact state versus when the dosage form is administered in a crushed or ground state.

27. The solid dosage form of claim 22, wherein the Tmax for oxycodone is decreased by about 10% to about 40% when the dosage form is administered in an intact state versus when the dosage form is administered in a crushed or ground state.

28. The solid dosage form of claim 22, wherein the Tmax for oxycodone is decreased by about 20% to about 60% when the dosage form is administered in an intact state versus when the dosage form is administered in a crushed or ground state.

29. The solid dosage form of claim 6, wherein the solid dosage form contains a total of about 325 mg of acetaminophen and about 5 mg of oxycodone or its pharmaceutically acceptable salt.

30. The solid dosage form of claim 6, wherein the solid dosage form contains a total of about 325 mg of acetaminophen and about 7.5 mg of oxycodone or its pharmaceutically acceptable salt.

31. The solid dosage form of claim 6, wherein the solid dosage form contains a total of about 325 mg of acetaminophen and about 10 mg of oxycodone or its pharmaceutically acceptable salt.

32. The solid dosage form of claim 6, wherein the solid dosage form contains a total of about 325 mg of acetaminophen and about 15 mg of oxycodone or its pharmaceutically acceptable salt.

33. The solid dosage form of claim 14, wherein the solid dosage form contains a total of about 325 mg of acetaminophen and about 5 mg of oxycodone or its pharmaceutically acceptable salt.

34. The solid dosage form of claim 14, wherein the solid dosage form contains a total of about 325 mg of acetaminophen and about 7.5 mg of oxycodone or its pharmaceutically acceptable salt.

35. The solid dosage form of claim 14, wherein the solid dosage form contains a total of about 325 mg of acetaminophen and about 10 mg of oxycodone or its pharmaceutically acceptable salt.

36. The solid dosage form of claim 14, wherein the solid dosage form contains a total of about 325 mg of acetaminophen and about 15 mg of oxycodone or its pharmaceutically acceptable salt.

37. The solid dosage form of claim 18, wherein the solid dosage form contains a total of about 325 mg of acetaminophen and about 5 mg of oxycodone or its pharmaceutically acceptable salt.

38. The solid dosage form of claim 18, wherein the solid dosage form contains a total of about 325 mg of acetaminophen and about 7.5 mg of oxycodone or its pharmaceutically acceptable salt.

39. The solid dosage form of claim 18, wherein the solid dosage form contains a total of about 325 mg of acetaminophen and about 10 mg of oxycodone or its pharmaceutically acceptable salt.

40. The solid dosage form of claim 18, wherein the solid dosage form contains a total of about 325 mg of acetaminophen and about 15 mg of oxycodone or its pharmaceutically acceptable salt.

41. The solid oral dosage form of claim 1, wherein upon oral administration of the dosage form to a subject, the dosage form provides a longer T_{max} for acetaminophen when the dosage form is administered to the subject in a crushed or ground state versus when the dosage form is administered to the subject in an intact state.

42. The solid oral dosage form of claim 41, wherein administration of the dosage form to a subject produces a mean T_{max} for acetaminophen that is at least about one hour greater when the dosage form is administered in a crushed or ground state as compared to an intact state.

43. The solid oral dosage form of claim 1, wherein upon oral administration of the dosage form to a subject, the dosage form provides a higher C_{max} for acetaminophen when the dosage form is administered to the subject in an intact state versus when the dosage form is administered to the subject in a crushed or ground state.

44. The solid oral dosage form of claim 1, wherein the total amount of acetaminophen in the composition is about 325 mg and the total amount of oxycodone or its pharmaceutically acceptable salt in the dosage form is about 7.5 mg.

45. The solid oral dosage form of claim 1, wherein the total amount of acetaminophen in the dosage form is about 325 mg and the total amount of

oxycodone or its pharmaceutically acceptable salt in the dosage form is about 5 mg.

46. The solid oral dosage form of claim 1, wherein the total amount of acetaminophen in the dosage form is about 325 mg and the total amount of oxycodone or its pharmaceutically acceptable salt in the dosage form is about 10 mg.

47. The solid oral dosage form of claim 1, wherein the total amount of acetaminophen in the dosage form is about 325 mg and the total amount of oxycodone or its pharmaceutically acceptable salt in the dosage form is about 15 mg.

48. A solid oral dosage form comprising:

(a) at least one immediate release portion comprising acetaminophen and oxycodone or a pharmaceutically acceptable salt thereof; and

(b) at least one extended release portion comprising acetaminophen, oxycodone or a pharmaceutically acceptable salt thereof, and an extended release component;

wherein the total amount of acetaminophen in the dosage form is about 325 mg to about 650 mg, and the total amount of oxycodone or its pharmaceutically acceptable salt in the dosage form is about 5 mg to about 15 mg; and

wherein upon oral administration of the dosage form to a subject, the dosage form provides an abuse quotient for oxycodone that is higher when the dosage form is administered to the subject in an intact state versus when the dosage form is administered to the subject in a crushed or ground state.

49. The solid oral dosage form of claim 48, wherein the abuse quotient for oxycodone is decreased by about 5% to about 90% when the dosage form is administered in a crushed or ground state versus when the dosage form is administered in an intact state.

50. The solid oral dosage form of claim 49, wherein the abuse quotient for oxycodone is decreased by about 10% to about 80% when the dosage form is administered in a crushed or ground state versus when the dosage form is administered in an intact state.

51. The solid oral dosage form of claim 49, wherein the abuse quotient for oxycodone is decreased by about 15% to about 70% when the dosage form is administered in a crushed or ground state versus when the dosage form is administered in an intact state.

52. The solid oral dosage form of claim 49, wherein the abuse quotient for oxycodone is decreased by about 20% to about 60% when the dosage form is administered in a crushed or ground state versus when the dosage form is administered in an intact state.

53. The solid oral dosage form of claim 48, wherein the solid dosage form contains a total of about 325 mg of acetaminophen and about 5 mg of oxycodone or its pharmaceutically acceptable salt.

54. The solid oral dosage form of claim 48, wherein the solid dosage form contains a total of about 325 mg of acetaminophen and about 7.5 mg of oxycodone or its pharmaceutically acceptable salt.

55. The solid oral dosage form of claim 48, wherein the solid dosage form contains a total of about 325 mg of acetaminophen and about 10 mg of oxycodone or its pharmaceutically acceptable salt.

56. The solid oral dosage form of claim 48, wherein the solid dosage form contains a total of about 325 mg of acetaminophen and about 15 mg of oxycodone or its pharmaceutically acceptable salt.

57. The solid oral dosage form of claim 48, wherein the extended release component is an extended release polymer.

58. The solid oral dosage form of claim 57, wherein the extended release portion comprises, by weight of the extended release portion, from about 30% to about 50% of the extended release polymer.

59. The solid oral dosage form of claim 57, wherein the extended release polymer is polyethylene oxide.

60. The solid oral dosage form of claim 59, wherein the polyethylene oxide has a molecular weight of about 900,000 Daltons to about 7,000,000 Daltons.

61. The solid oral dosage form of claim 48, wherein administration of the dosage form to a subject produces a mean $T_{\max}$ for oxycodone that is at least about 30 minutes greater when the dosage form is administered in a crushed or ground state versus when the dosage form is administered in an intact state.

62. The solid oral dosage form of claim 48, wherein administration of the dosage form to a subject produces a mean $T_{\max}$ for oxycodone that is at least about 45 minutes greater when the dosage form is administered in a crushed or ground state versus when the dosage form is administered in an intact state.

63. The solid oral dosage form of claim 48, wherein administration of the dosage form to a subject produces a mean $T_{\max}$ for oxycodone that is at least about 60 minutes greater when the dosage form is administered in a crushed or ground state versus when the dosage form is administered in an intact state.

64. The solid oral dosage form of claim 48, wherein administration of the dosage form to a subject produces a mean $T_{\max}$ for oxycodone that is at least about 75 minutes greater when the dosage form is administered in a crushed or ground state versus when the dosage form is administered in an intact state.

65. The solid oral dosage form of claim 48, wherein administration of the dosage form to a subject produces a mean $T_{\max}$ for oxycodone that is at least

about 90 minutes greater when the dosage form is administered in a crushed or ground state versus when the dosage form is administered in an intact state.

66. A solid oral dosage form comprising:

(a) at least one immediate release portion comprising acetaminophen and oxycodone or a pharmaceutically acceptable salt thereof; and

(b) at least one extended release portion comprising acetaminophen, oxycodone or a pharmaceutically acceptable salt thereof, and an extended release component;

wherein the total amount of acetaminophen in the dosage form is about 325 mg to about 650 mg, and the total amount of oxycodone or its pharmaceutically acceptable salt in the dosage form is about 5 mg to about 15 mg; and

wherein administration of the dosage form to a subject produces a mean T_{max} for oxycodone that is at least about 30 minutes greater when the dosage form is administered in a crushed or ground state versus when the dosage form is administered in an intact state.

67. The solid oral dosage form of claim 66, wherein administration of the dosage form to a subject produces a mean T_{max} for oxycodone that is at least about 60 minutes greater when the dosage form is administered in a crushed or ground state versus when the dosage form is administered in an intact state.

68. The solid oral dosage form of claim 66, wherein administration of the dosage form to a subject produces a mean T_{max} for oxycodone that is at least about 75 minutes greater when the dosage form is administered in a crushed or ground state versus when the dosage form is administered in an intact state.

69. The solid oral dosage form of claim 66, wherein administration of the dosage form to a subject produces a mean T_{max} for oxycodone that is at least about 90 minutes greater when the dosage form is administered in a crushed or ground state versus when the dosage form is administered in an intact state.

70. The solid oral dosage form of claim 66, wherein the extended release portion comprises, by weight of the extended release portion, from about 30% to about 50% of an extended release polymer comprising polyethylene oxide having a molecular weight of about 900,000 Daltons to about 7,000,000 Daltons.

71. The solid oral dosage form of claim 66, wherein the solid dosage form contains a total of about 325 mg of acetaminophen and about 5 mg of oxycodone or its pharmaceutically acceptable salt.

72. The solid oral dosage form of claim 66, wherein the solid dosage form contains a total of about 325 mg of acetaminophen and about 7.5 mg of oxycodone or its pharmaceutically acceptable salt.

73. The solid oral dosage form of claim 66, wherein the solid dosage form contains a total of about 325 mg of acetaminophen and about 10 mg of oxycodone or its pharmaceutically acceptable salt.

74. The solid oral dosage form of claim 66, wherein the solid dosage form contains a total of about 325 mg of acetaminophen and about 15 mg of oxycodone or its pharmaceutically acceptable salt.

75. The solid oral dosage form of claim 70, wherein upon oral administration of the dosage form to a subject, the dosage form provides a AUC(0-1hr) for oxycodone that is about 50% to about 1000% higher when the dosage form is administered to the subject in an intact state versus when the dosage form is administered to the subject in a crushed or ground state.

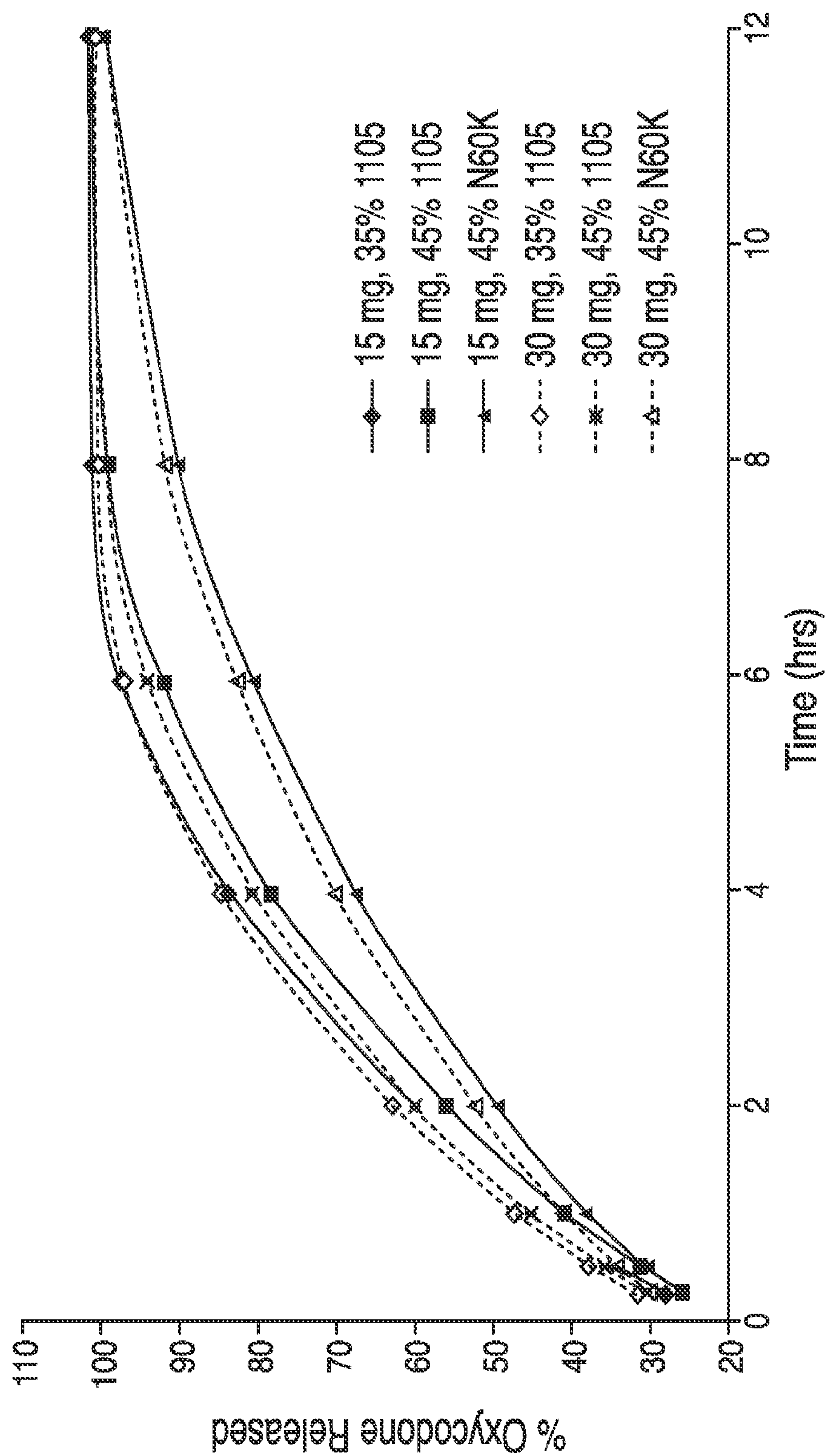


FIG. 1

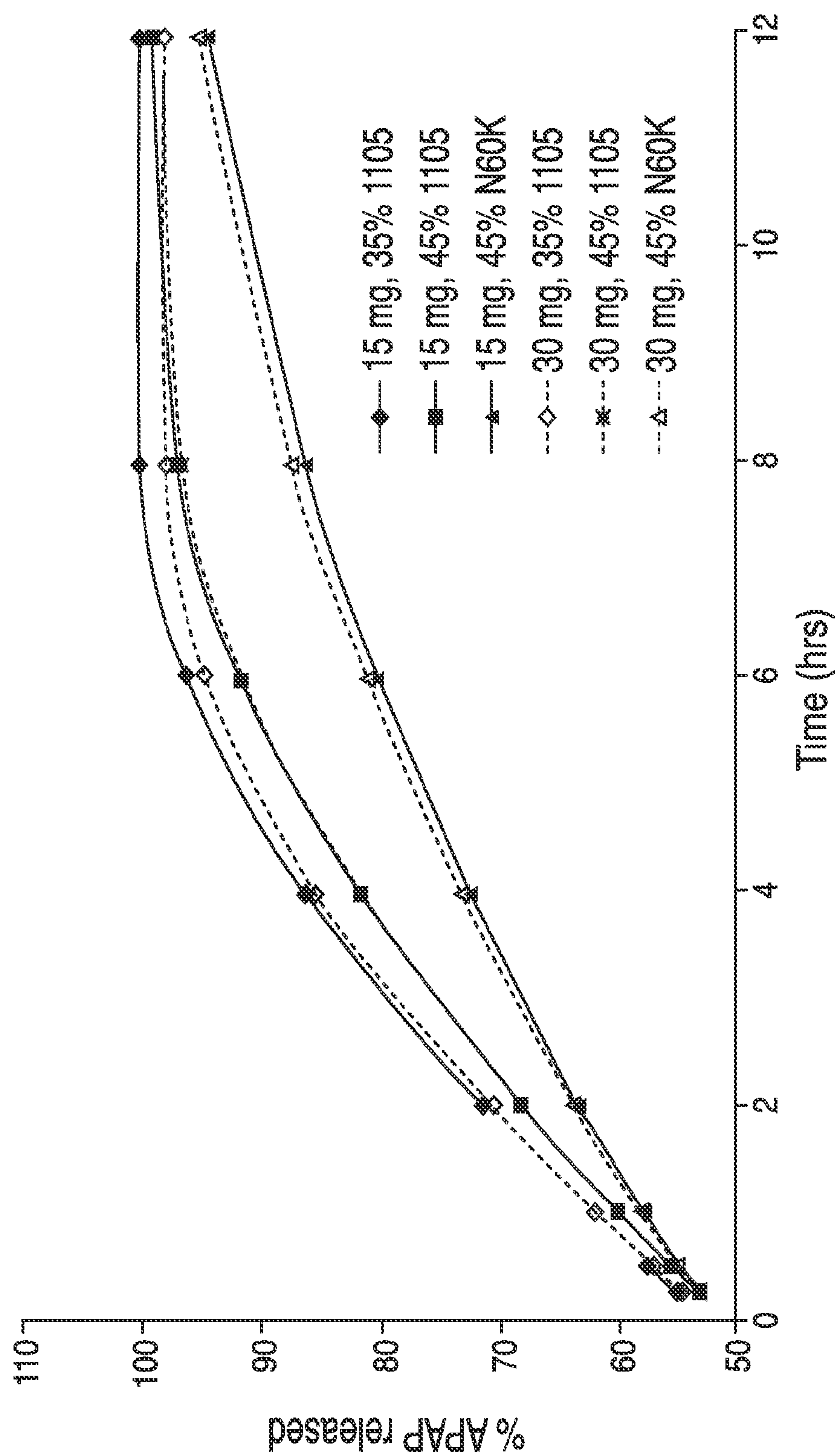


FIG. 2

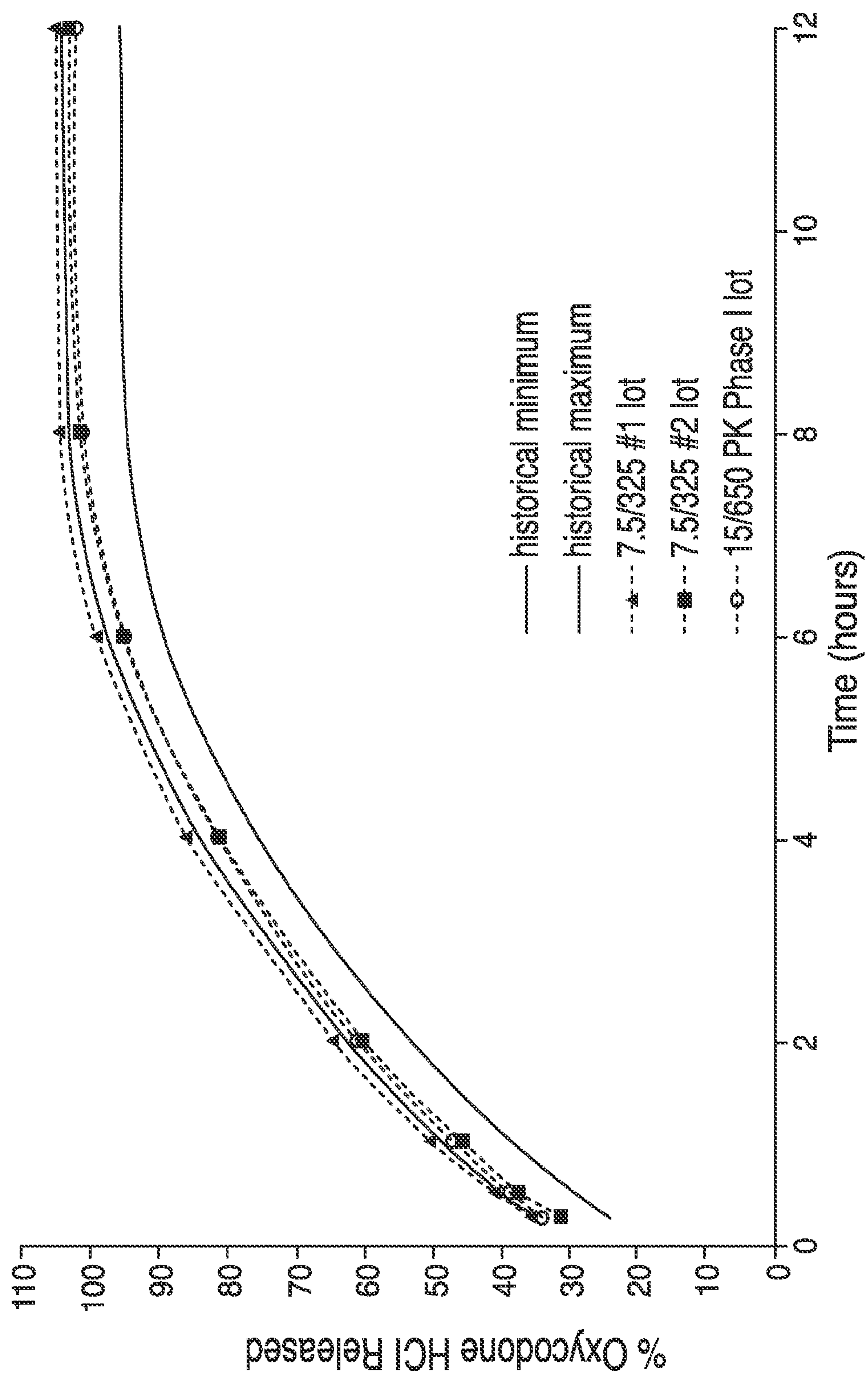


FIG. 3

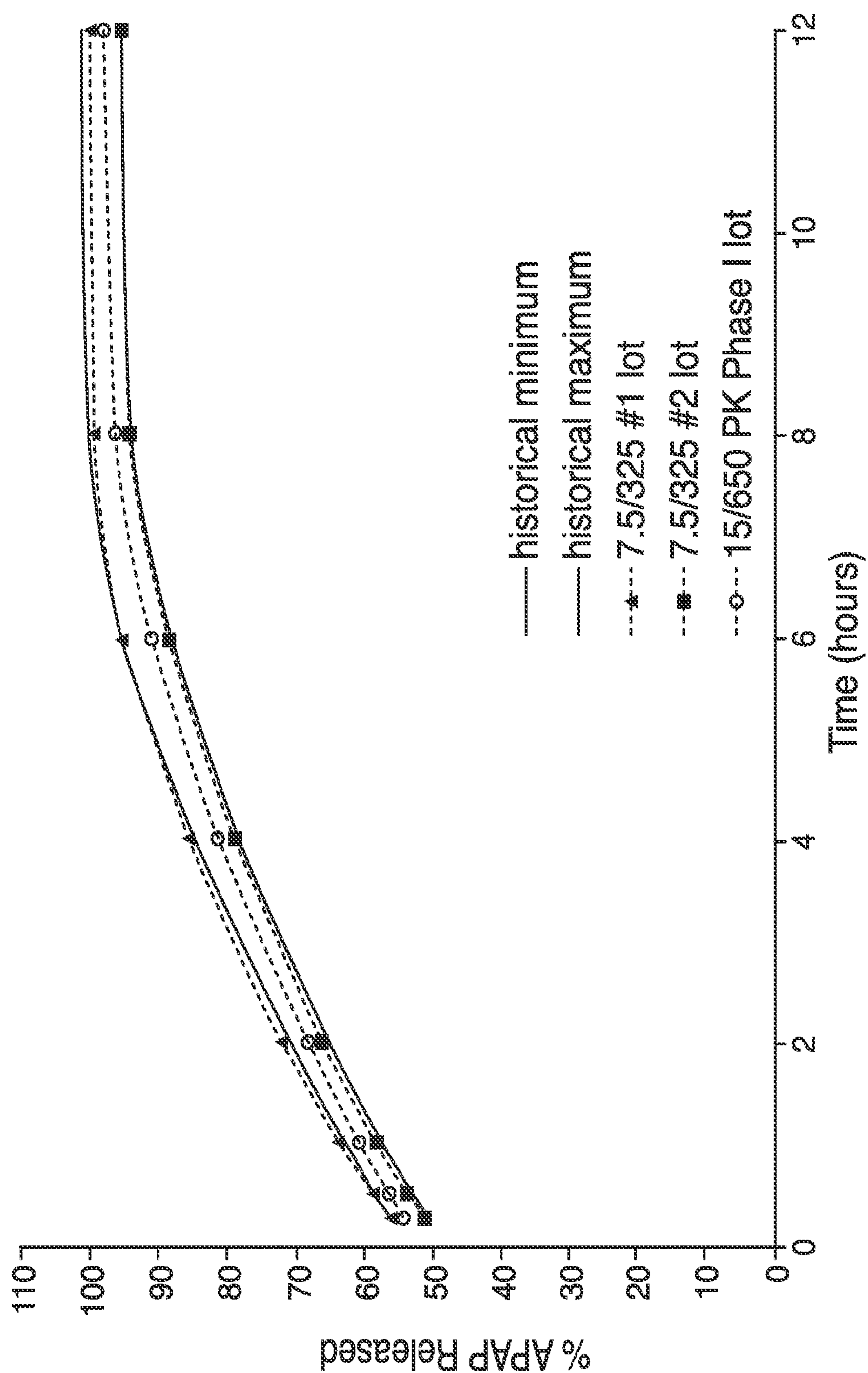


FIG. 4

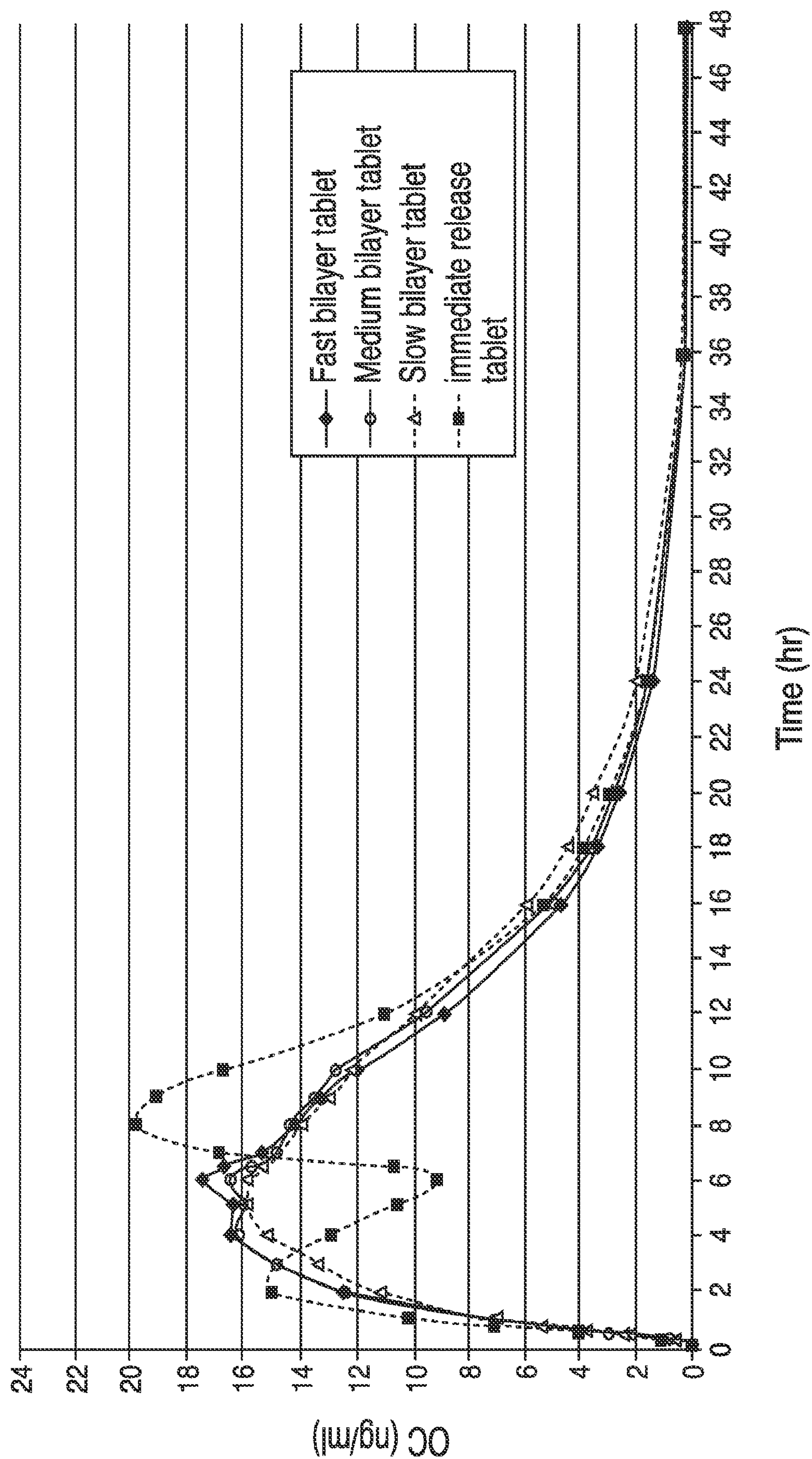


FIG. 5

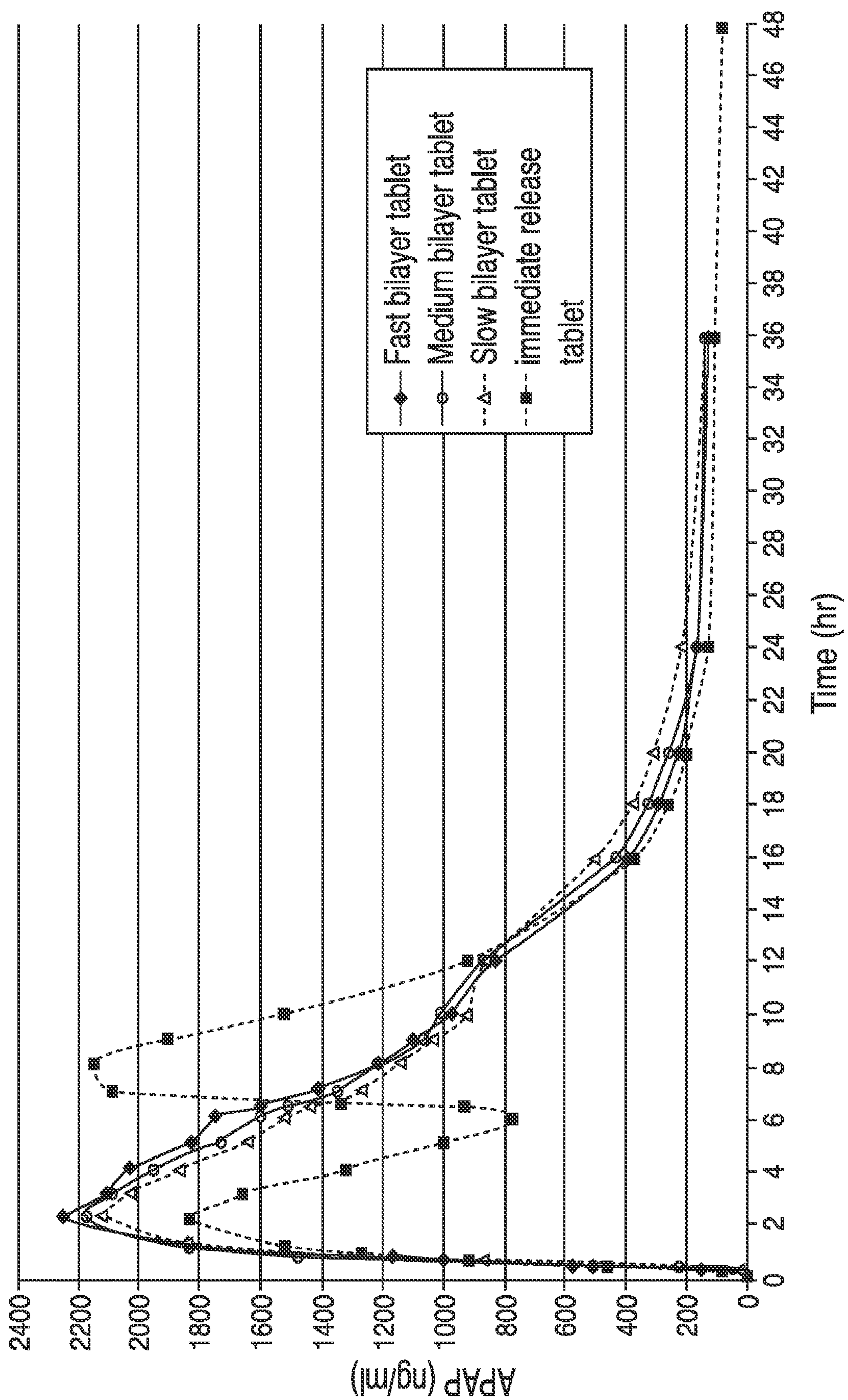


FIG. 6

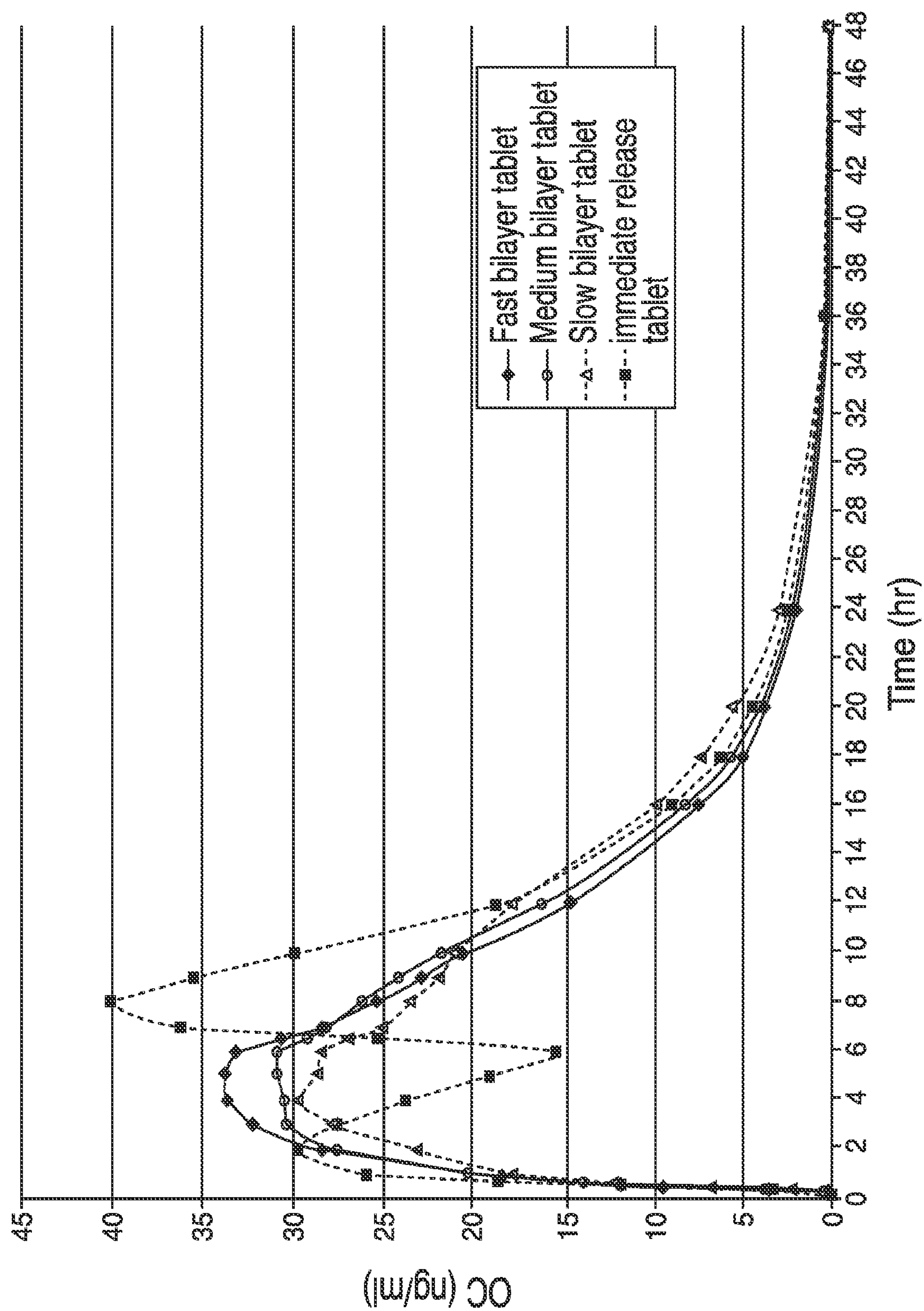


FIG. 7

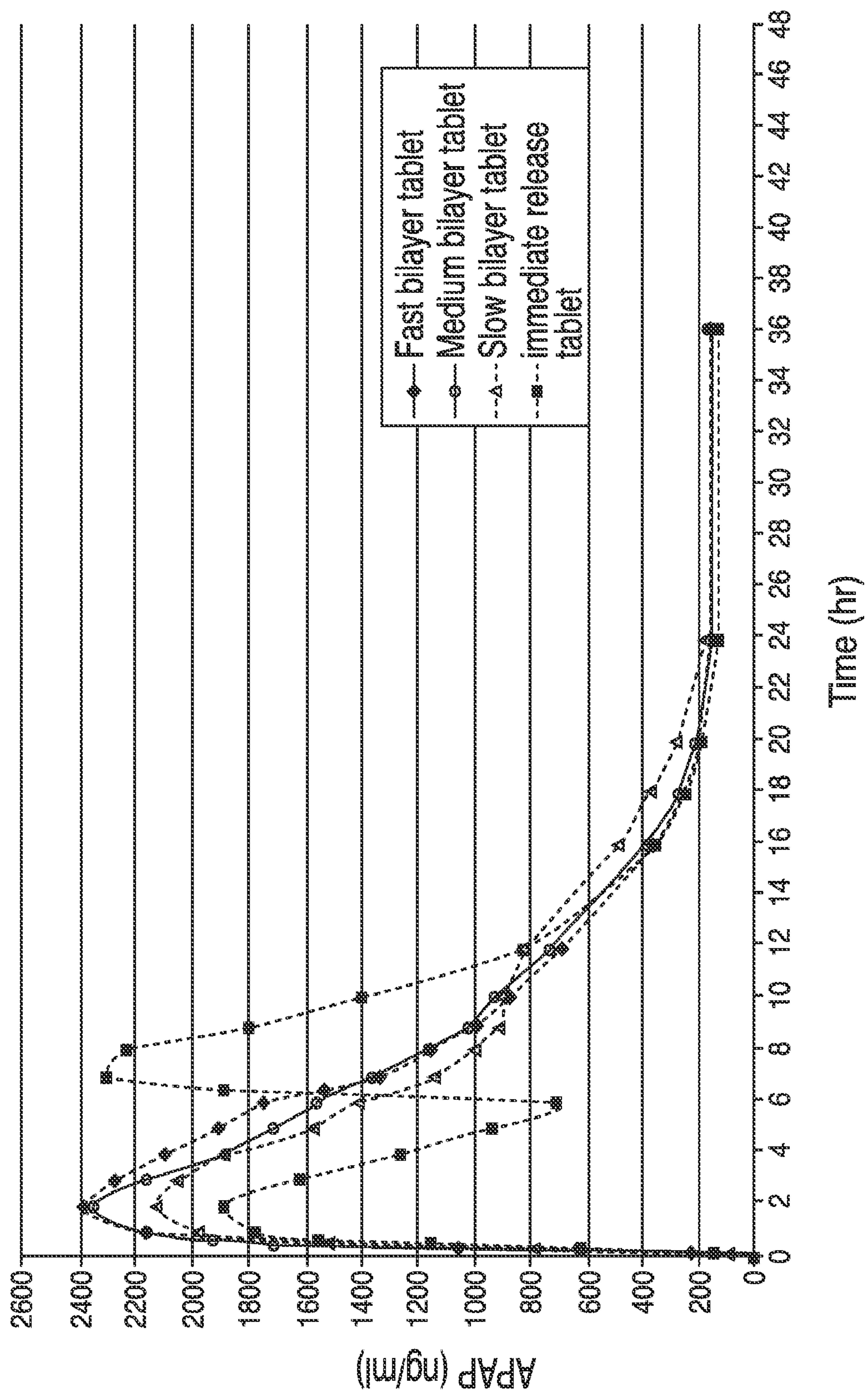


FIG. 8

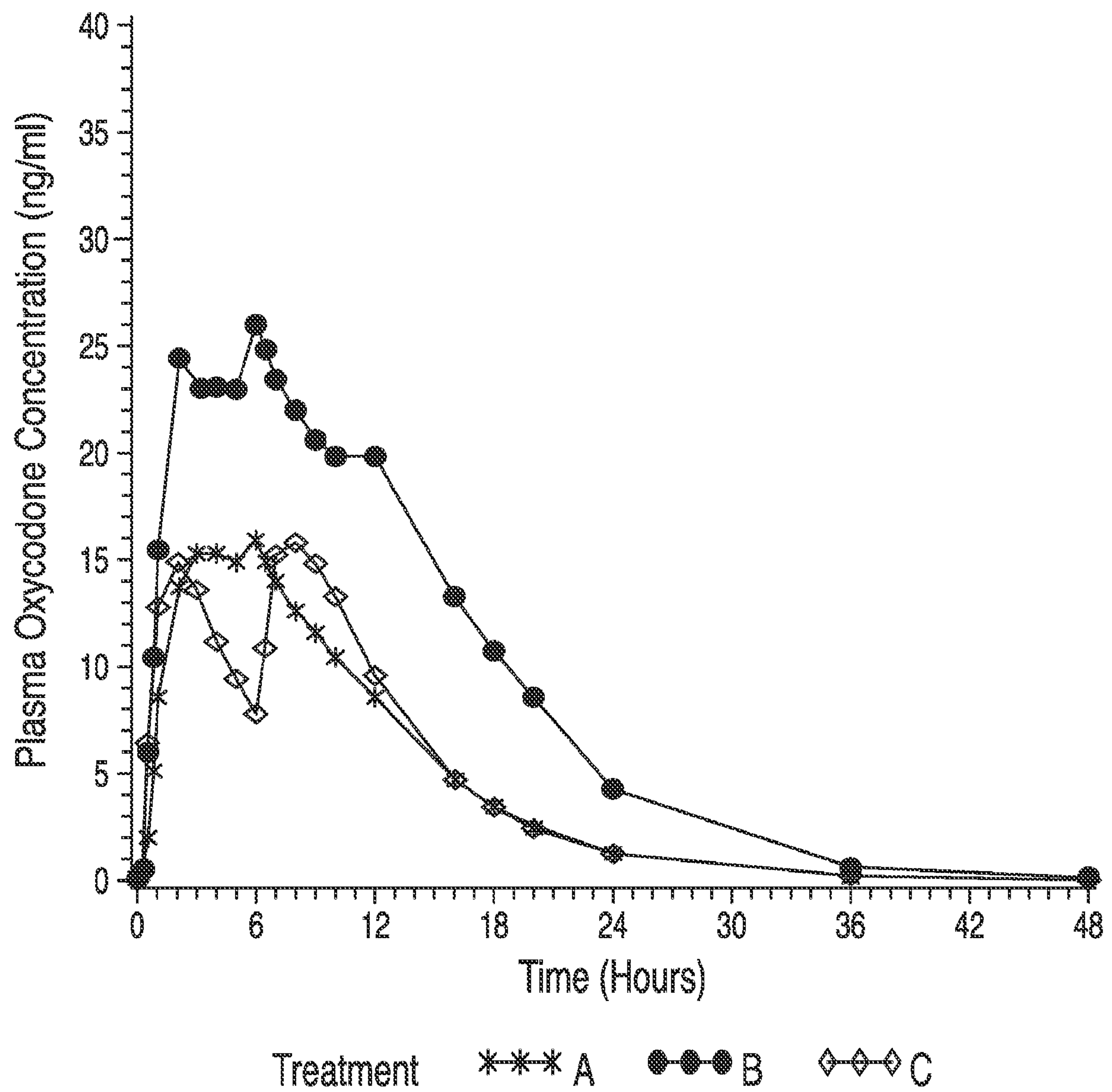


FIG. 9

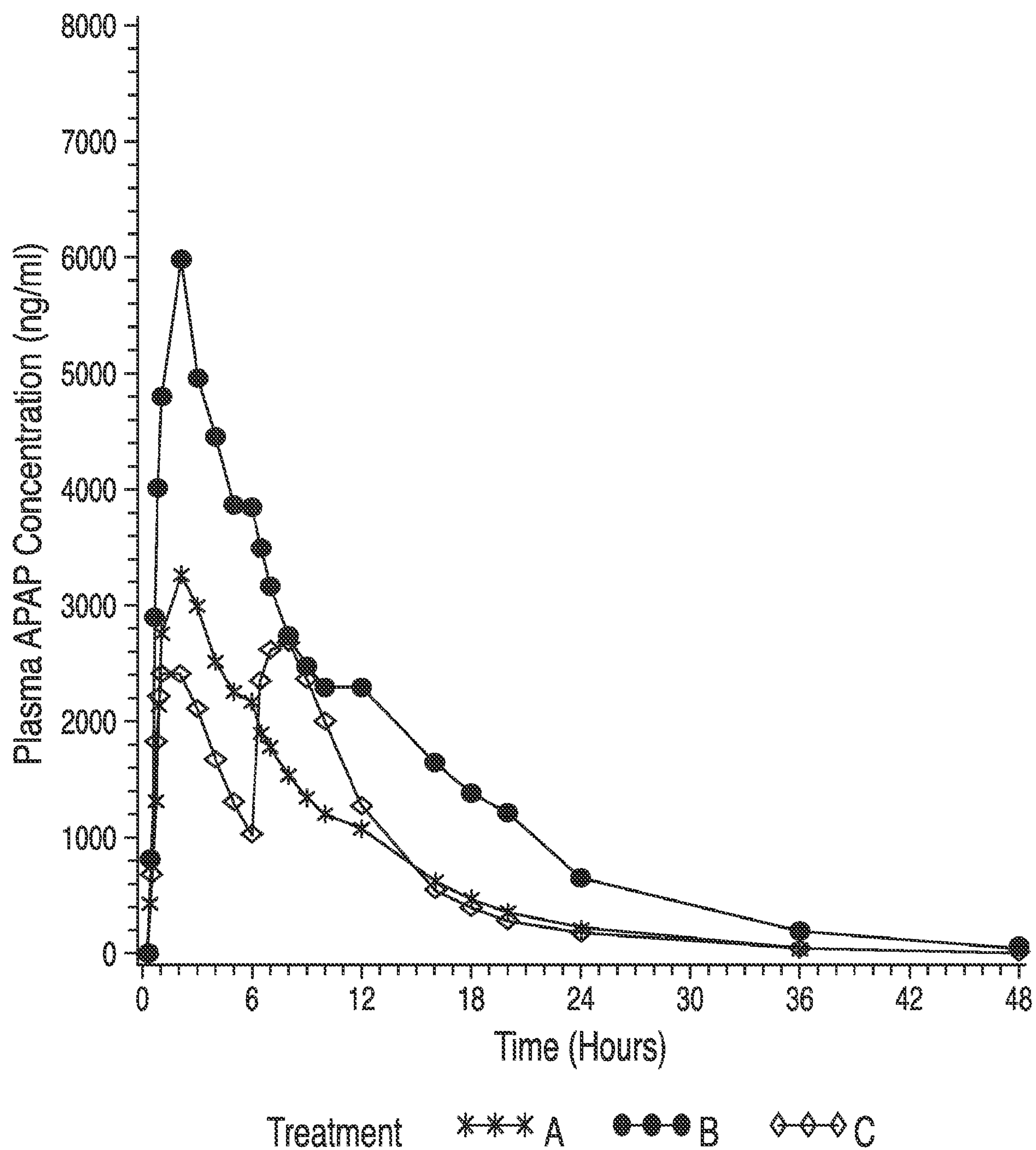


FIG. 10

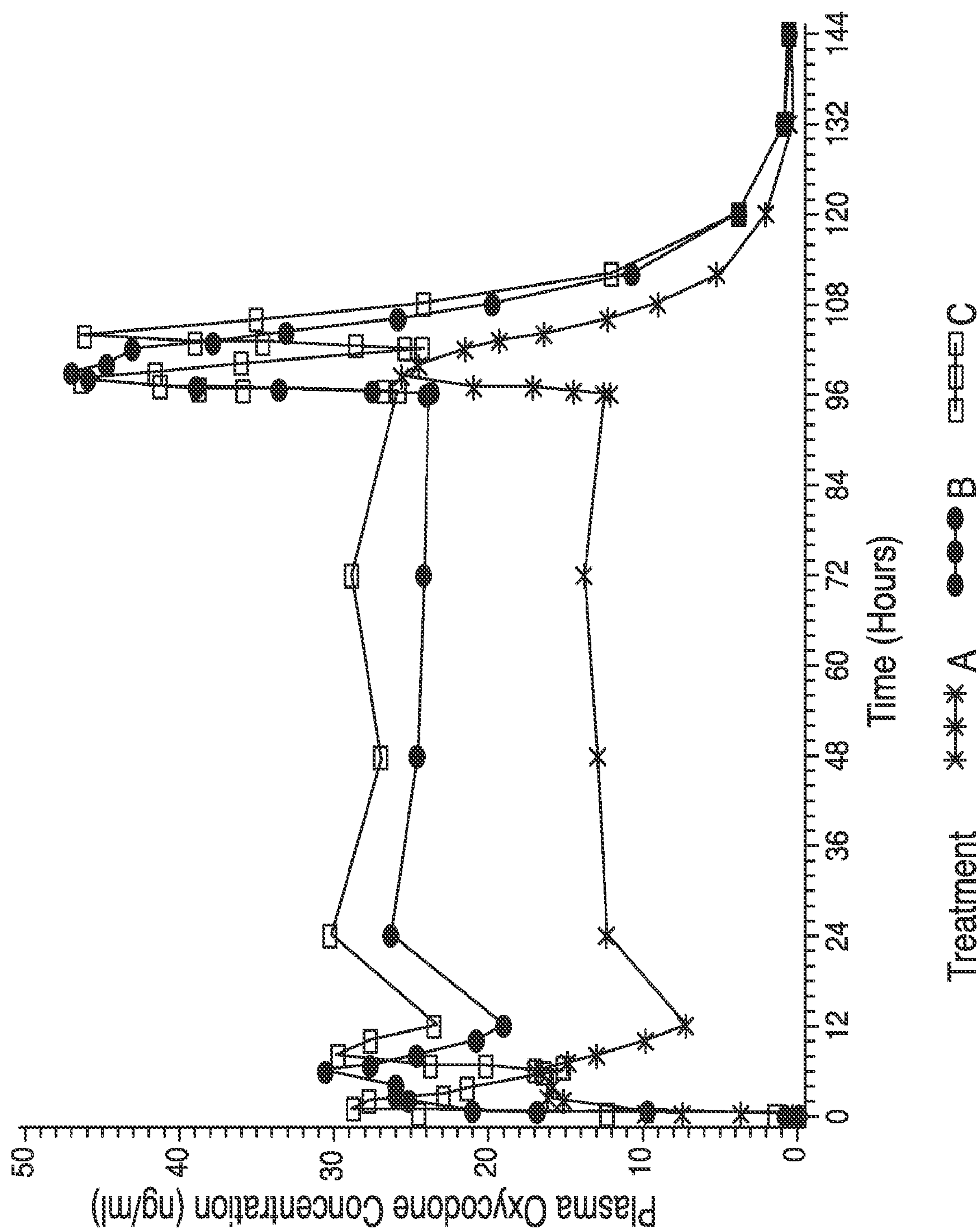


FIG. 11

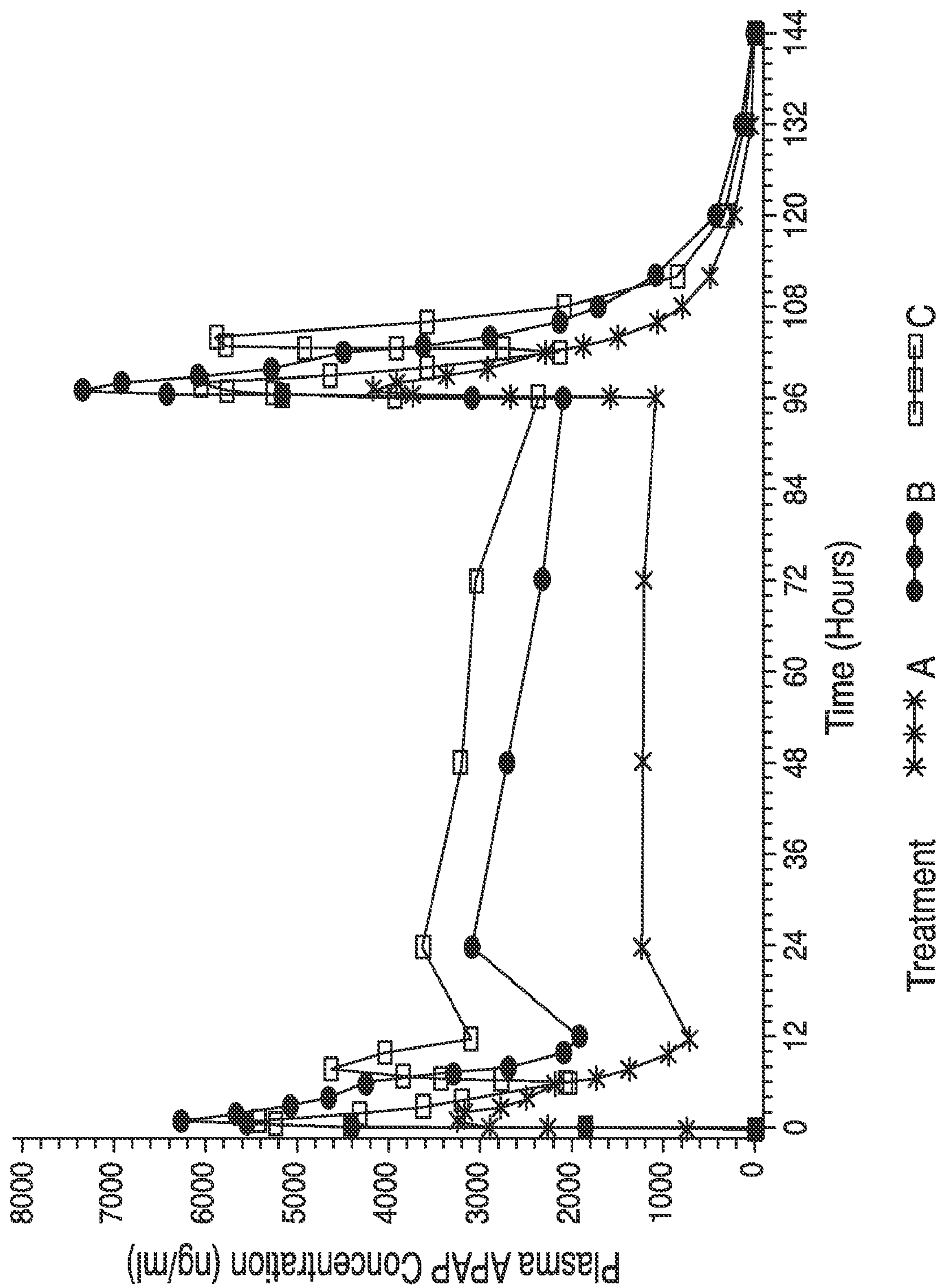


FIG. 12

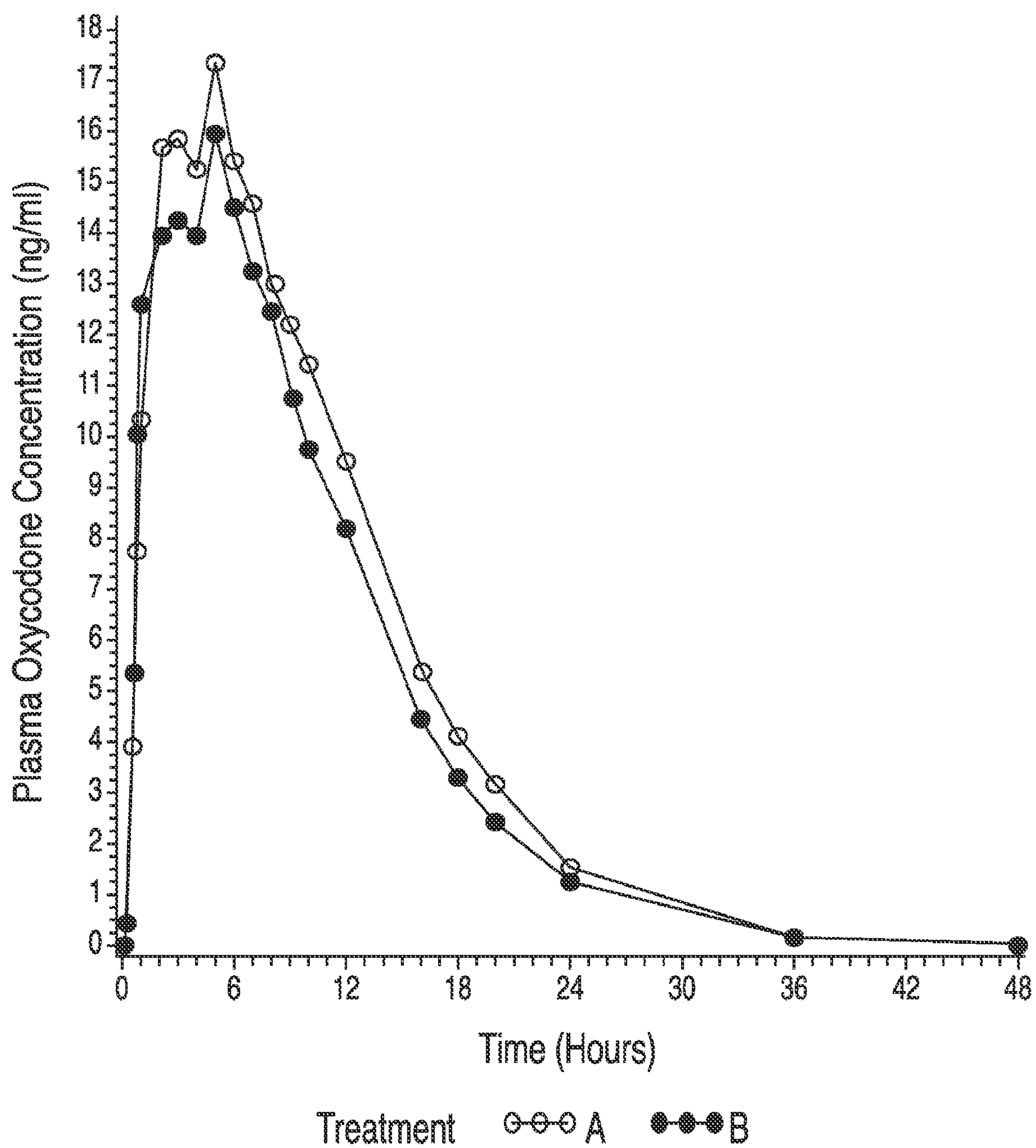


FIG. 13

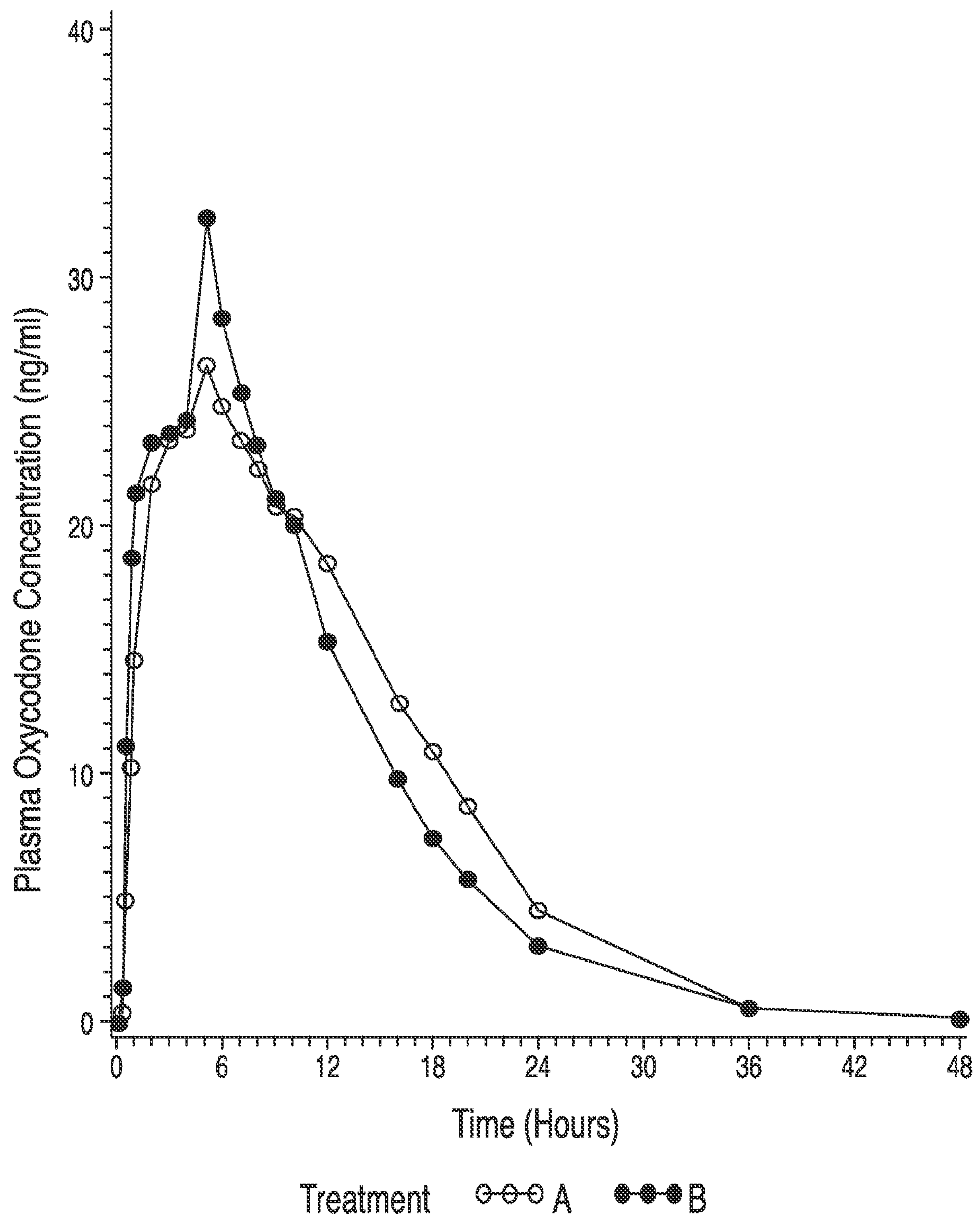


FIG. 14

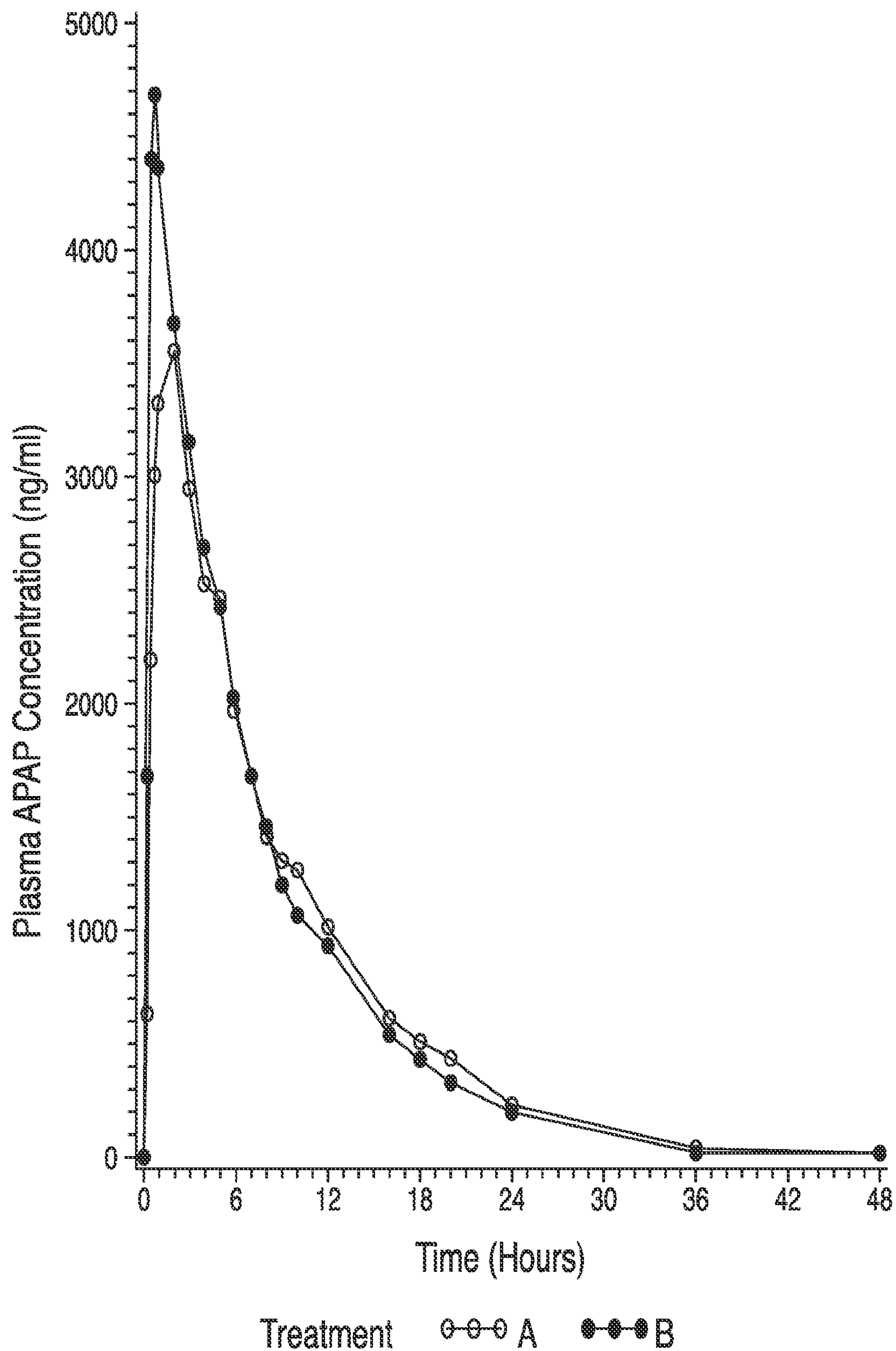


FIG. 15

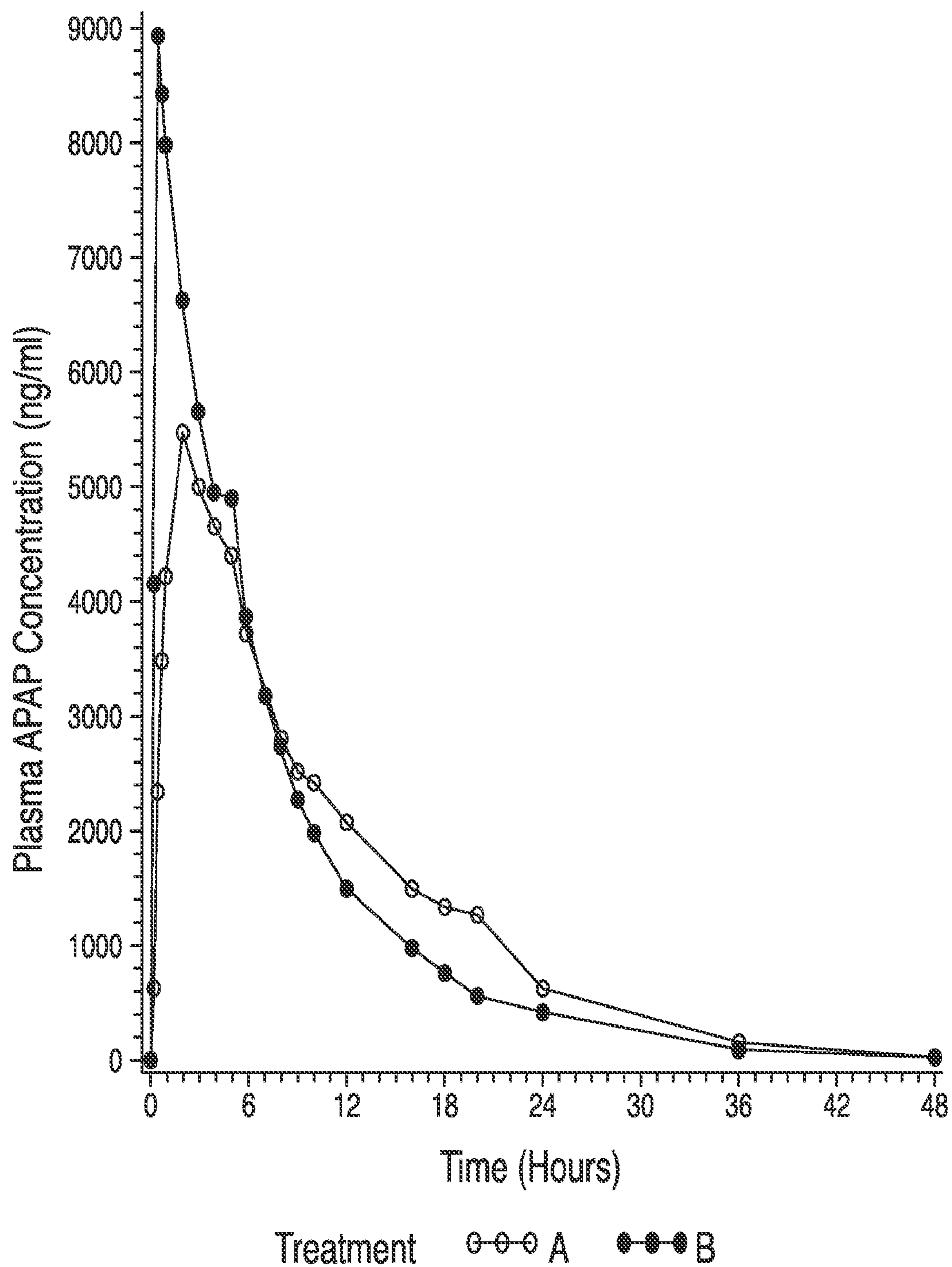


FIG. 16

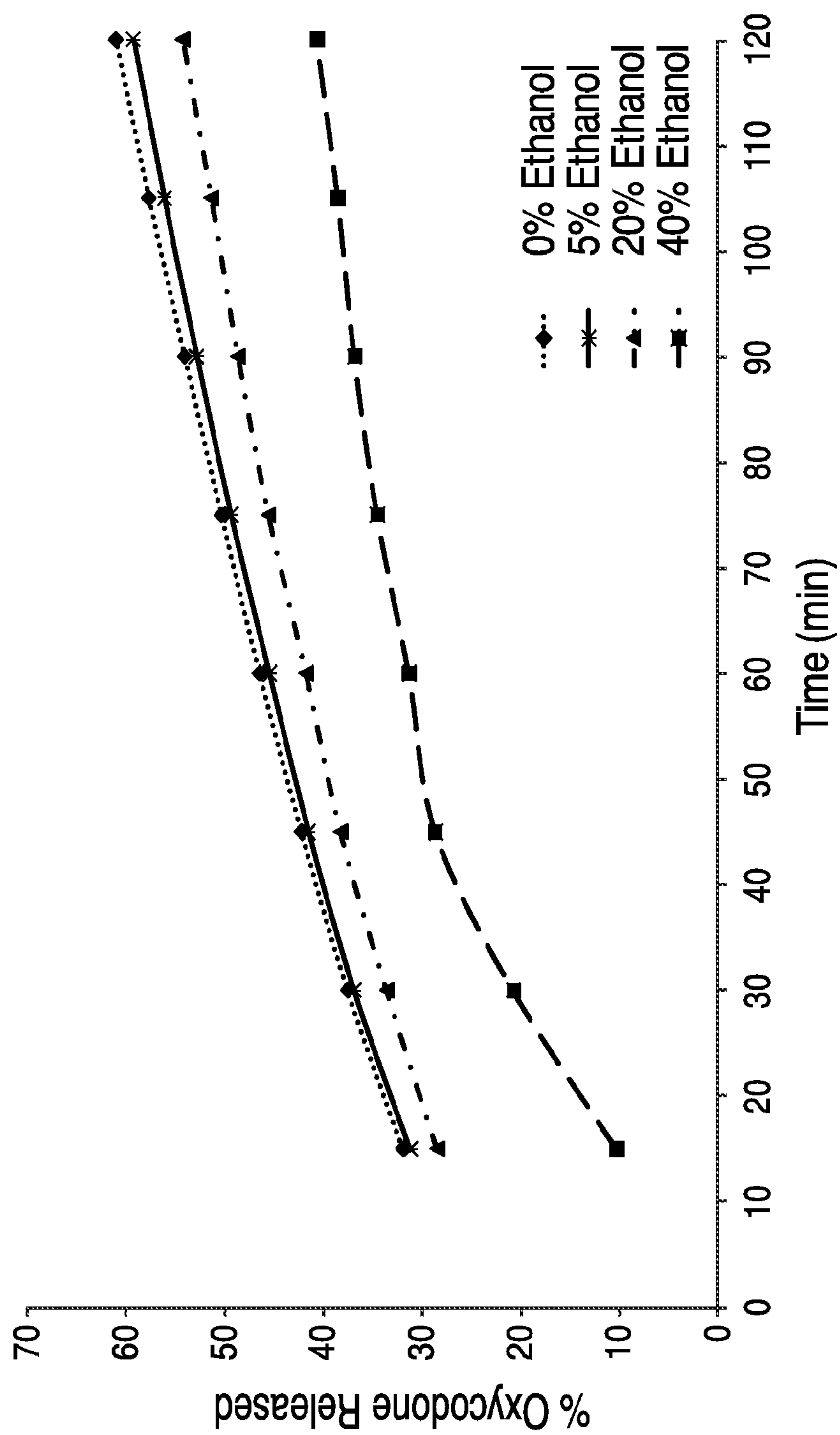


FIG. 17

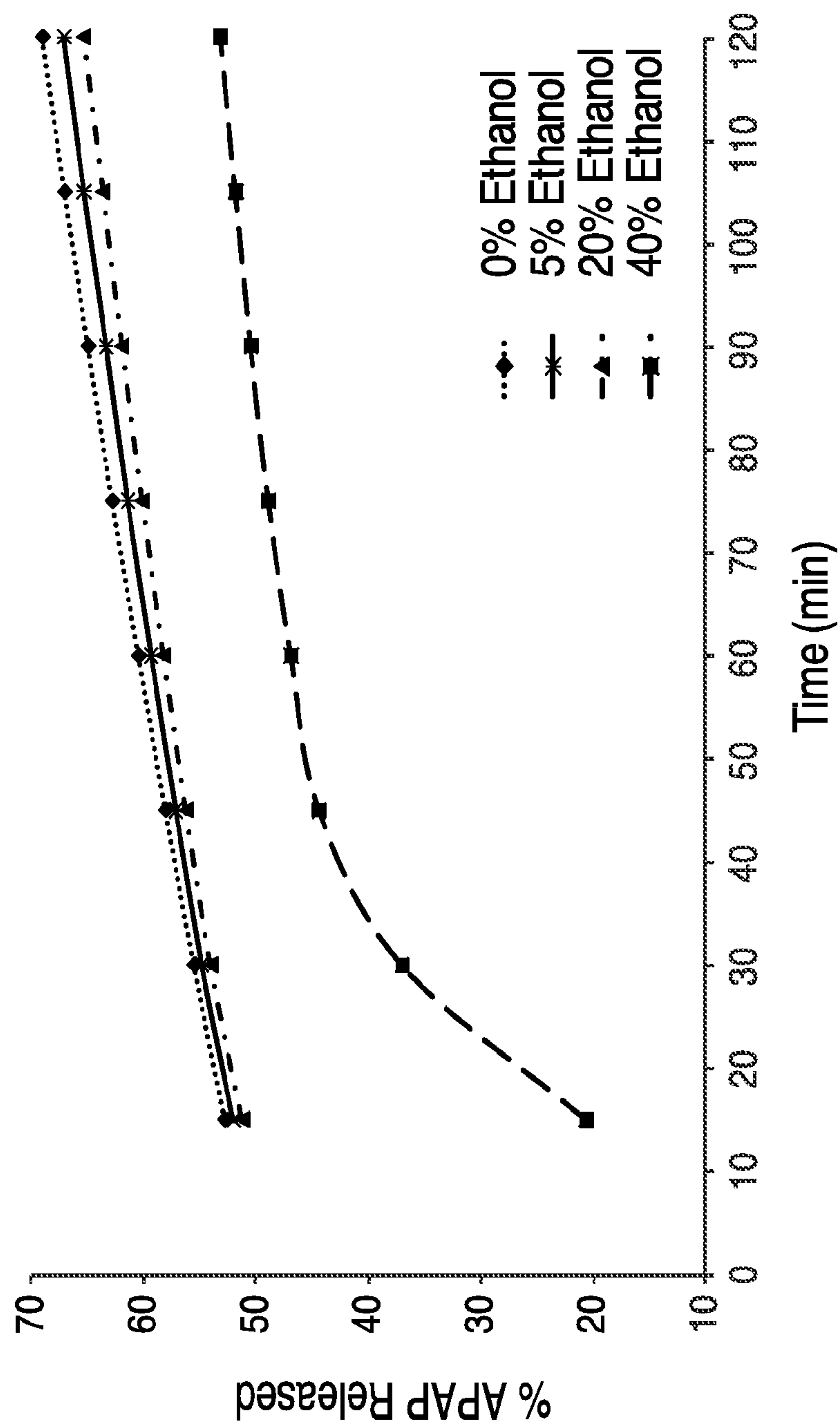


FIG. 18

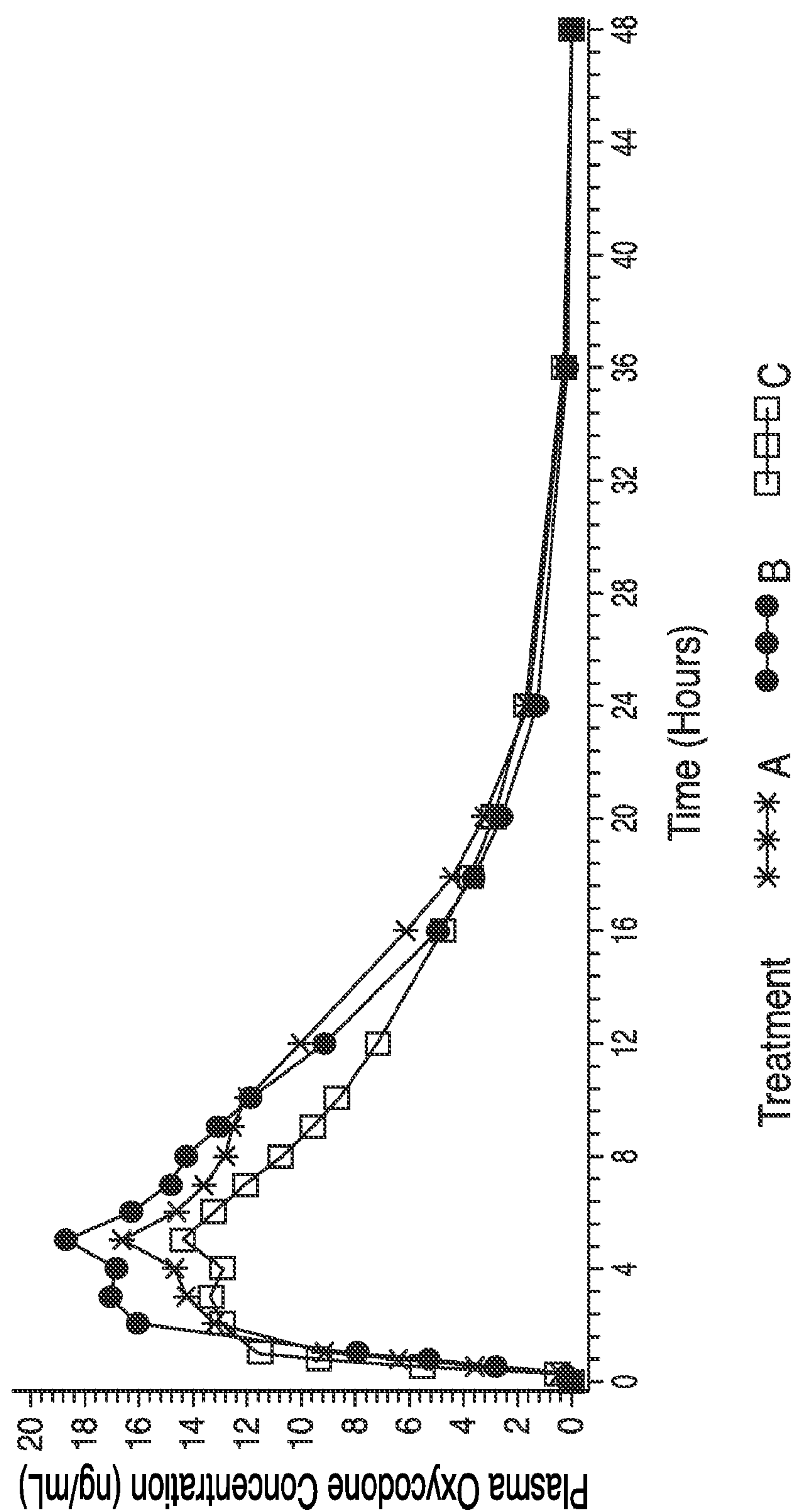


FIG. 19

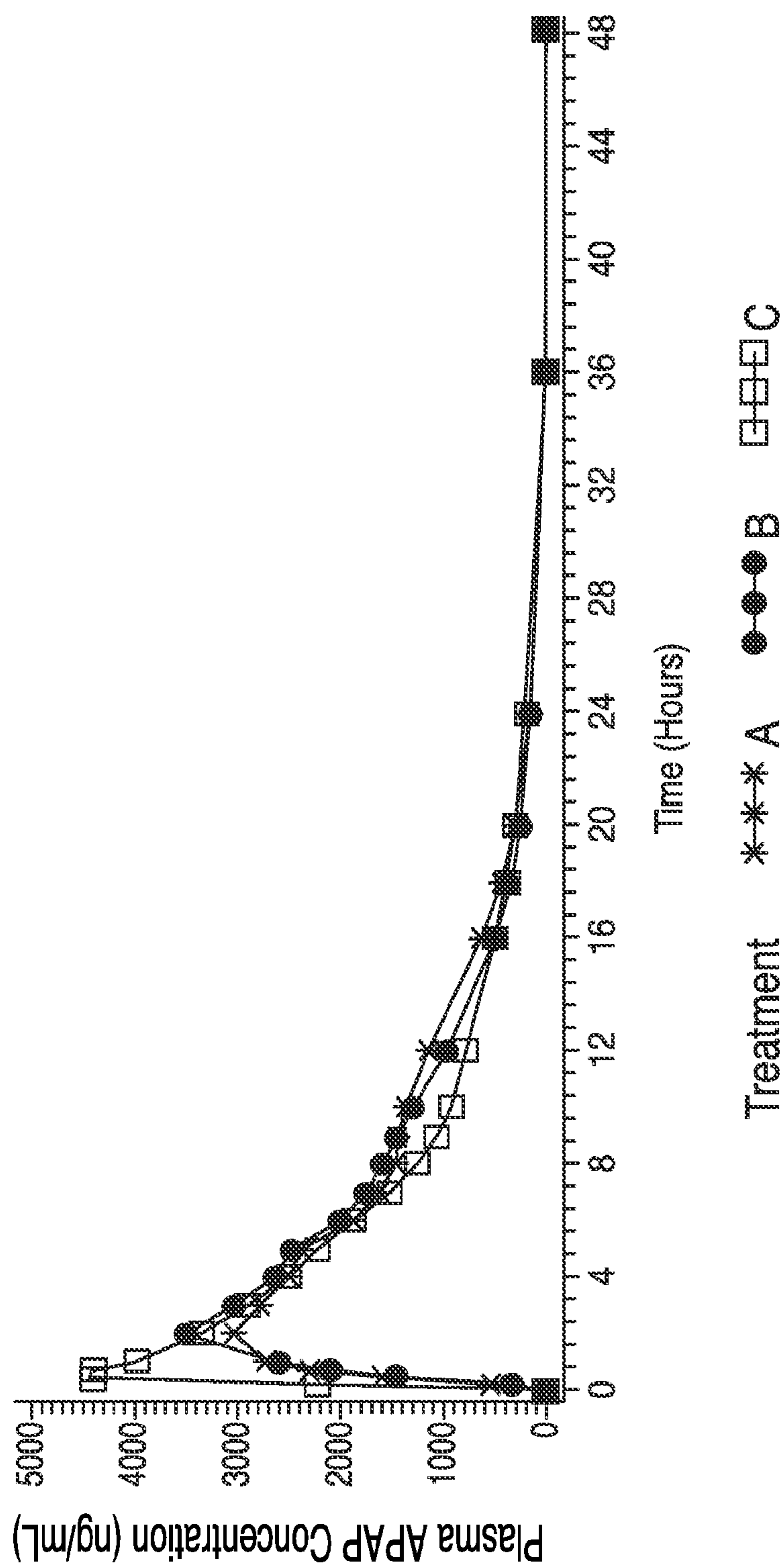


FIG. 20

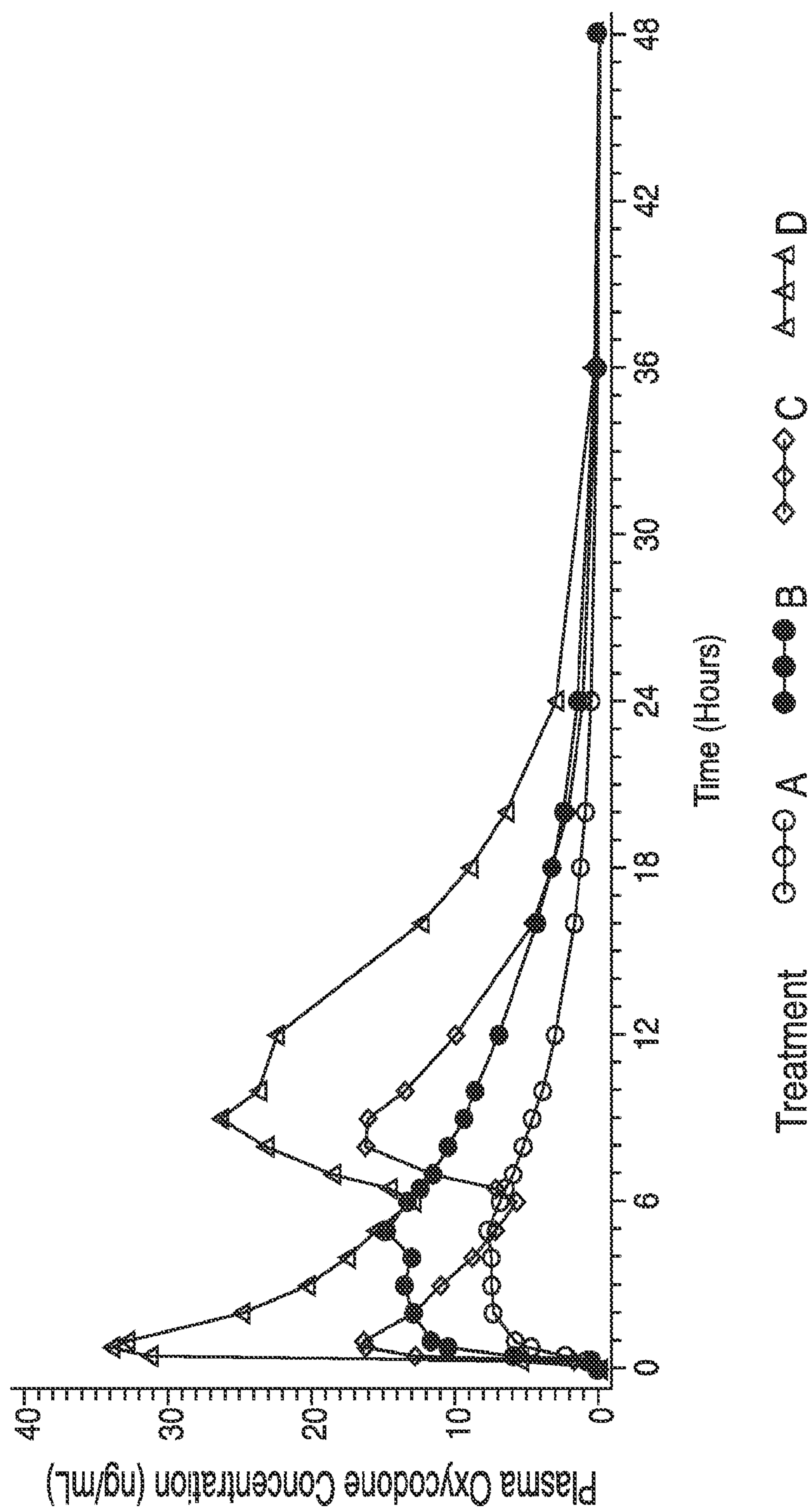


FIG. 21

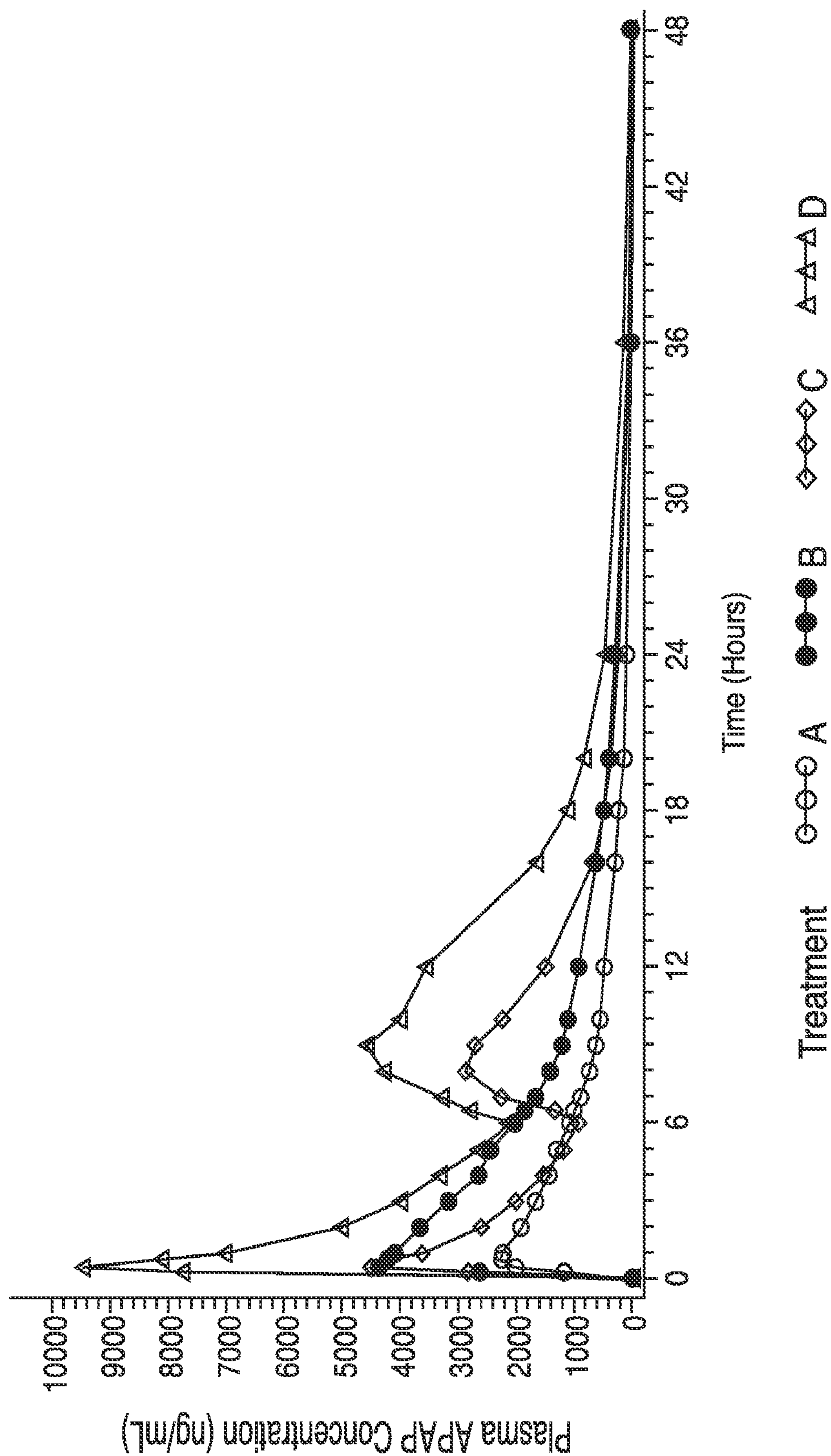


FIG. 22

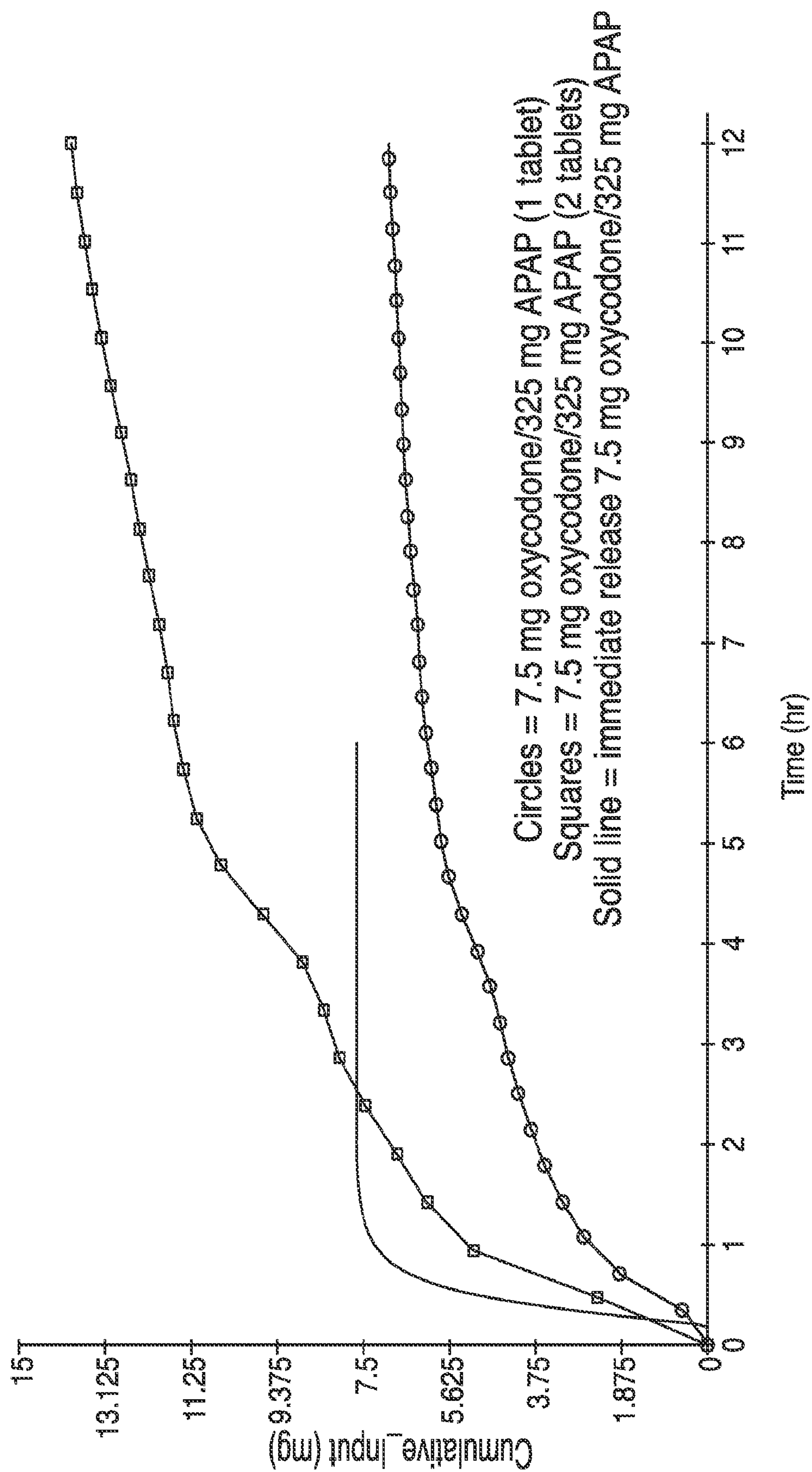


FIG. 23

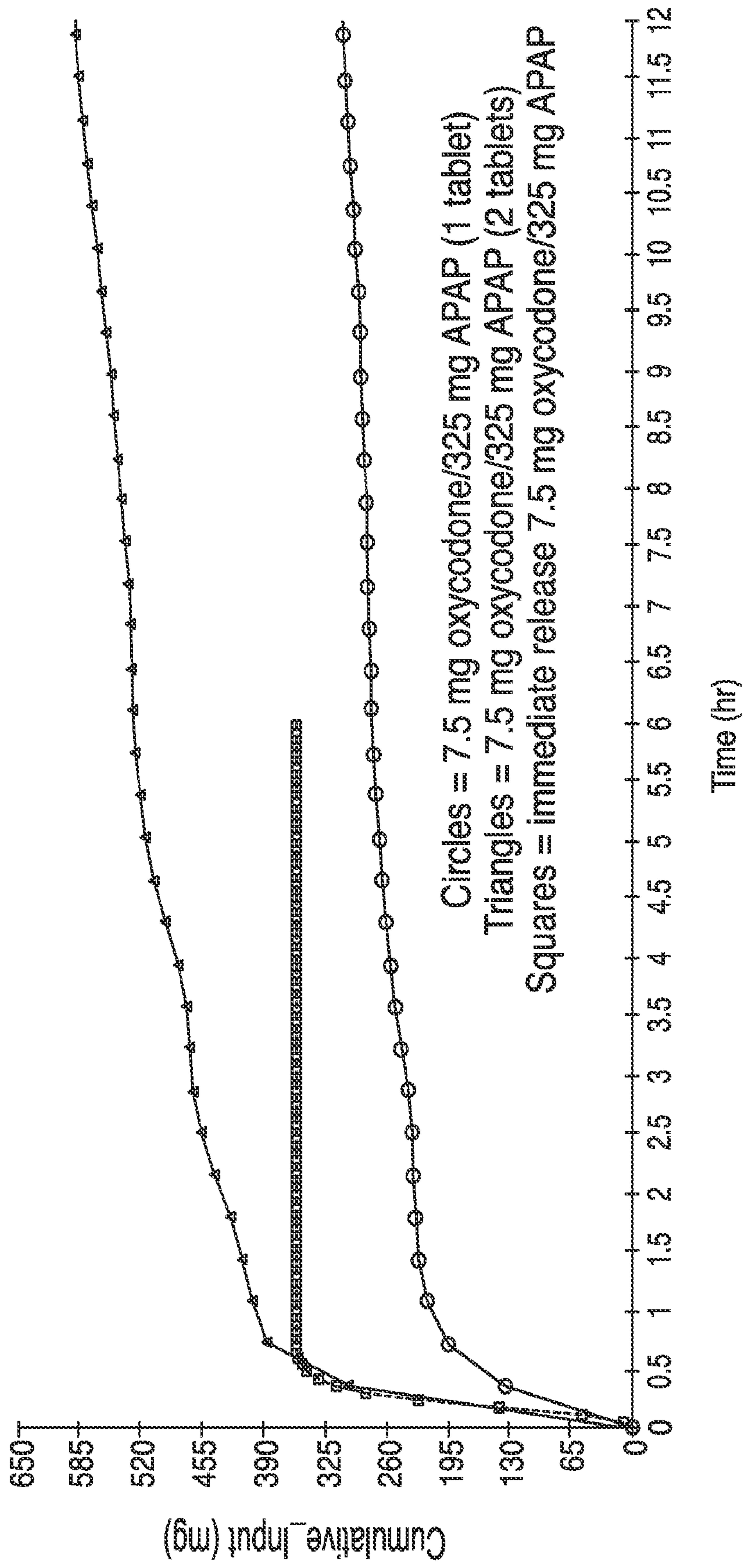


FIG. 24

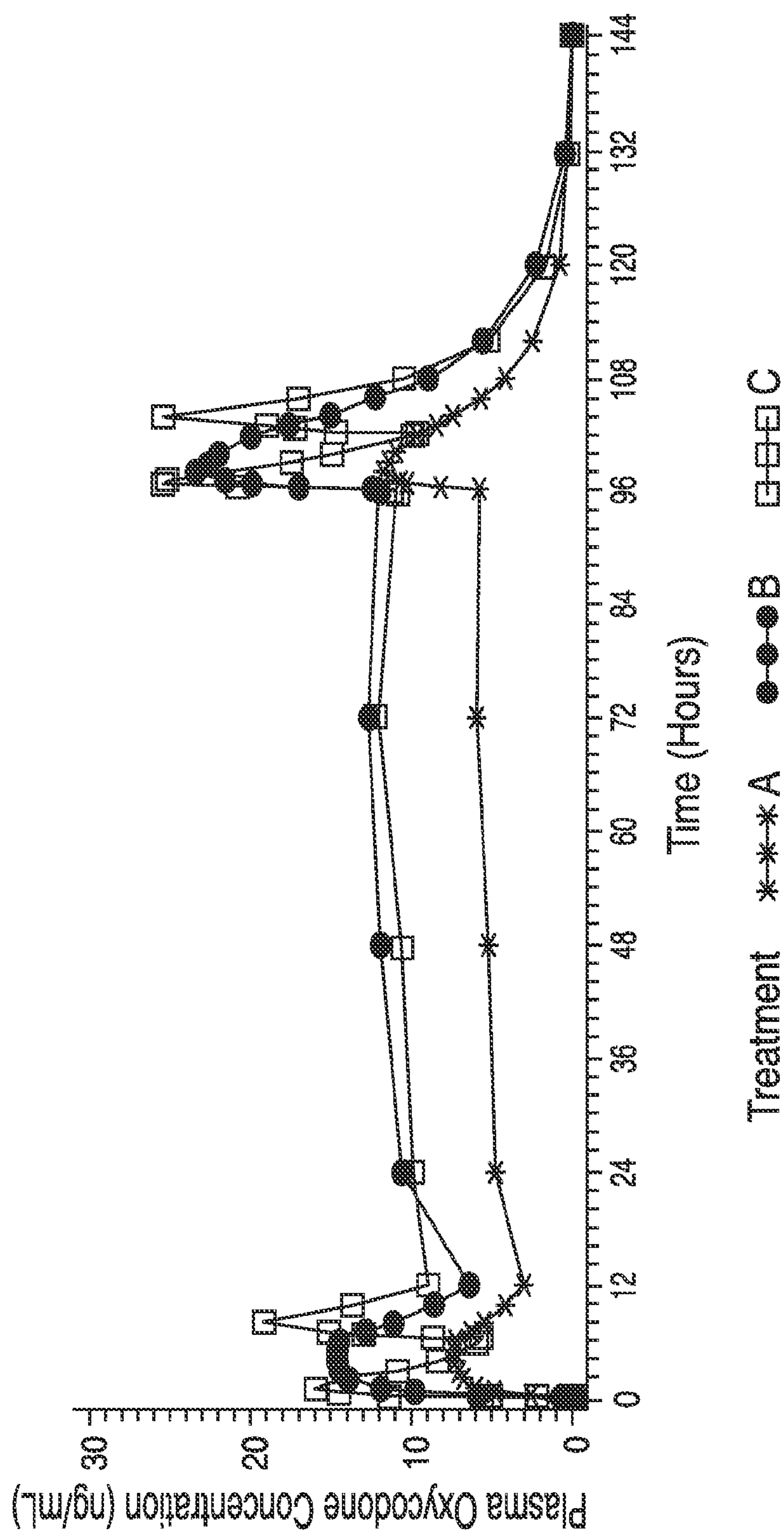


FIG. 25

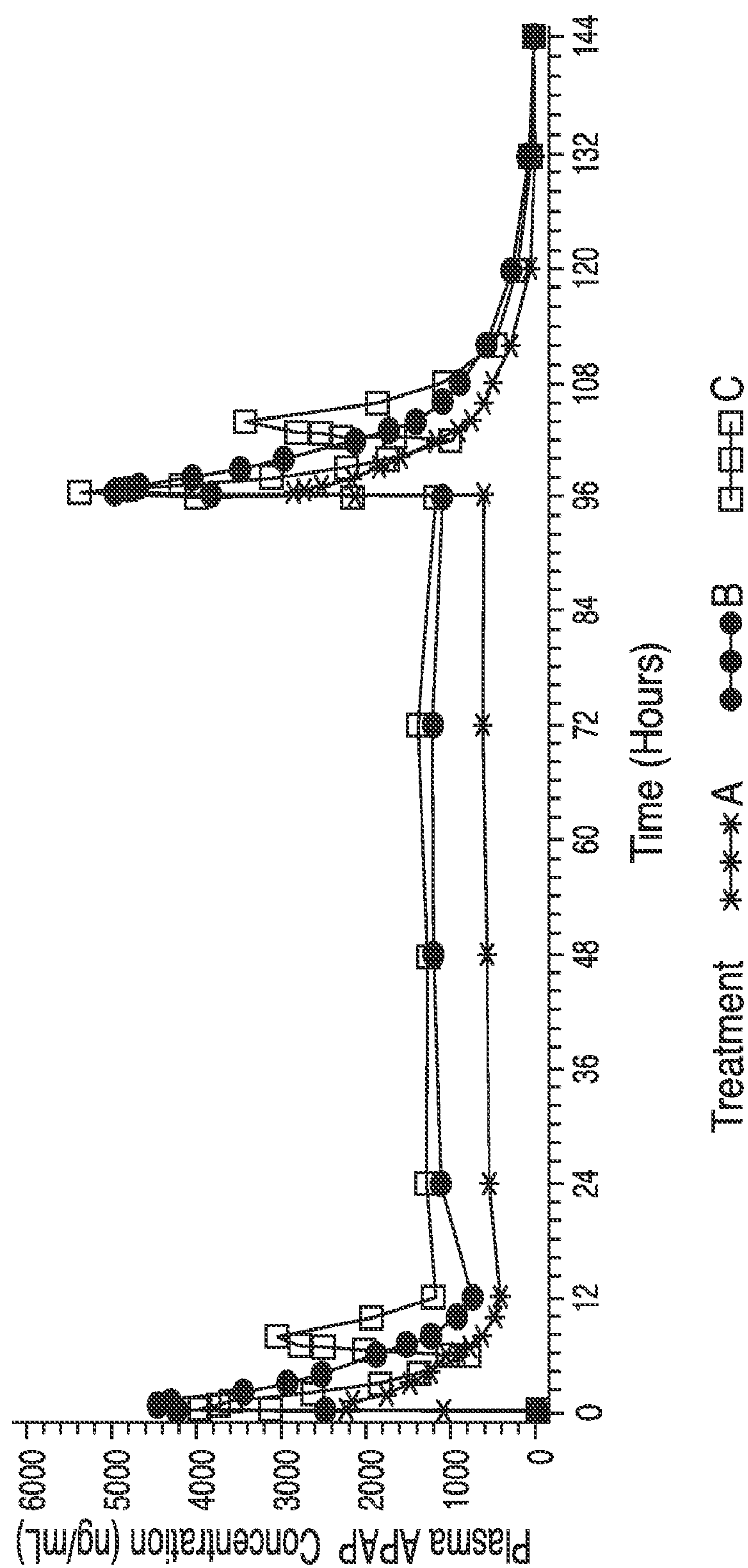


FIG. 26

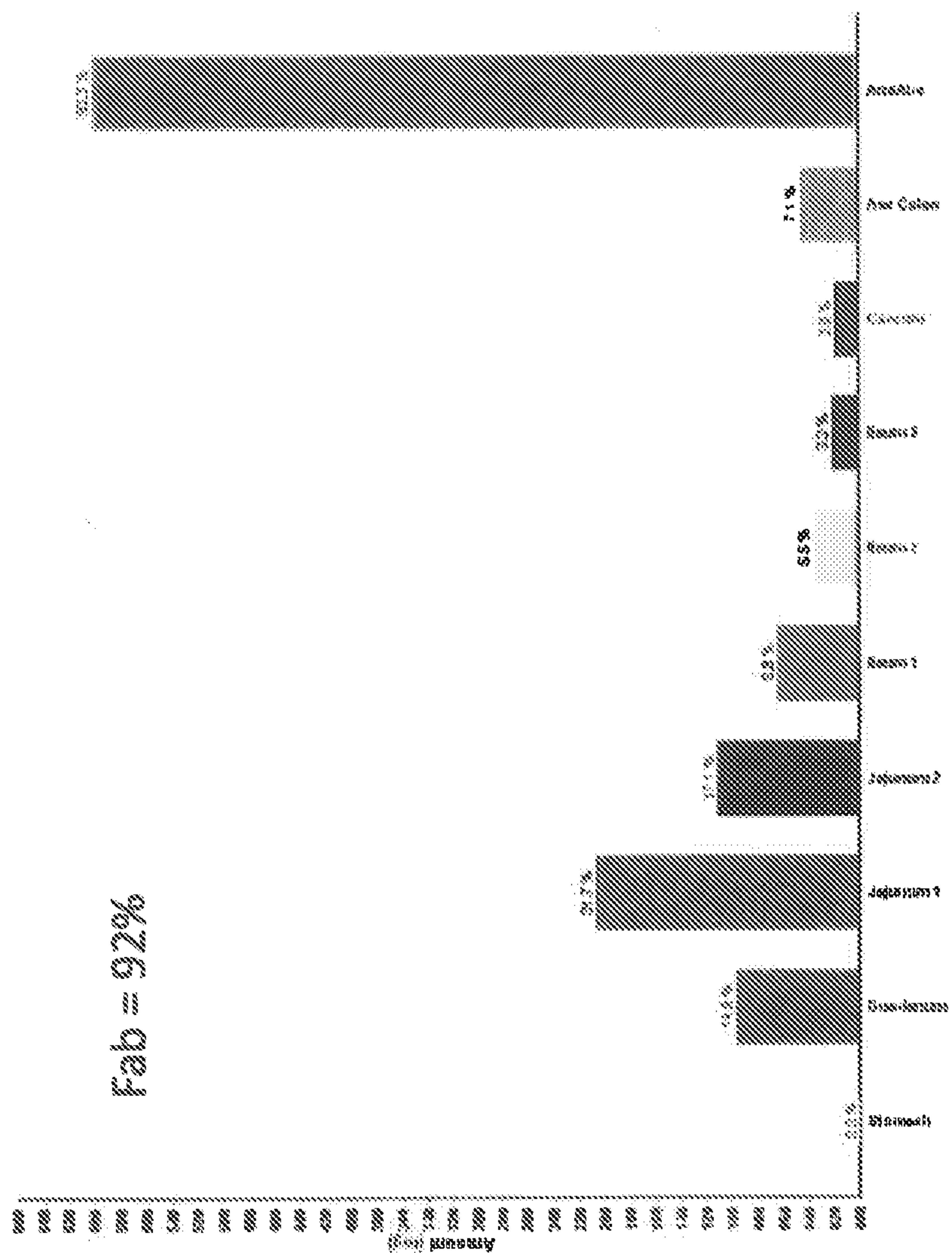


FIG. 27A

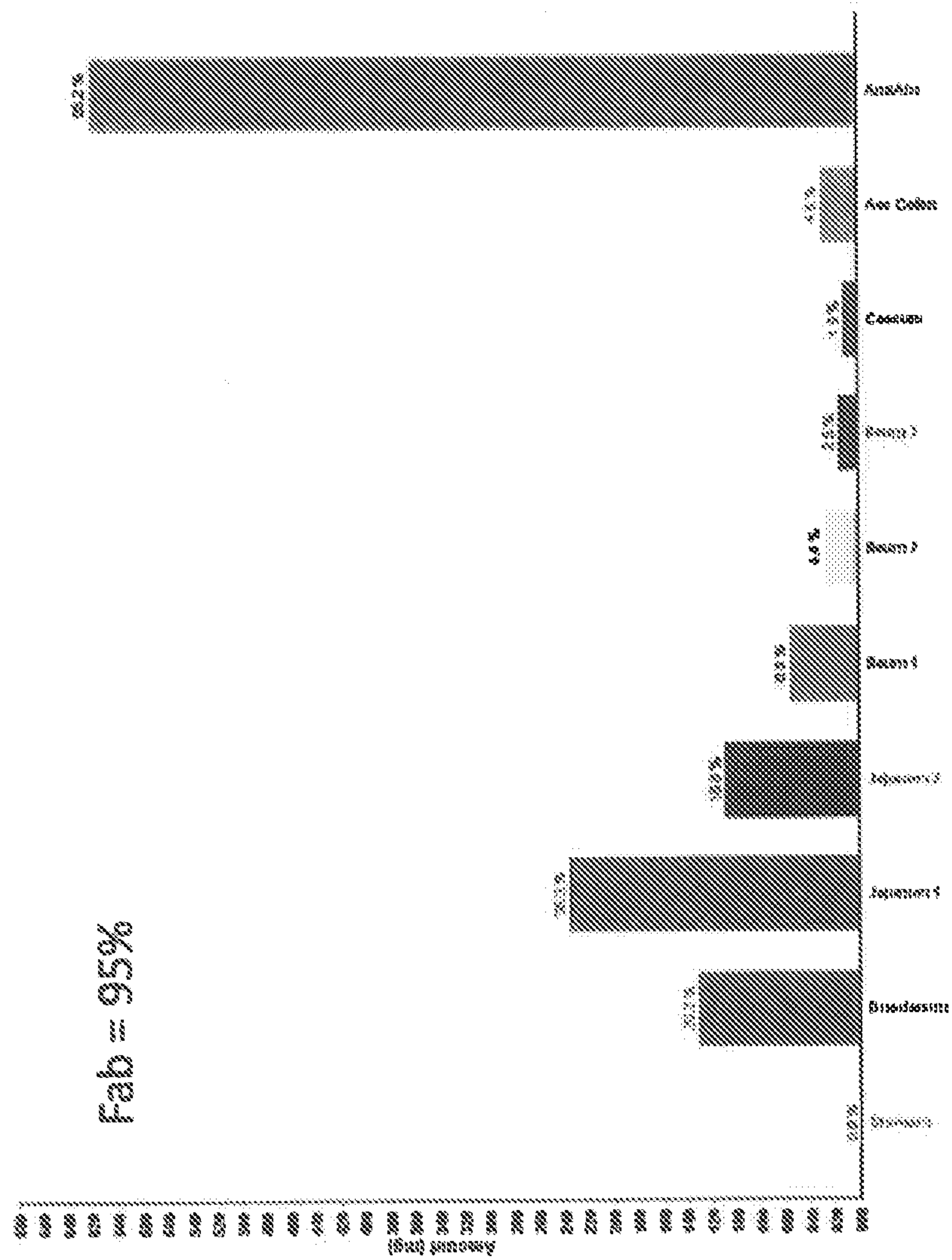


FIG. 27B

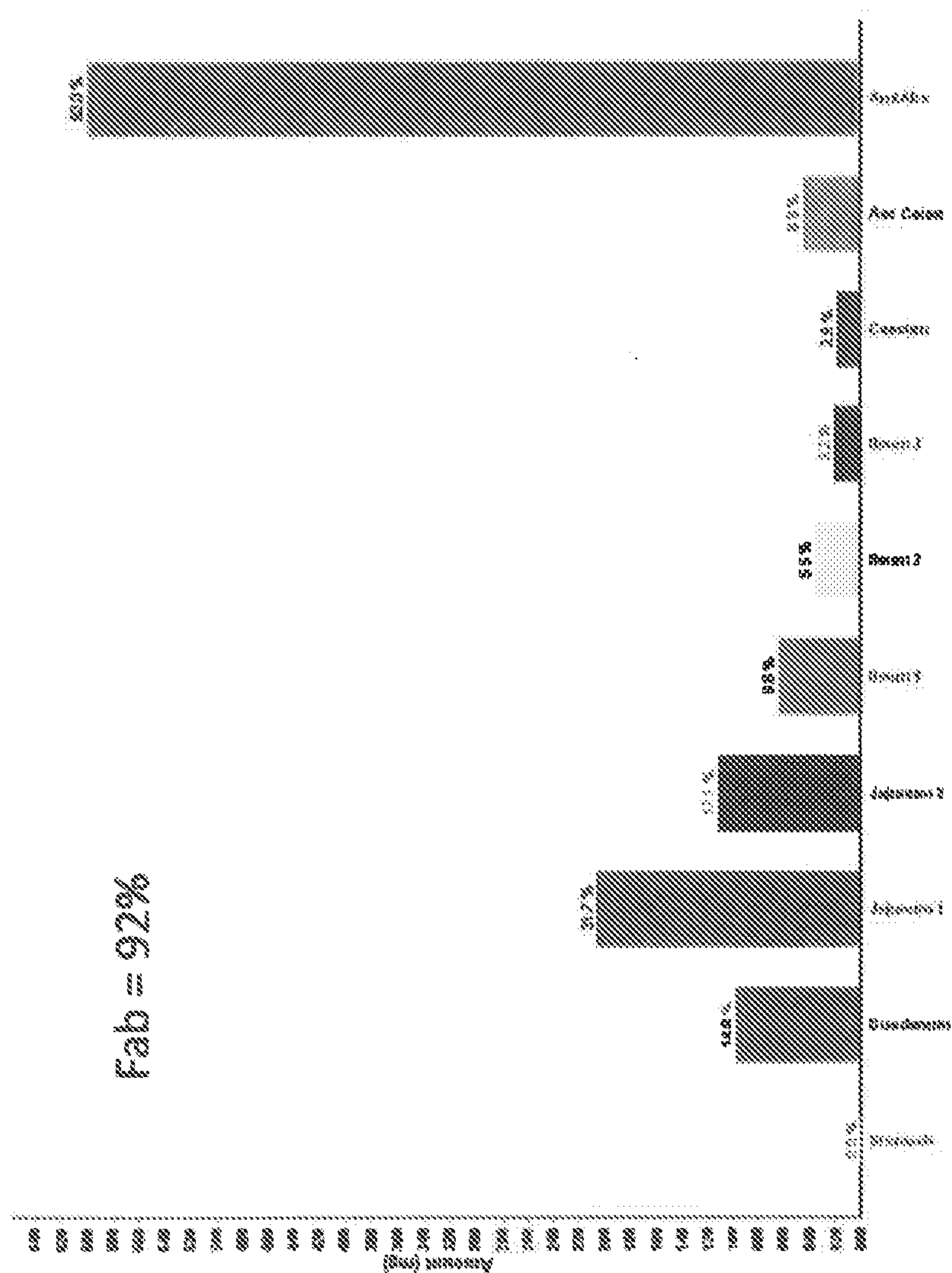


FIG. 27C

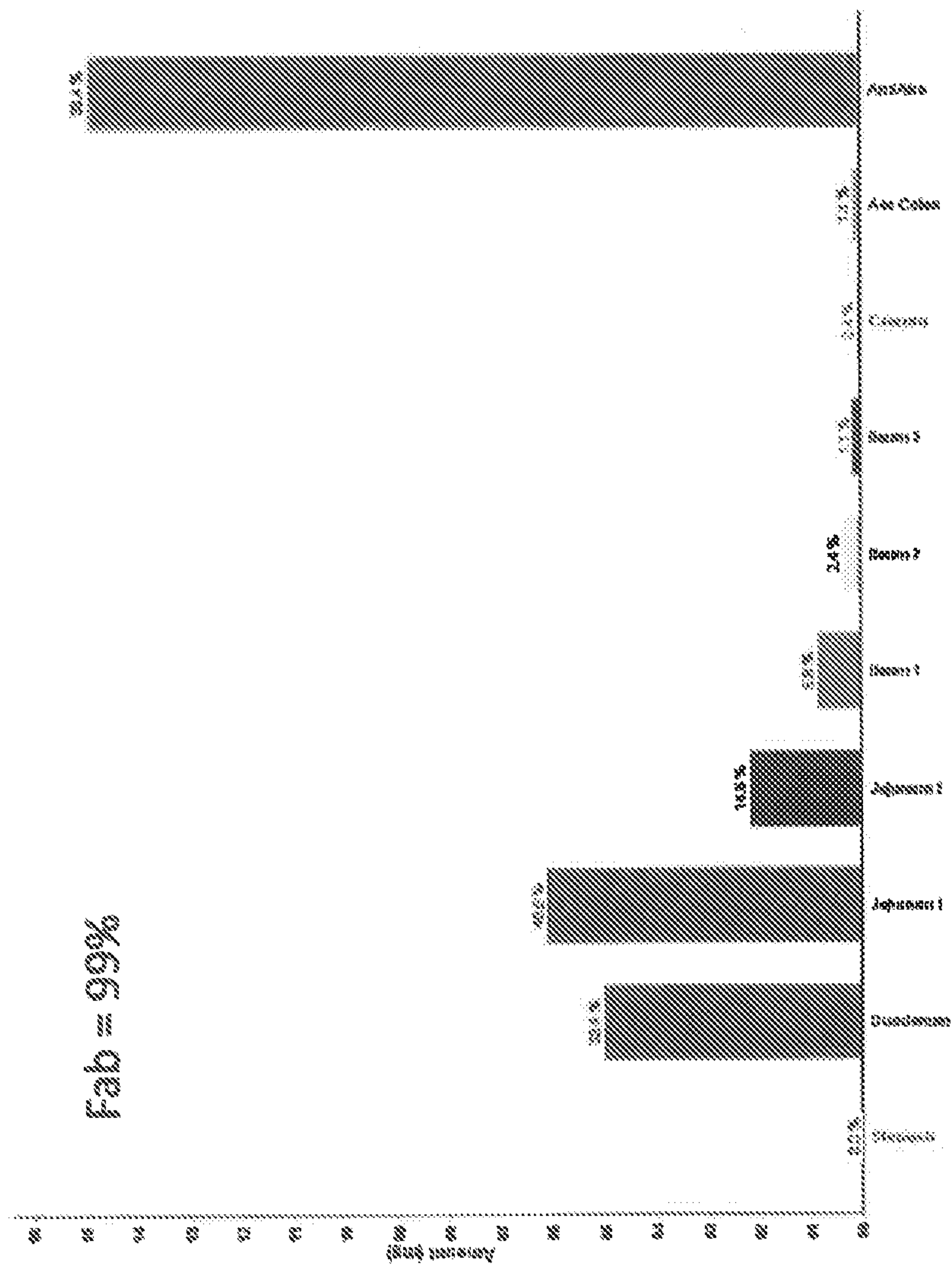
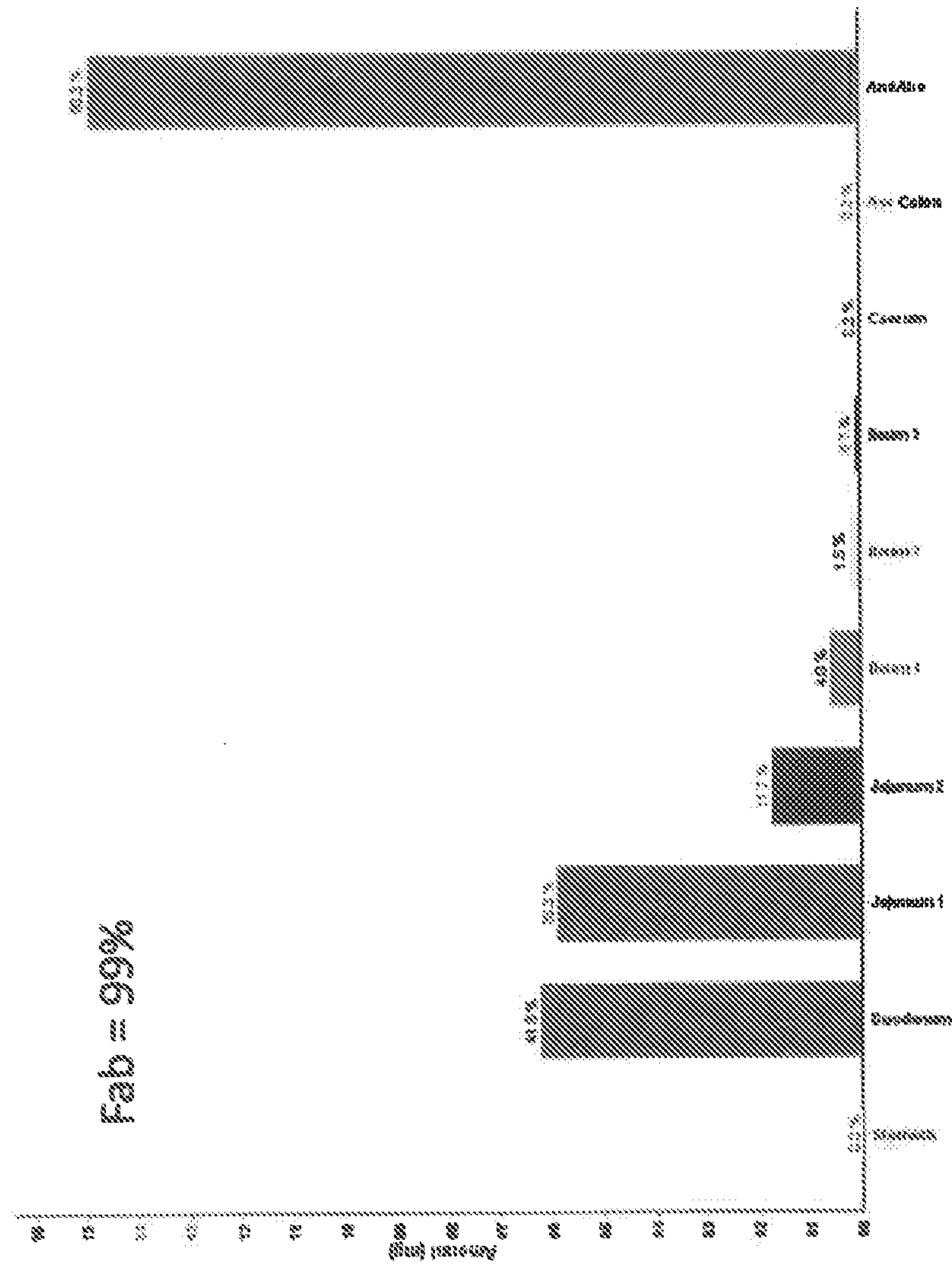
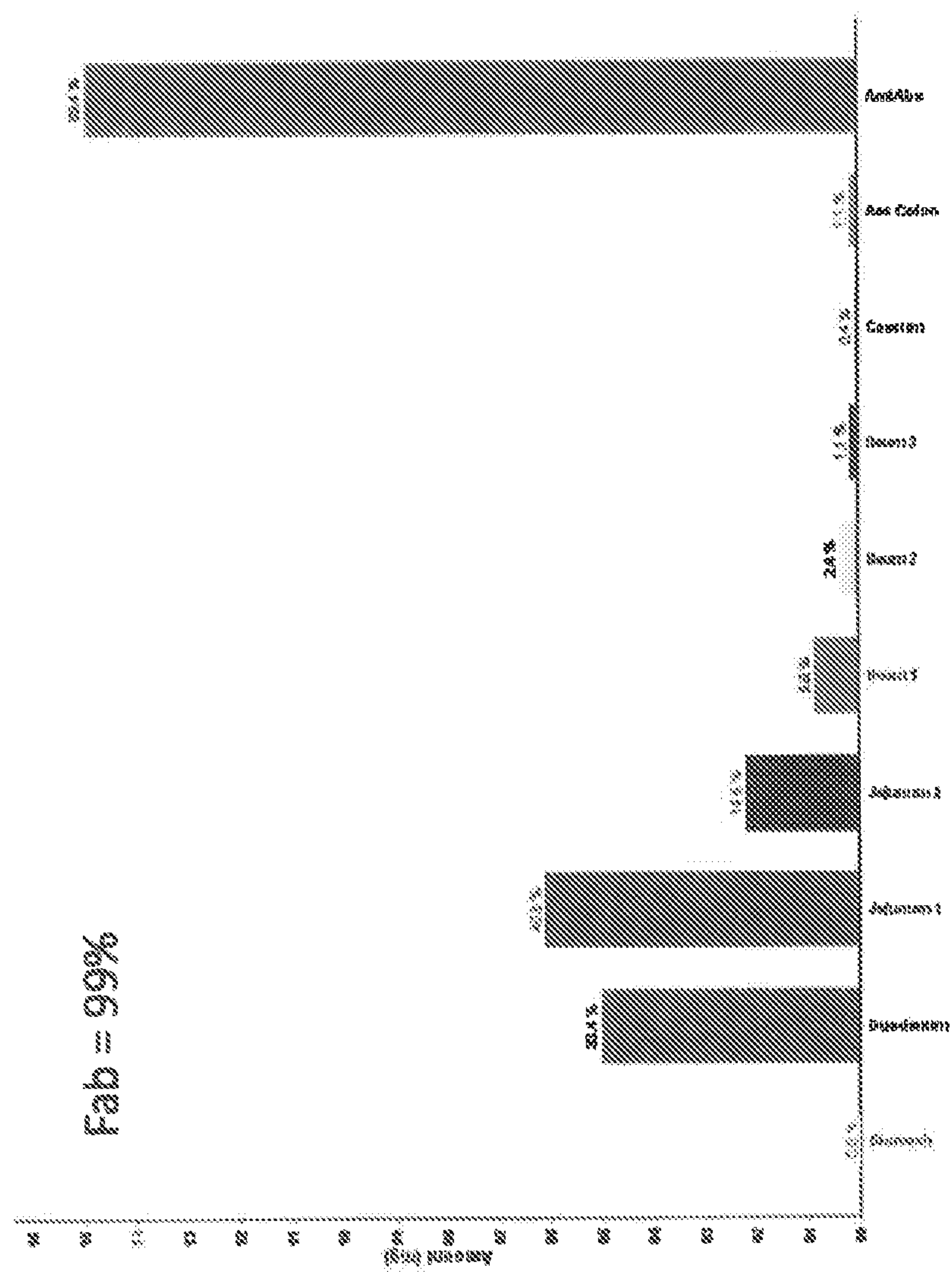


FIG. 28A





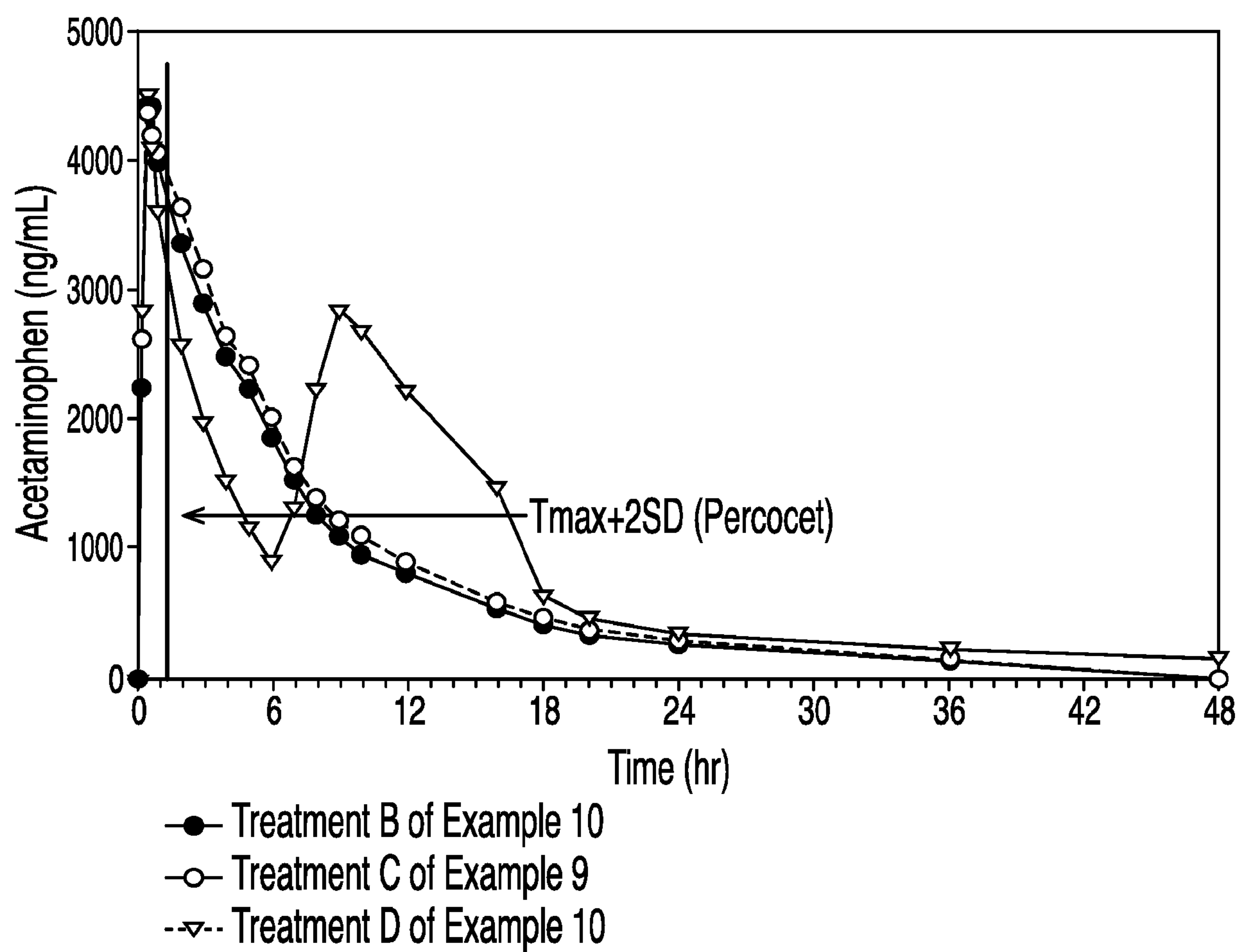


FIG. 29A

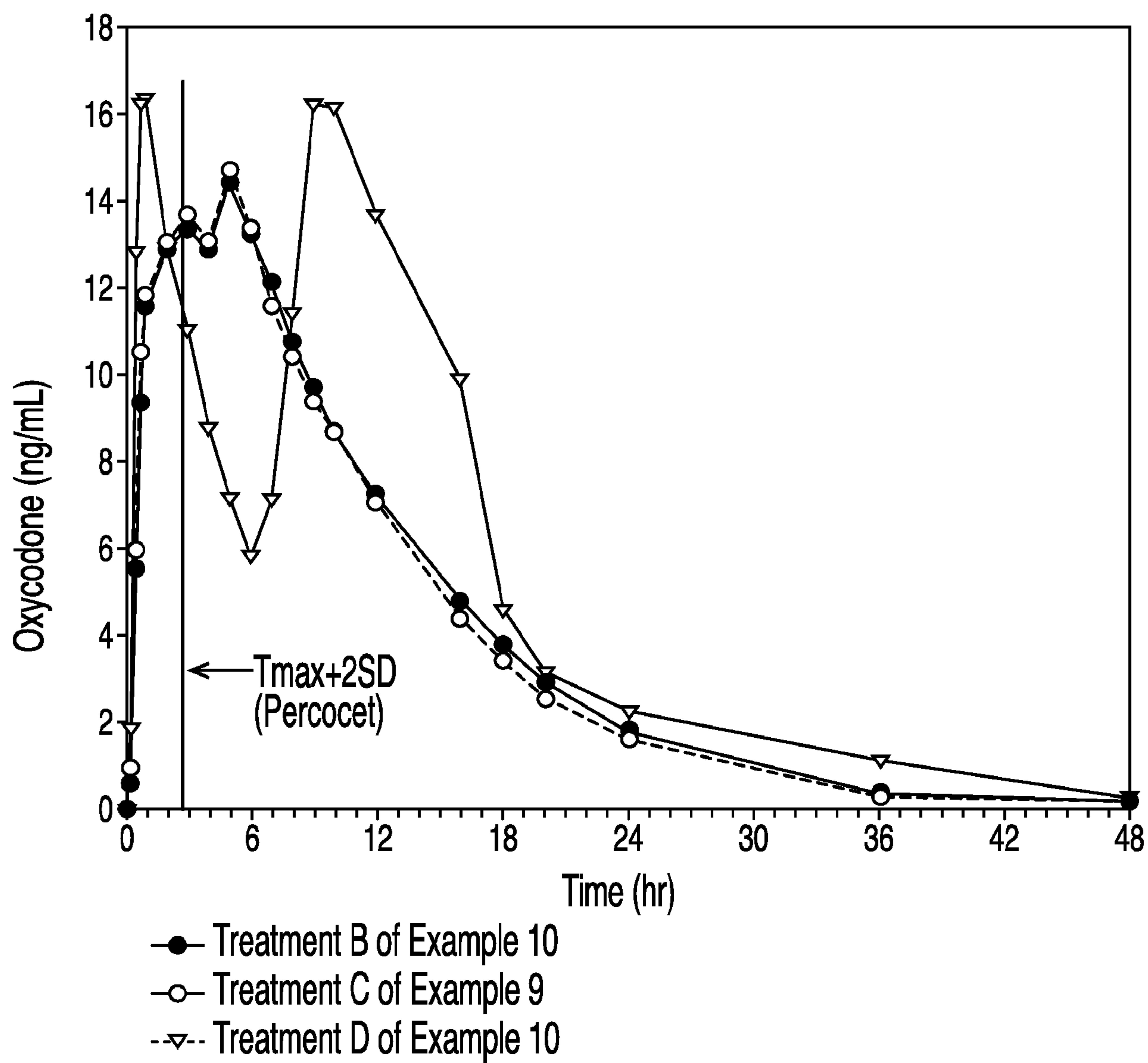


FIG. 29B

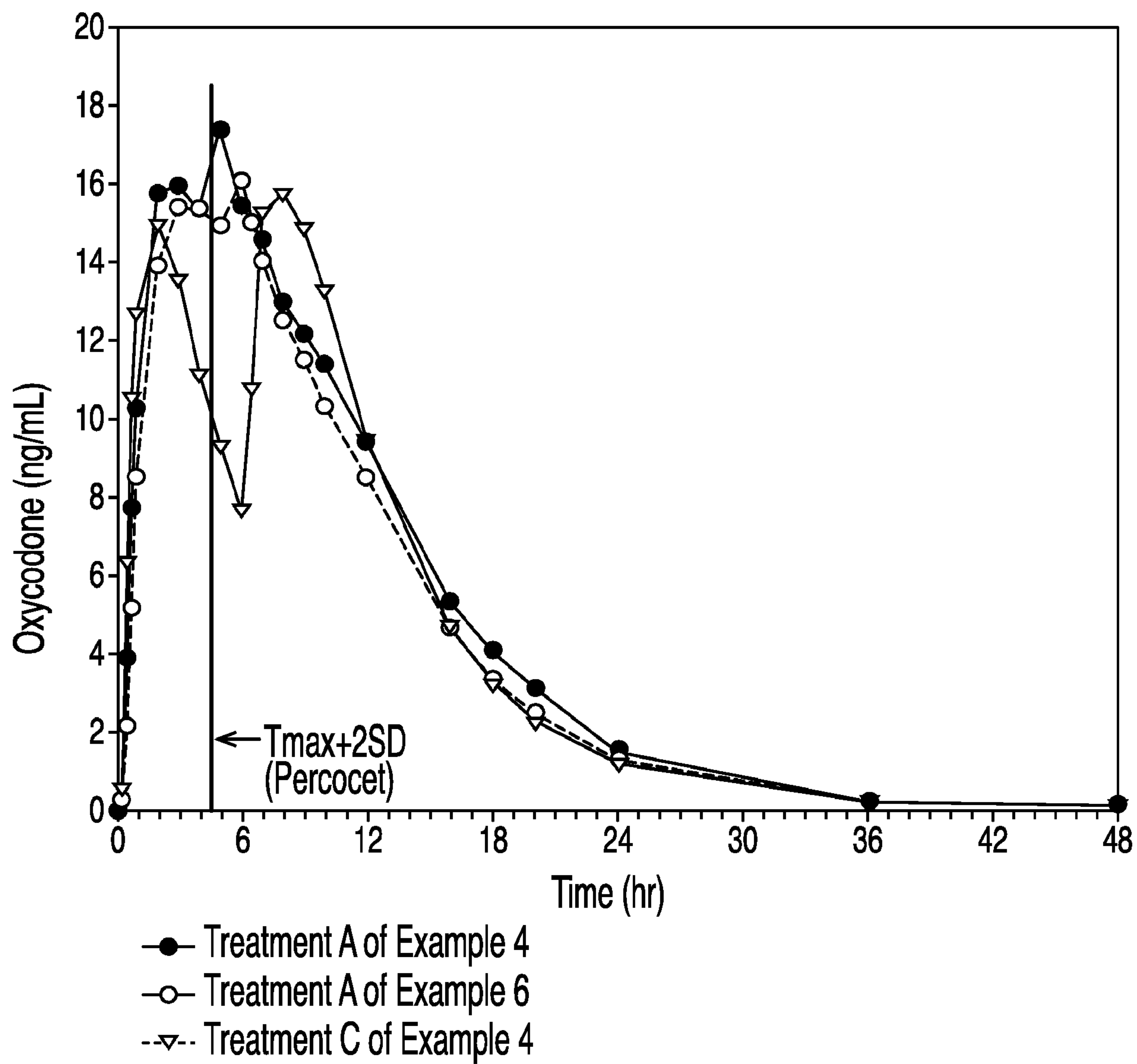


FIG. 30A

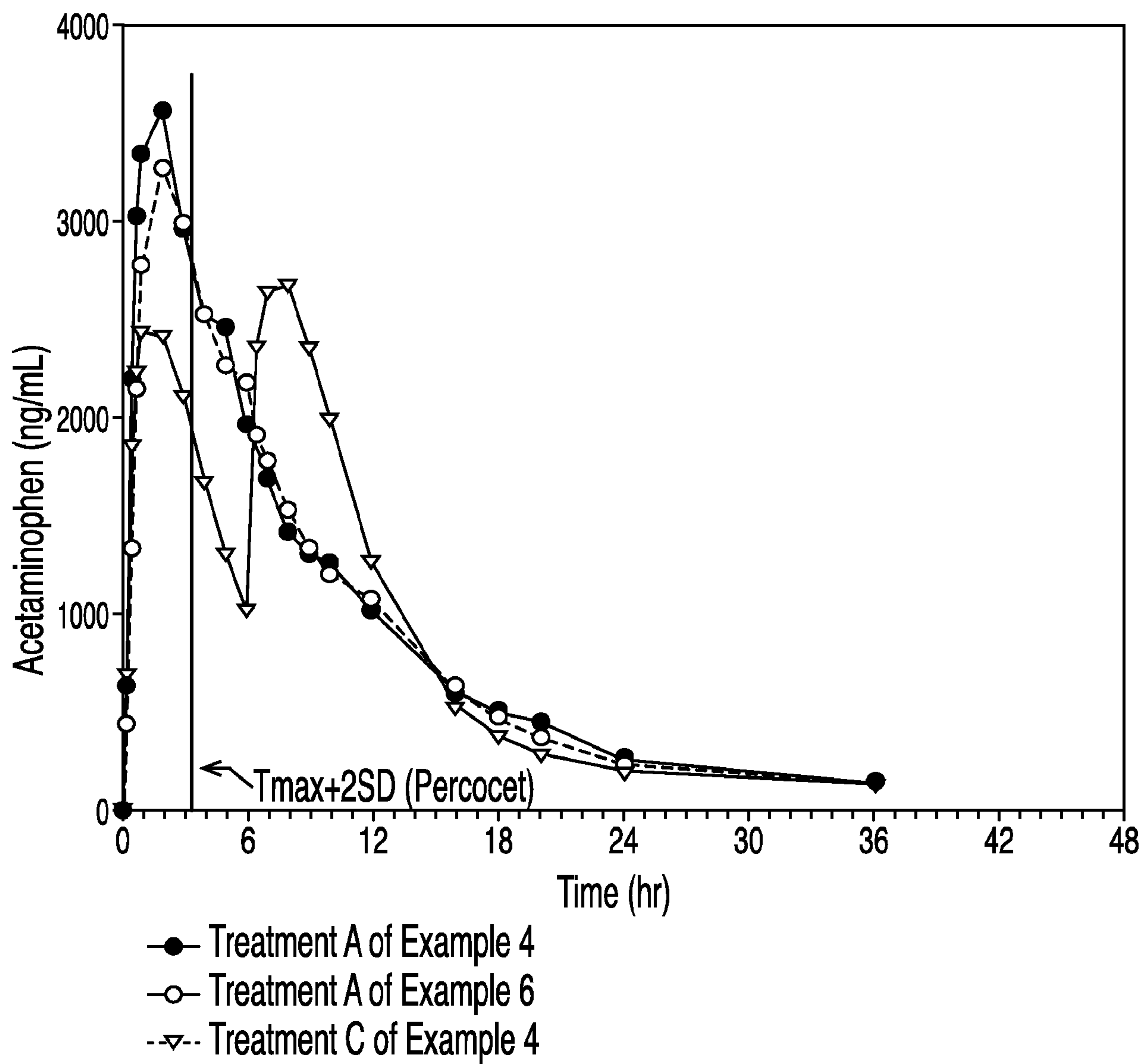


FIG. 30B

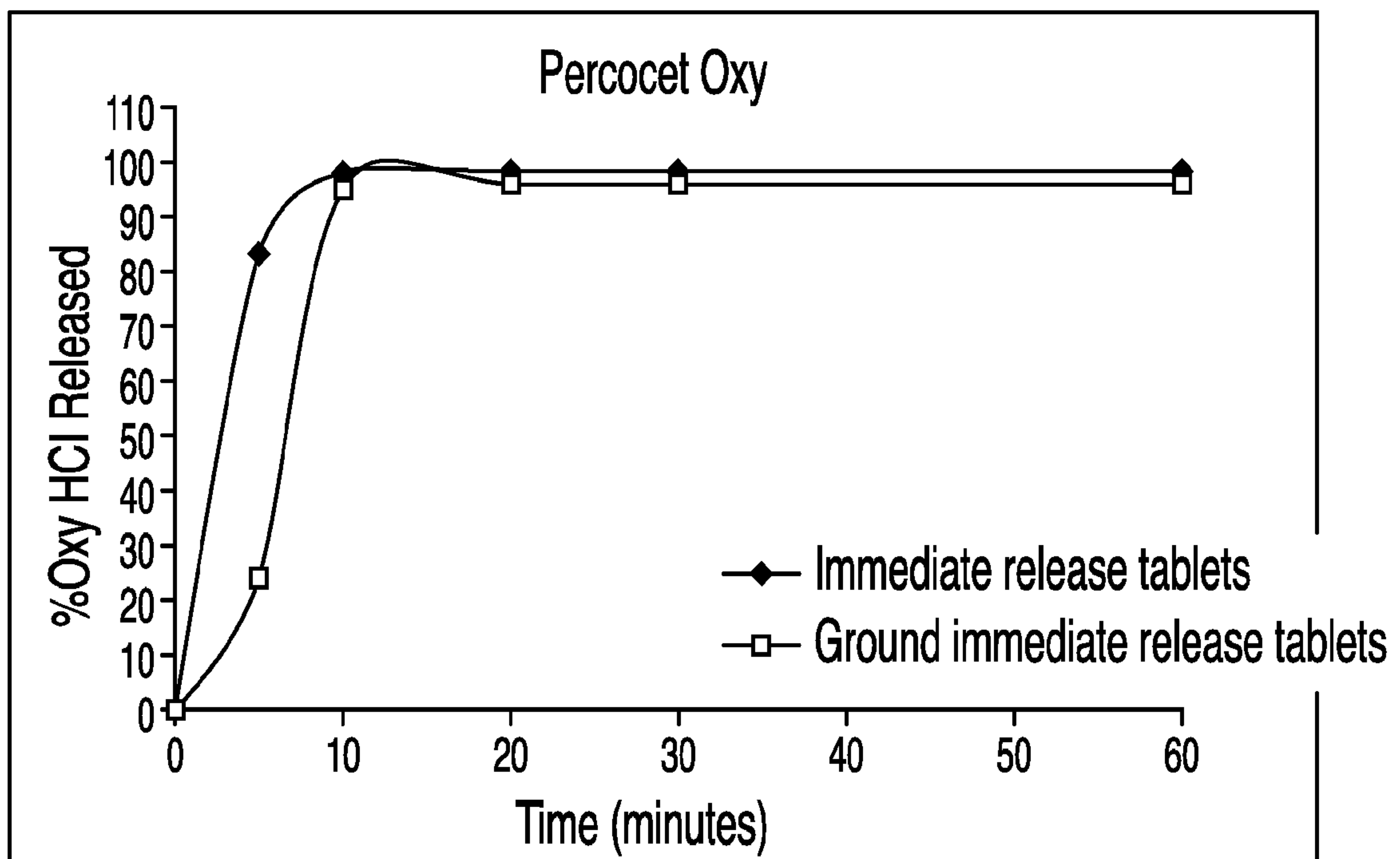
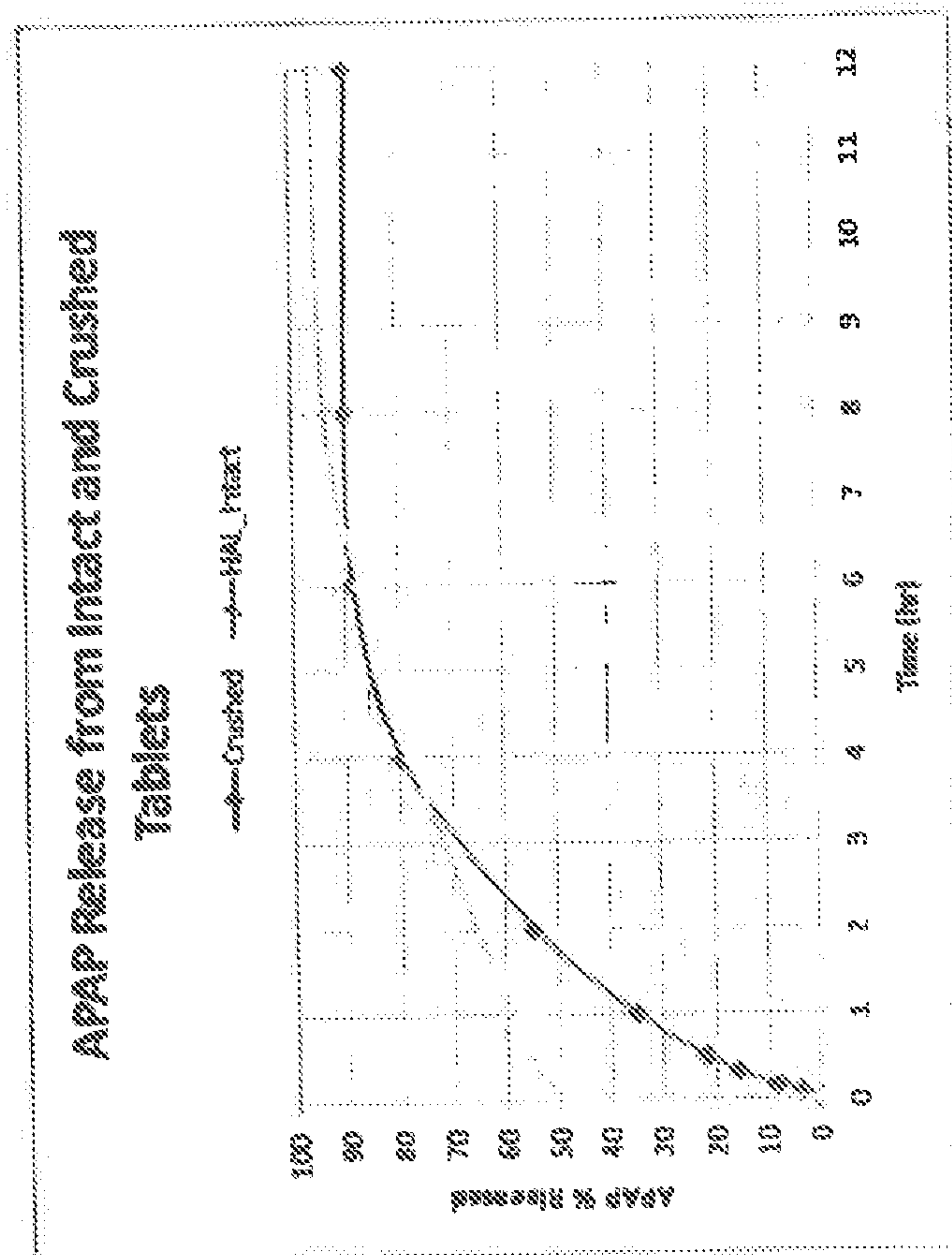
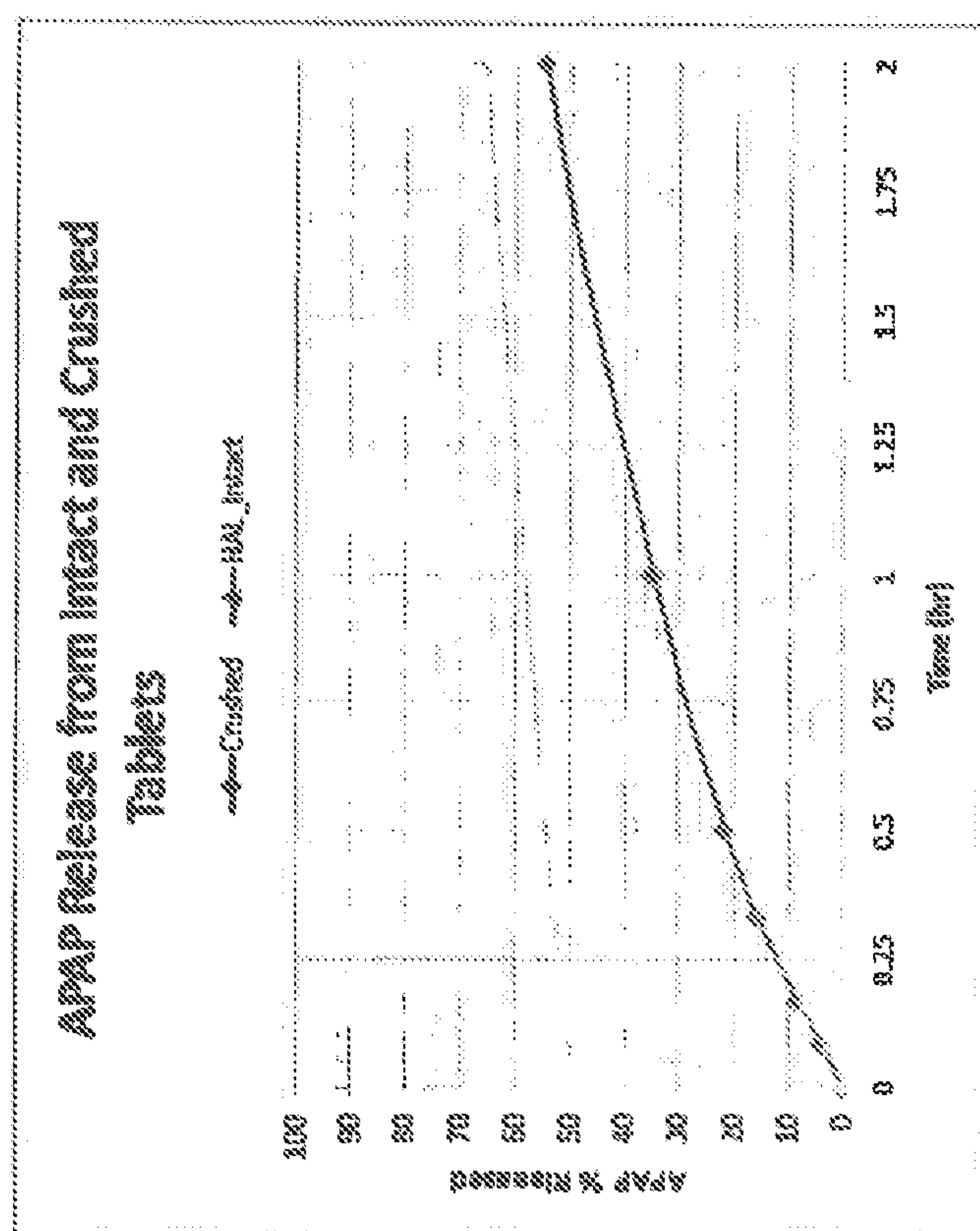


FIG. 31

**FIG. 32A**

**FIG. 32B**

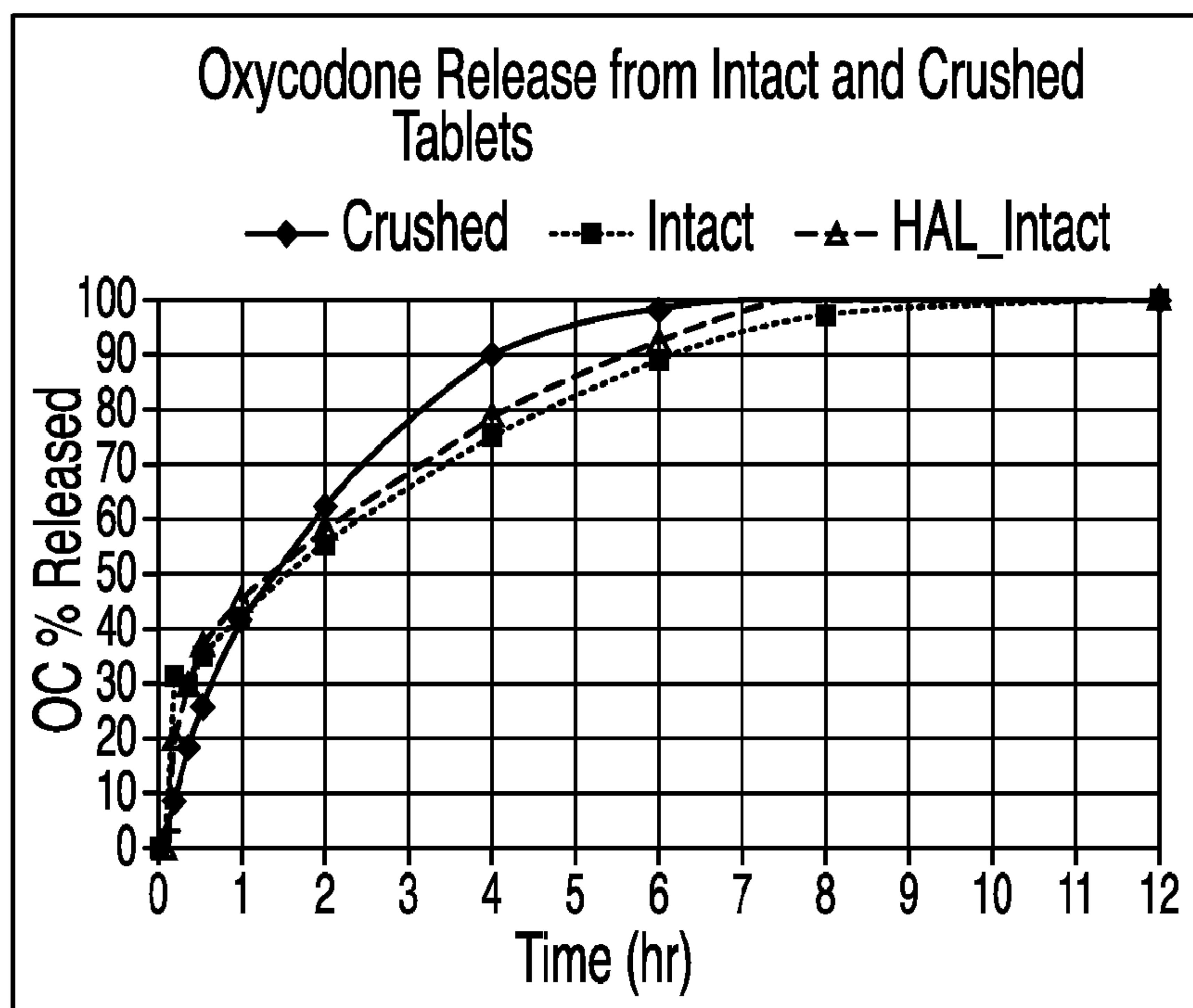


FIG. 33A

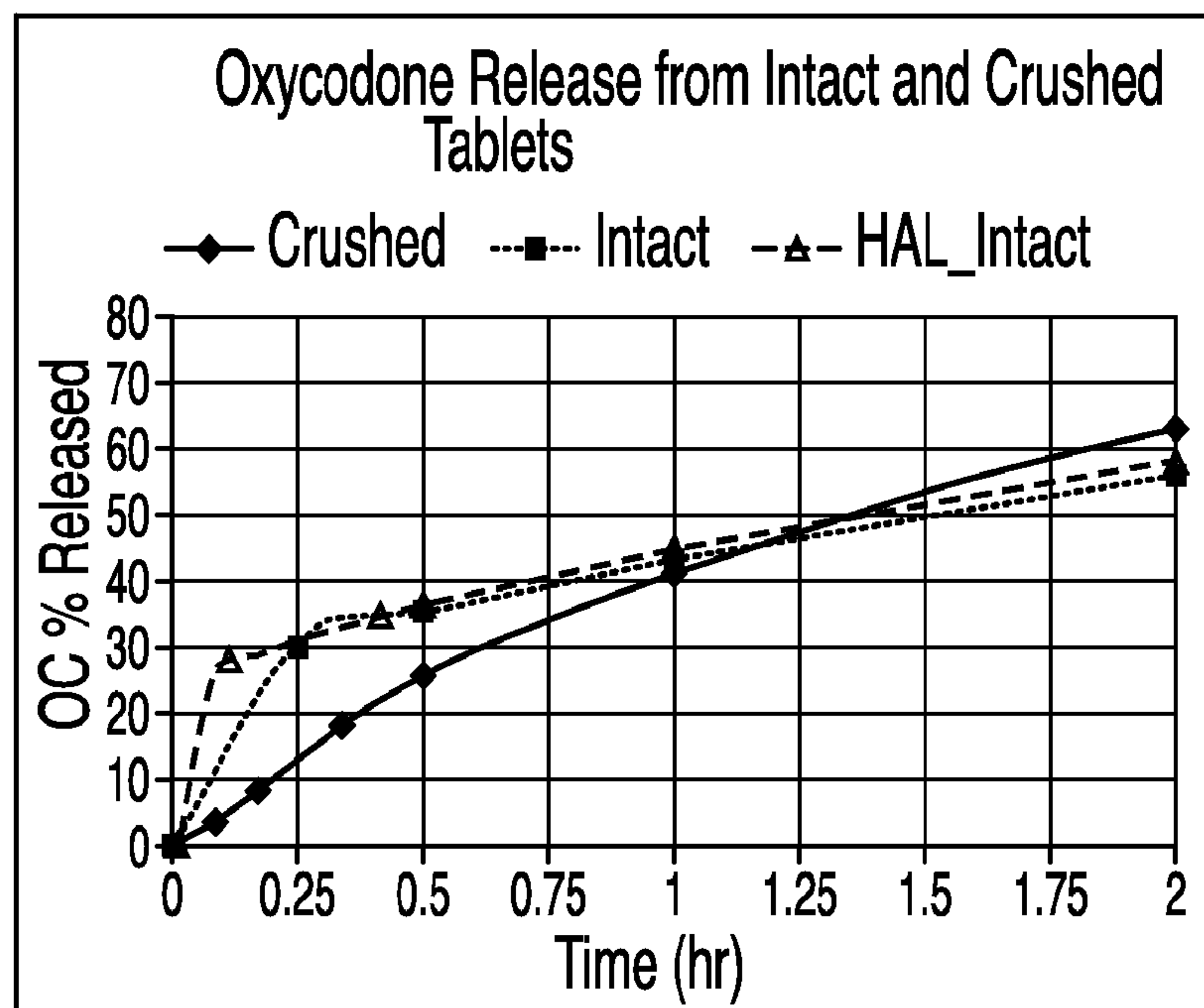


FIG. 33B

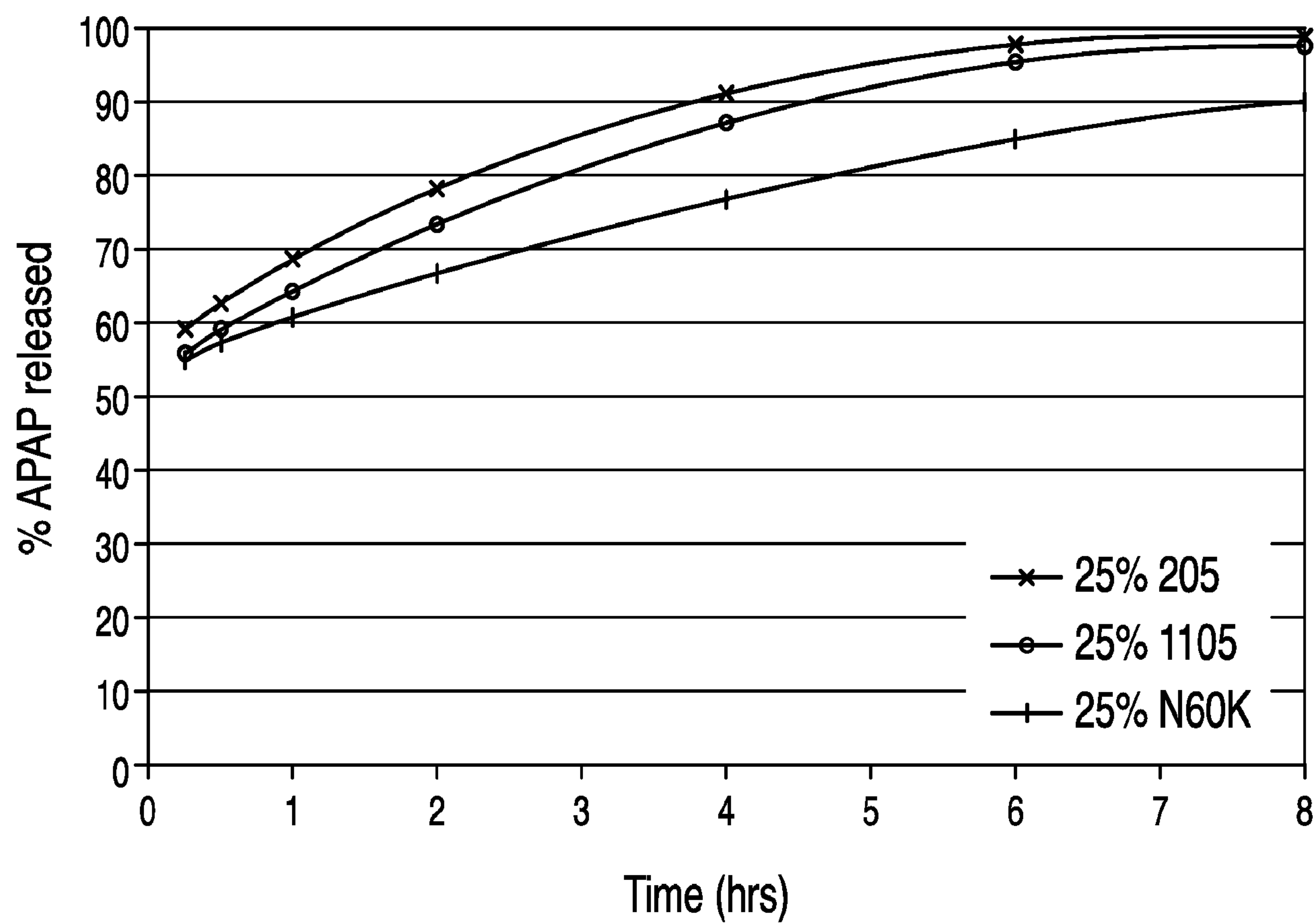


FIG. 34

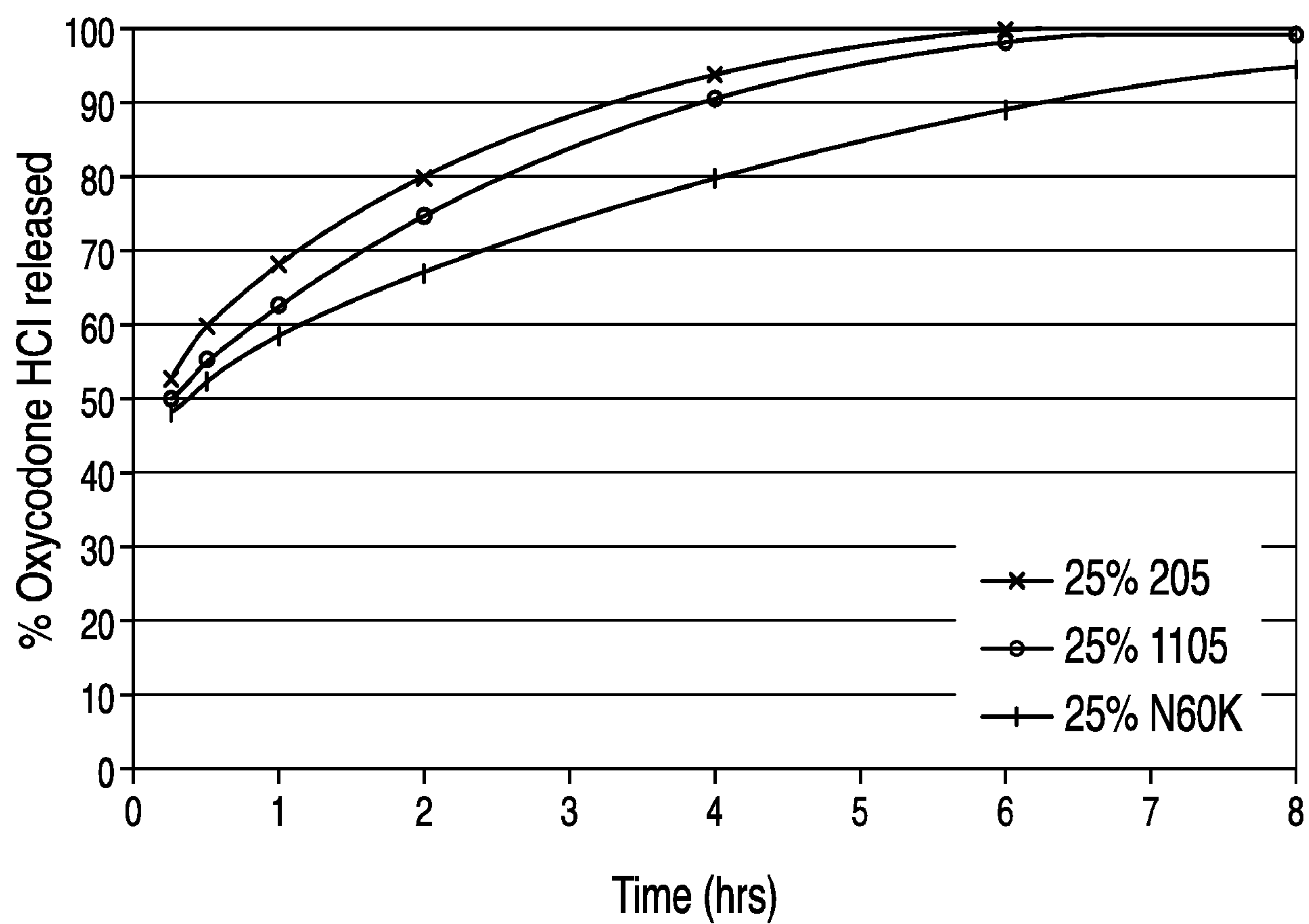


FIG. 35

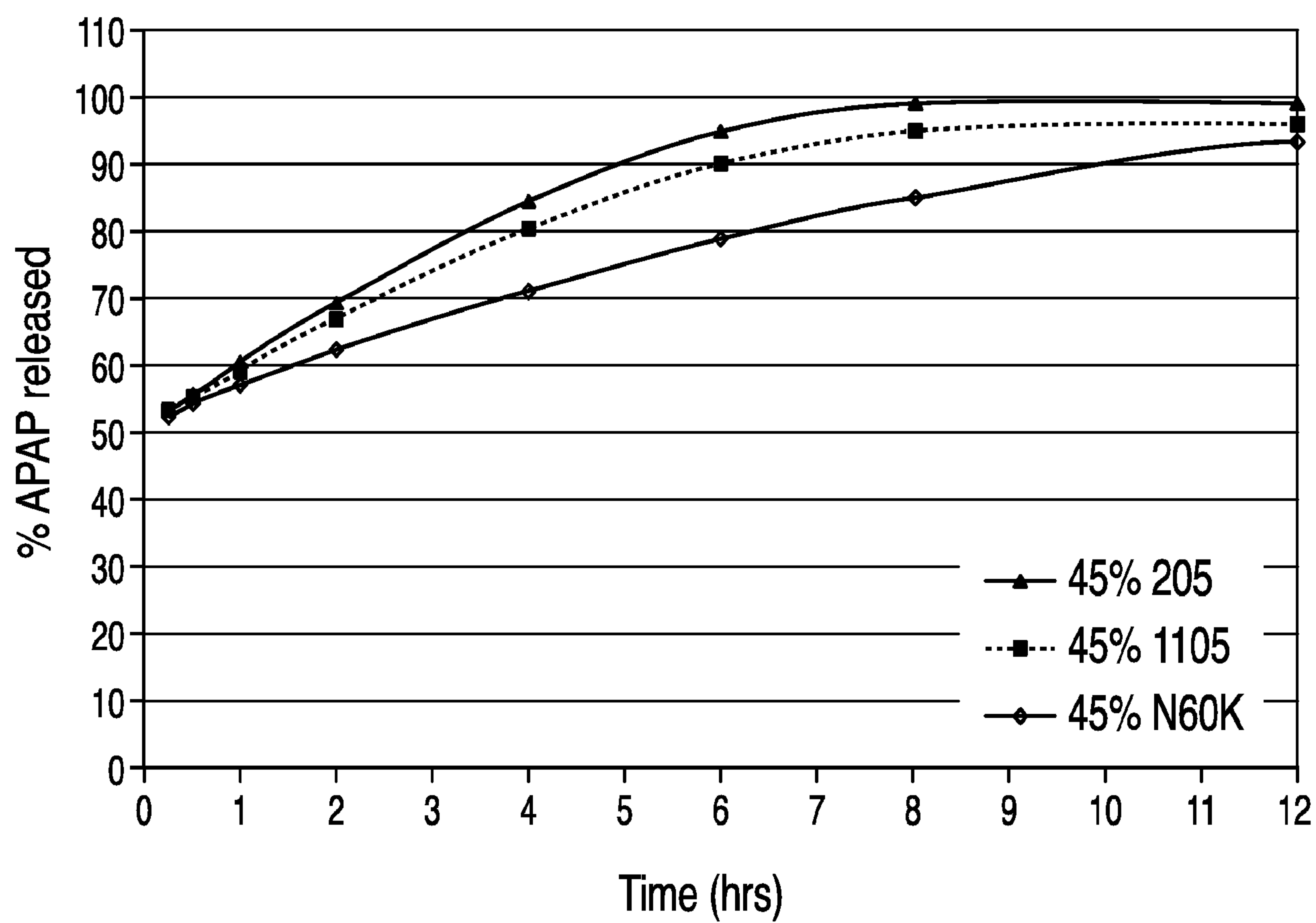


FIG. 36

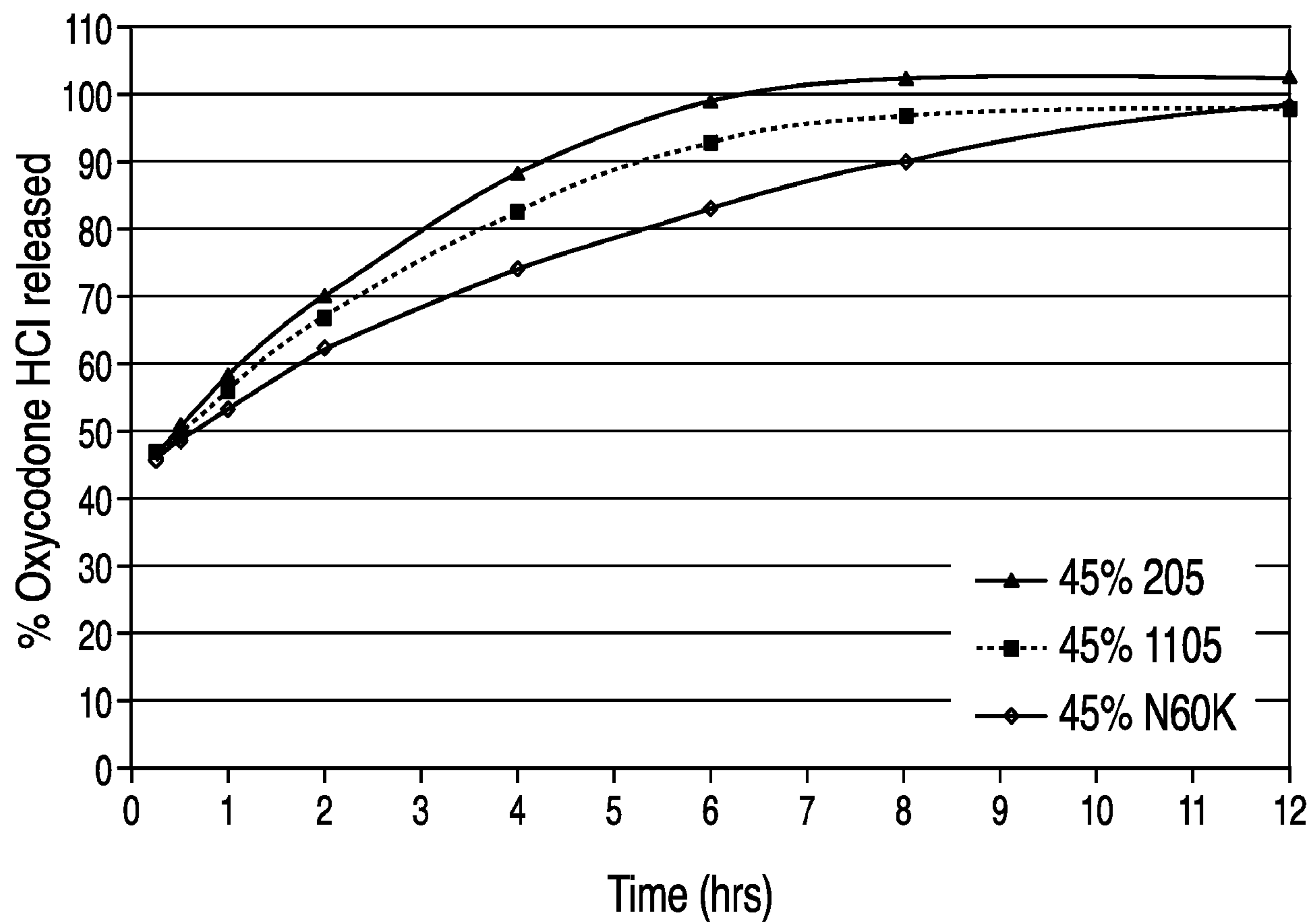


FIG. 37

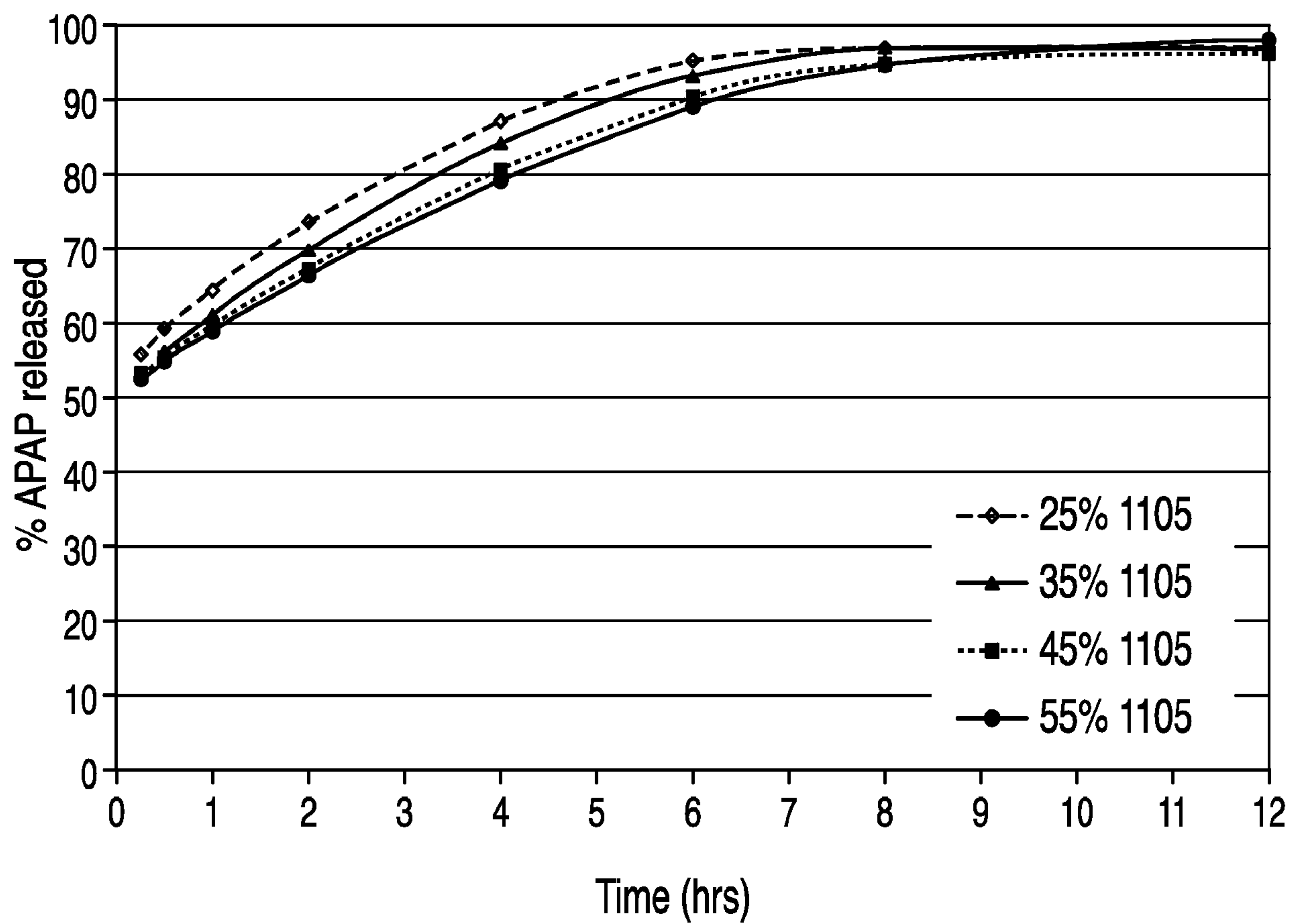


FIG. 38

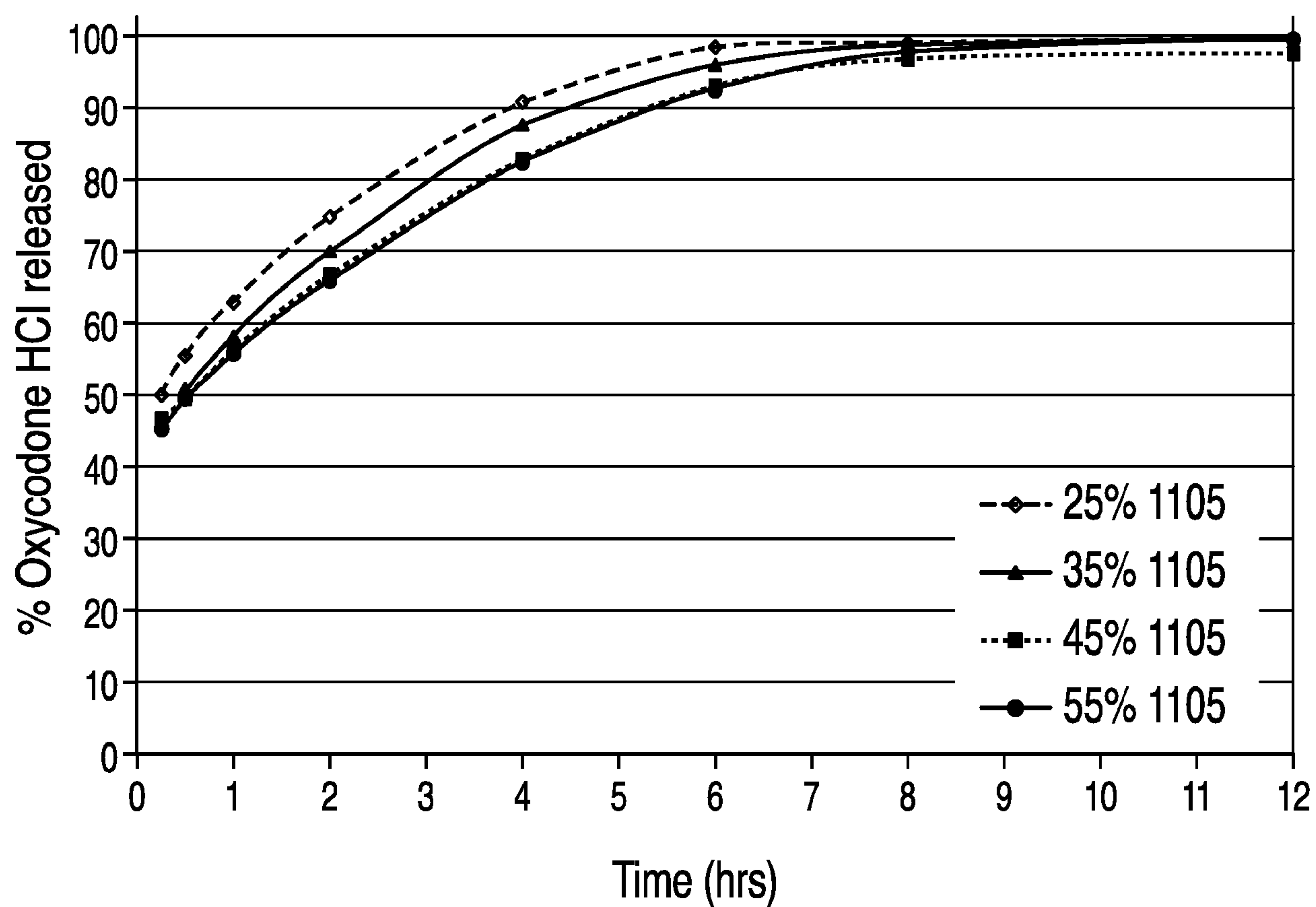


FIG. 39

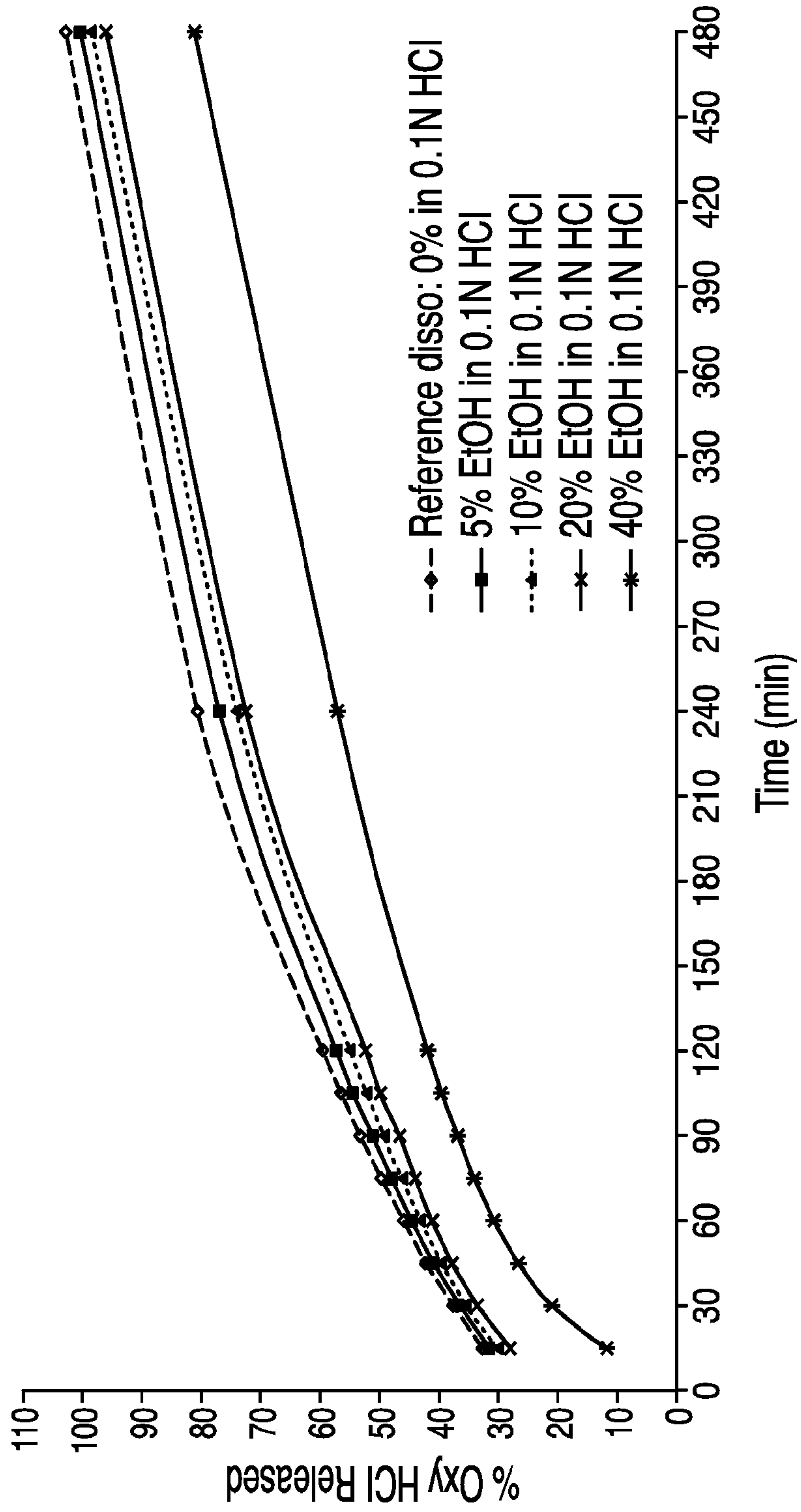


FIG. 40

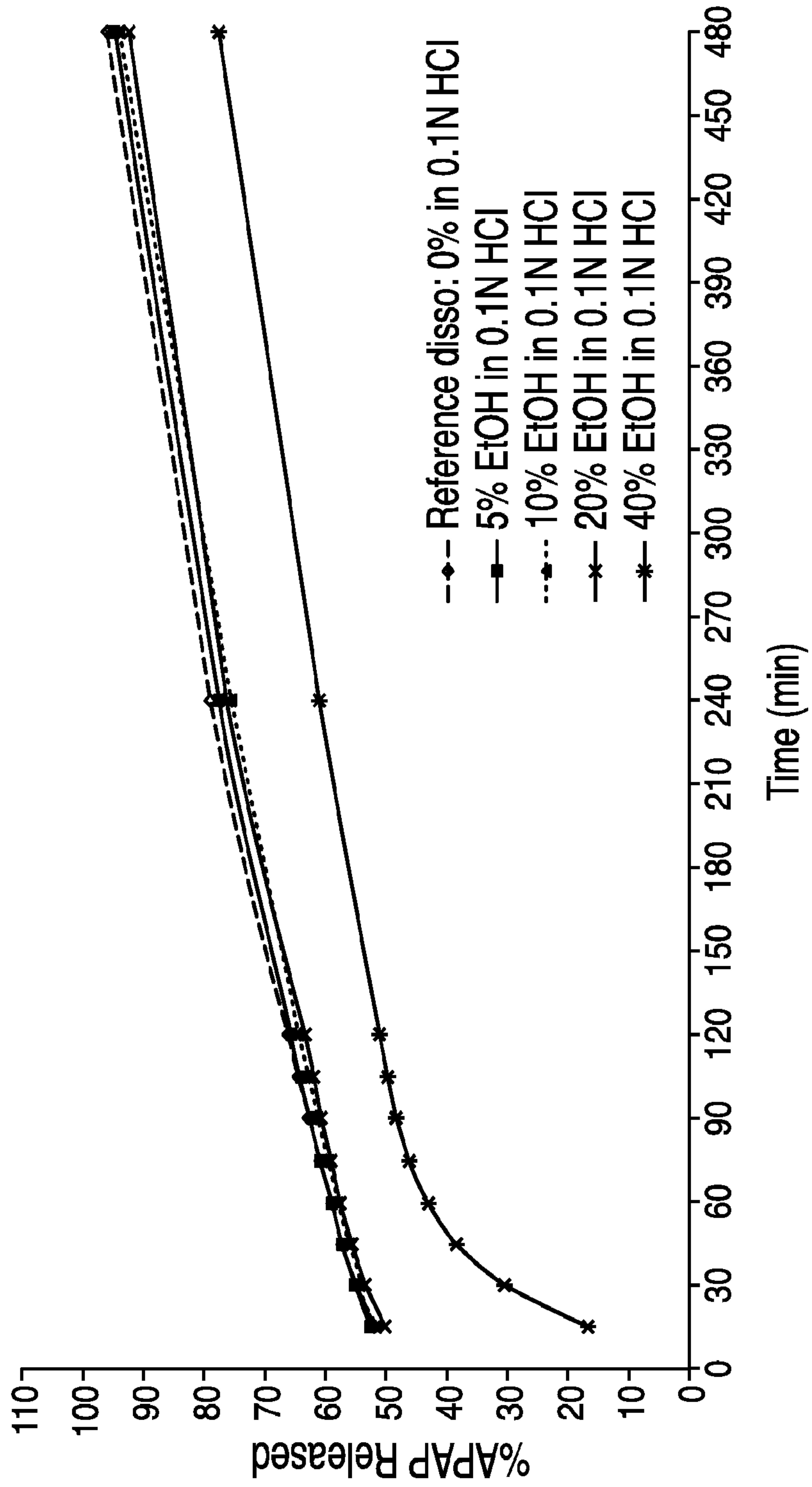


FIG. 41

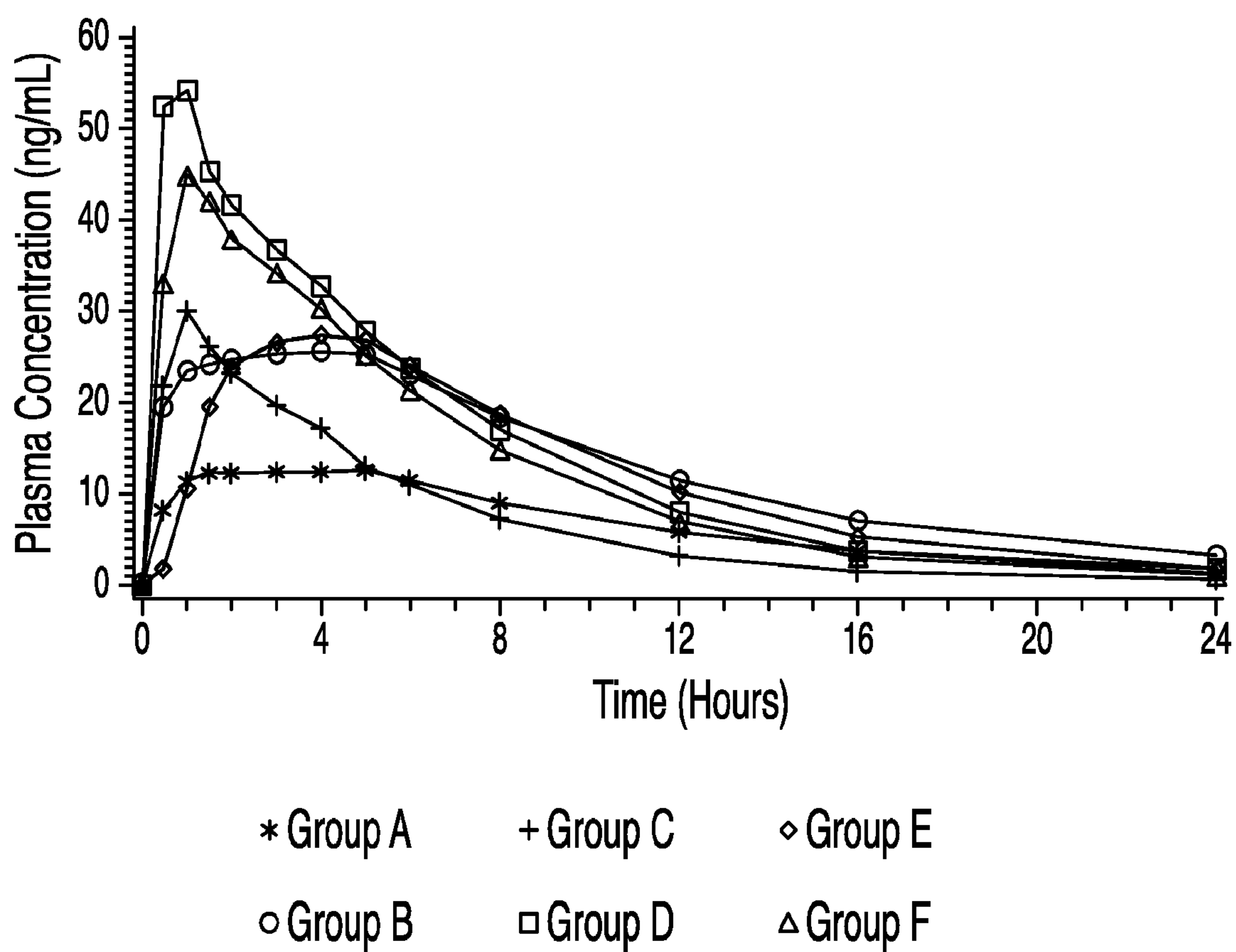


FIG. 42

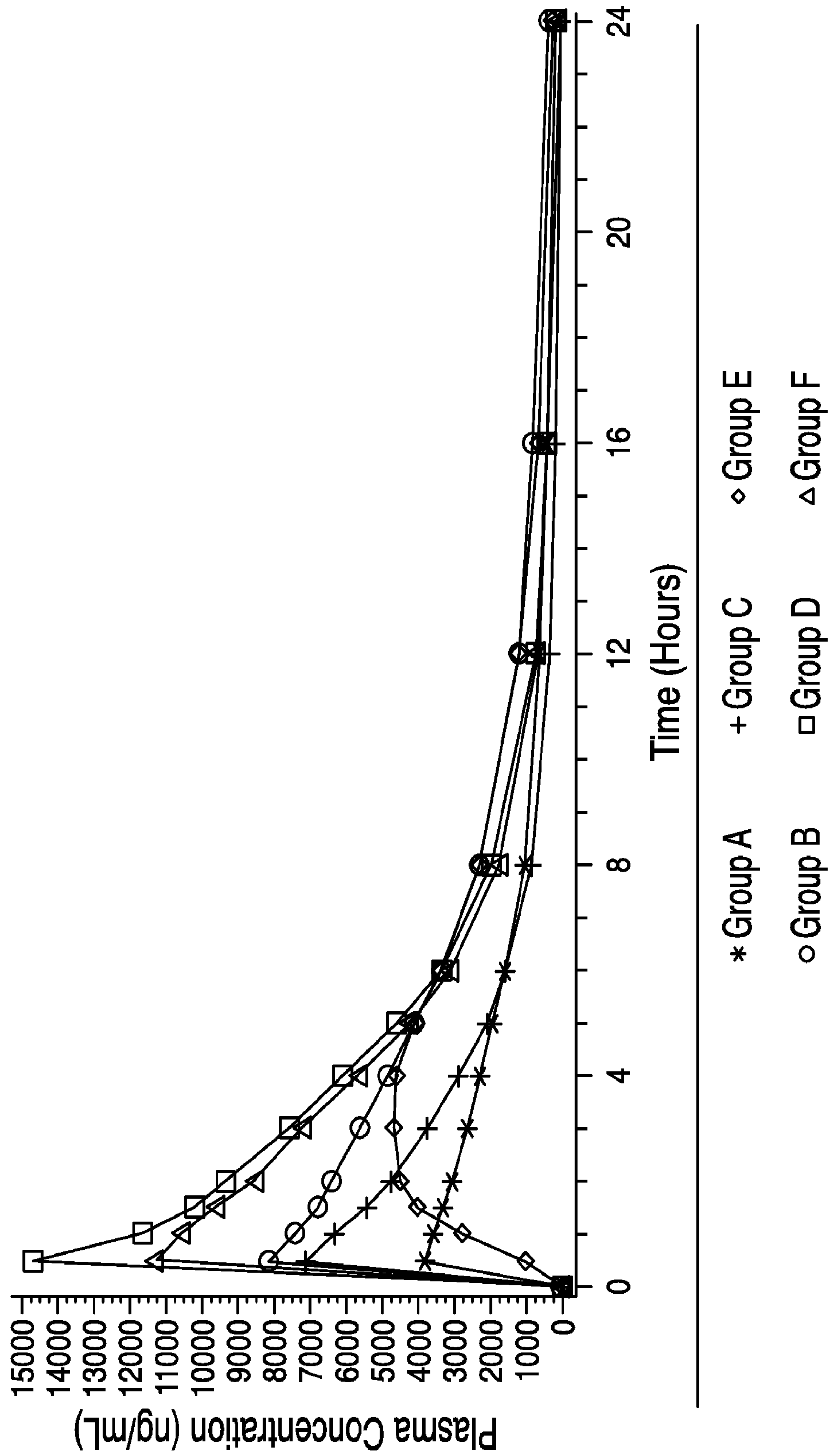
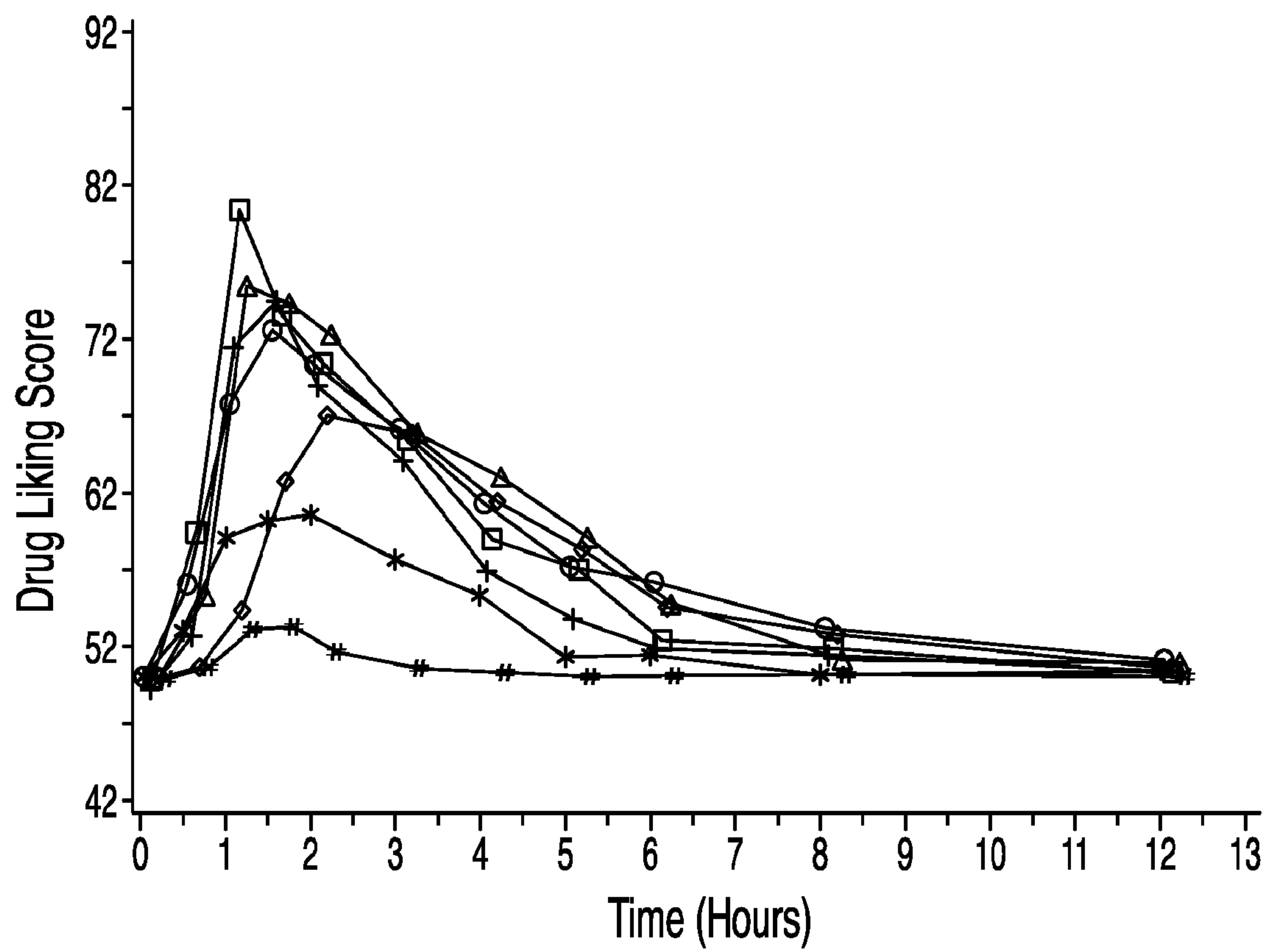


FIG. 43



* Group A + Group C ◇ Group E # Group G
o Group B □ Group D △ Group F

FIG. 44

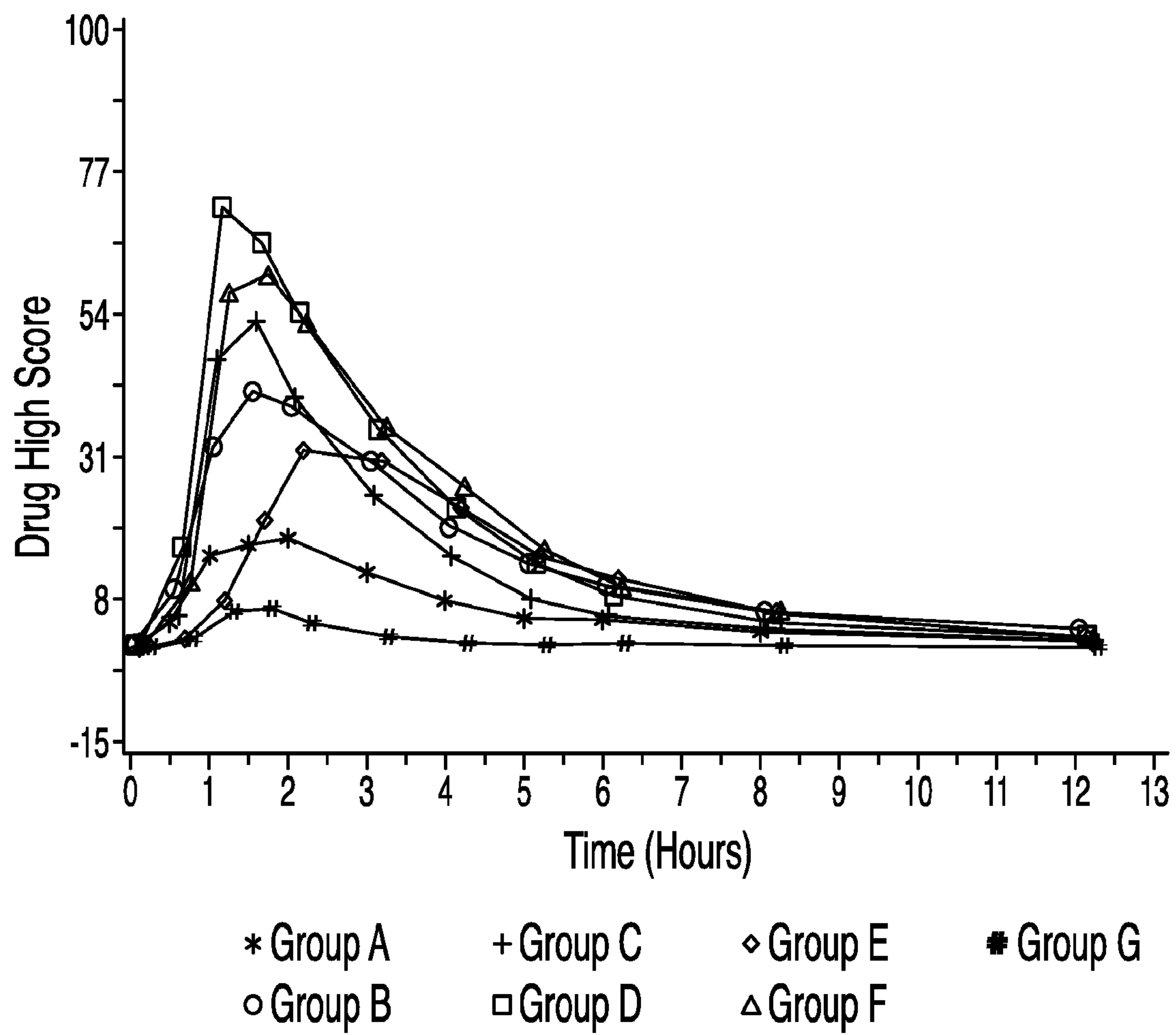


FIG. 45

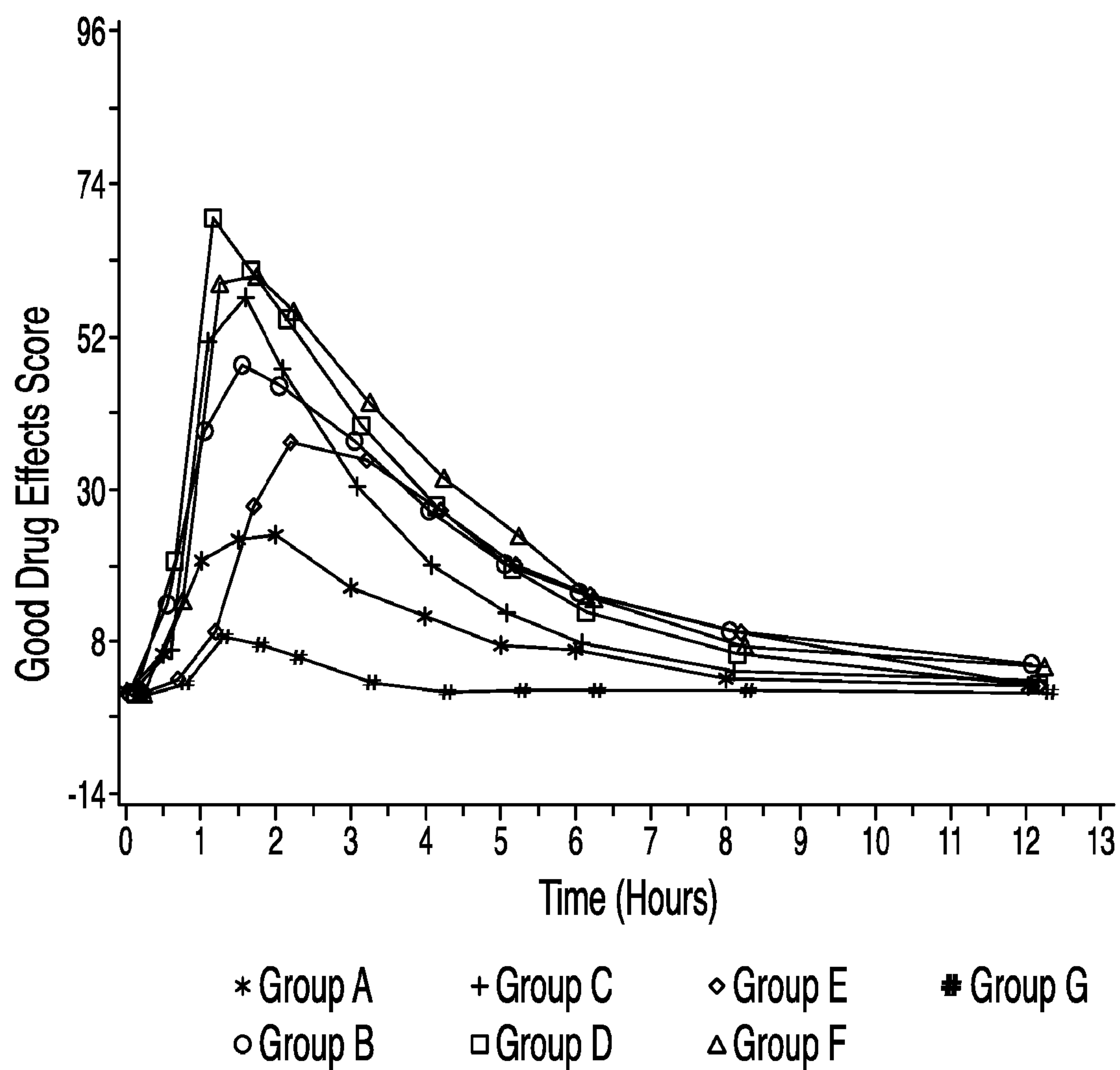


FIG. 46

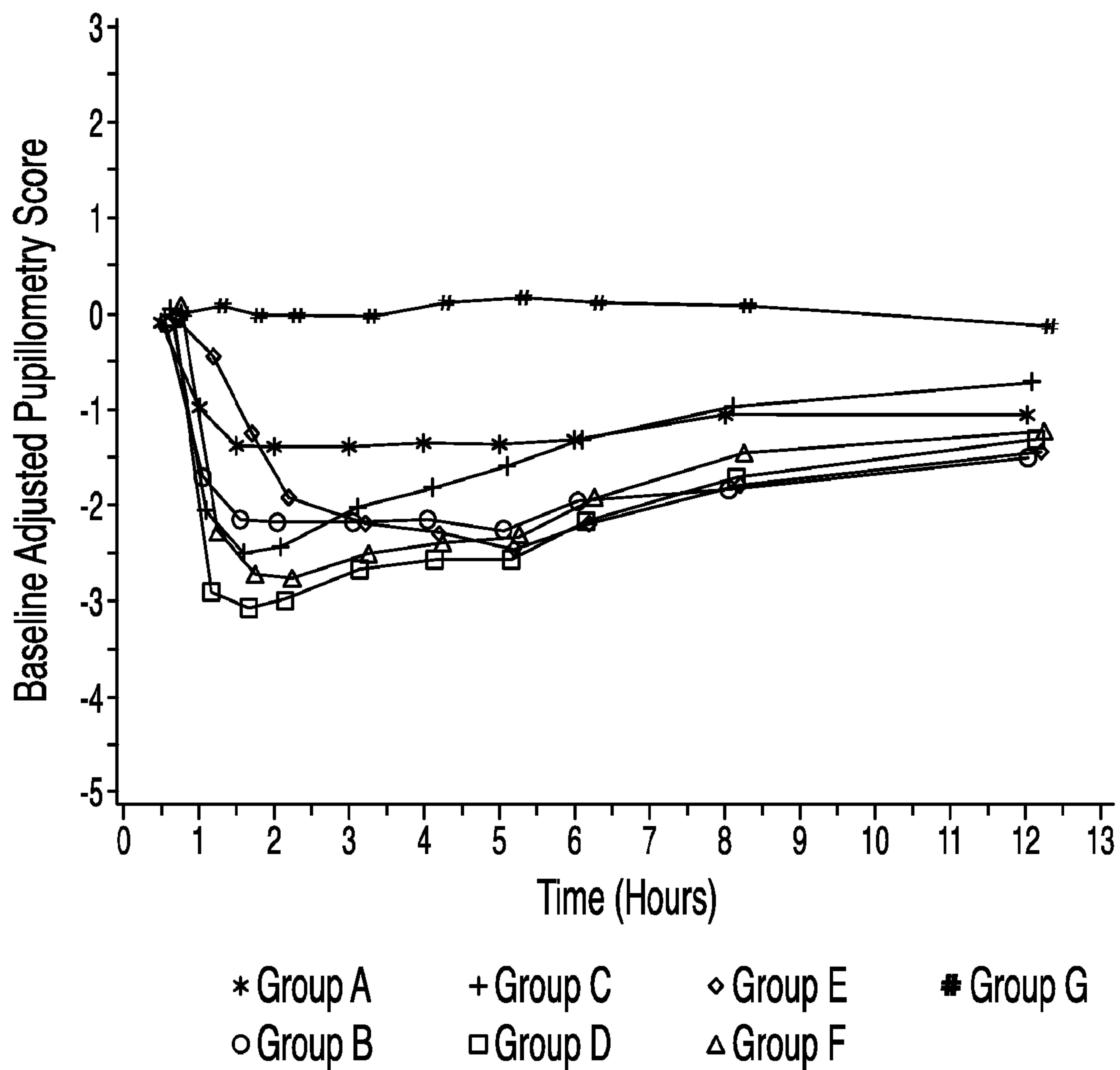


FIG. 47

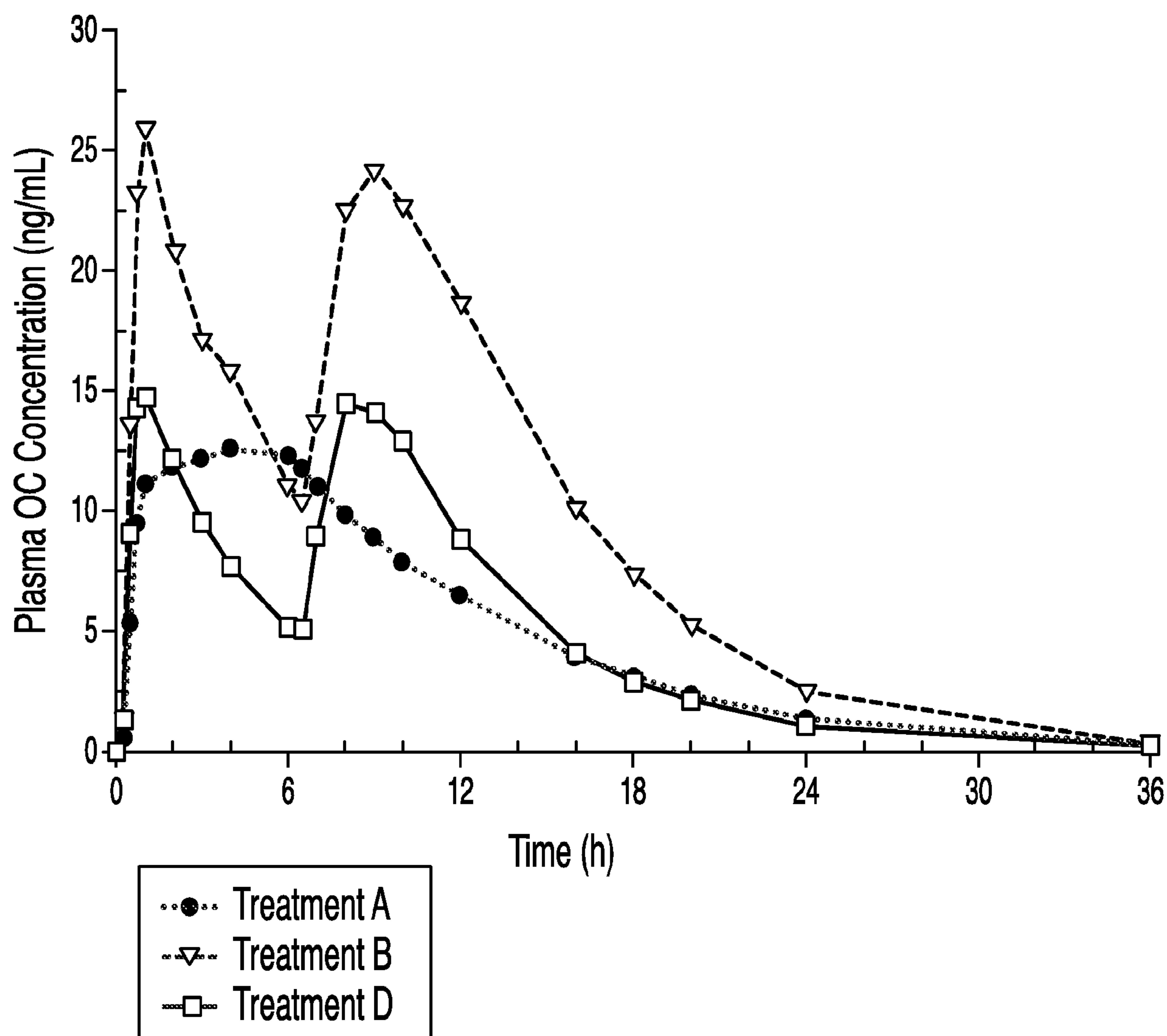


FIG. 48

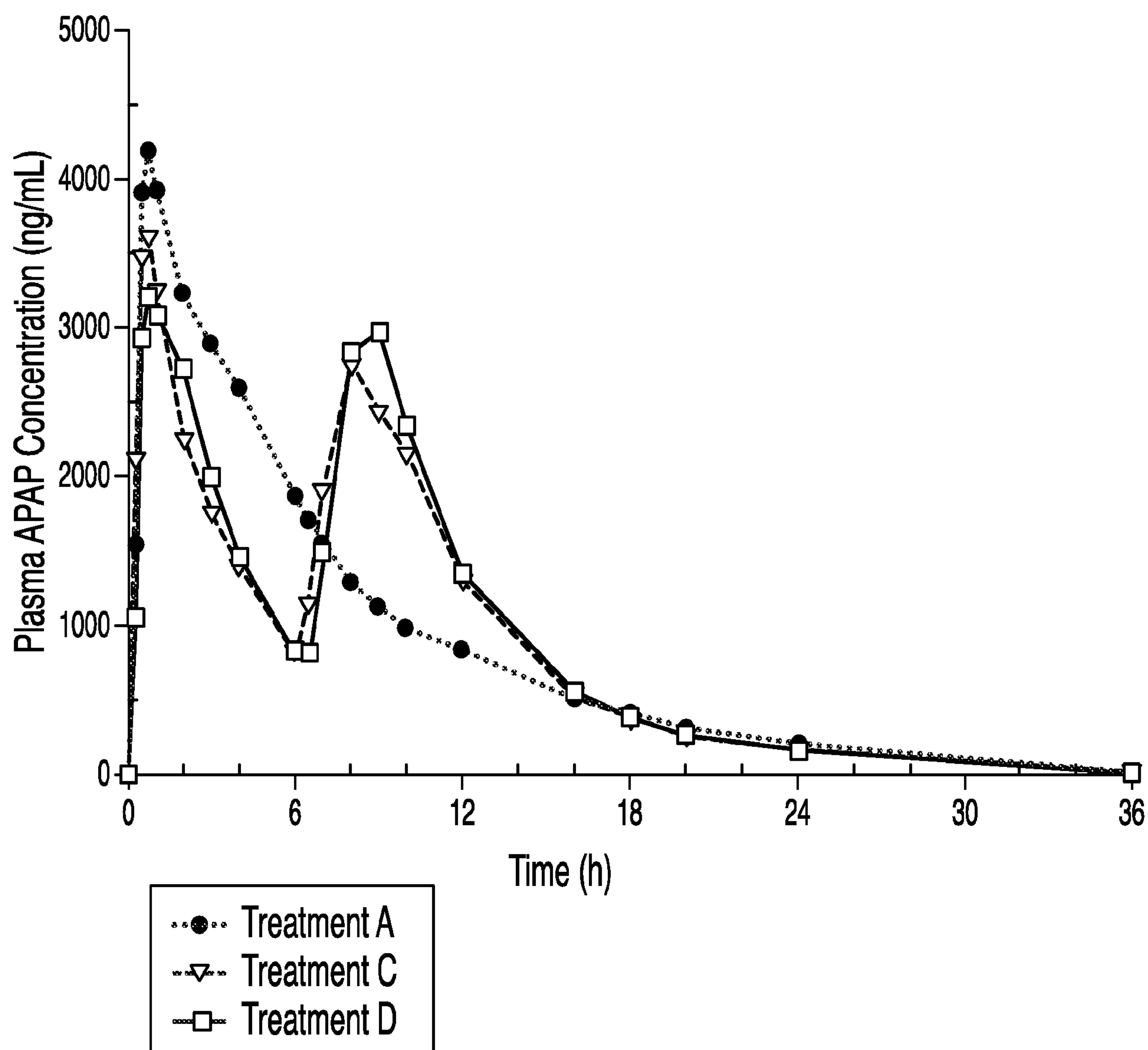


FIG. 49

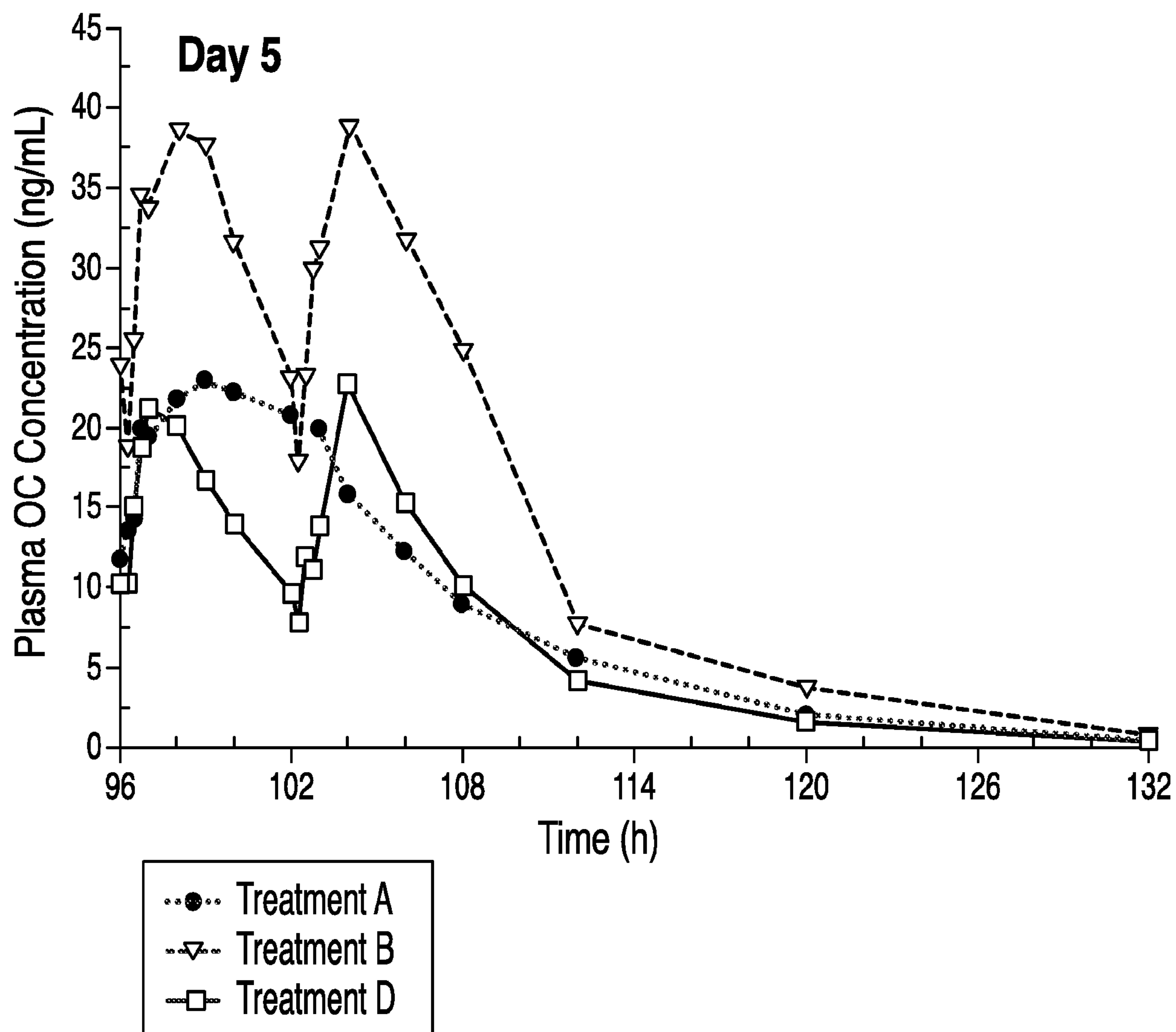


FIG. 50

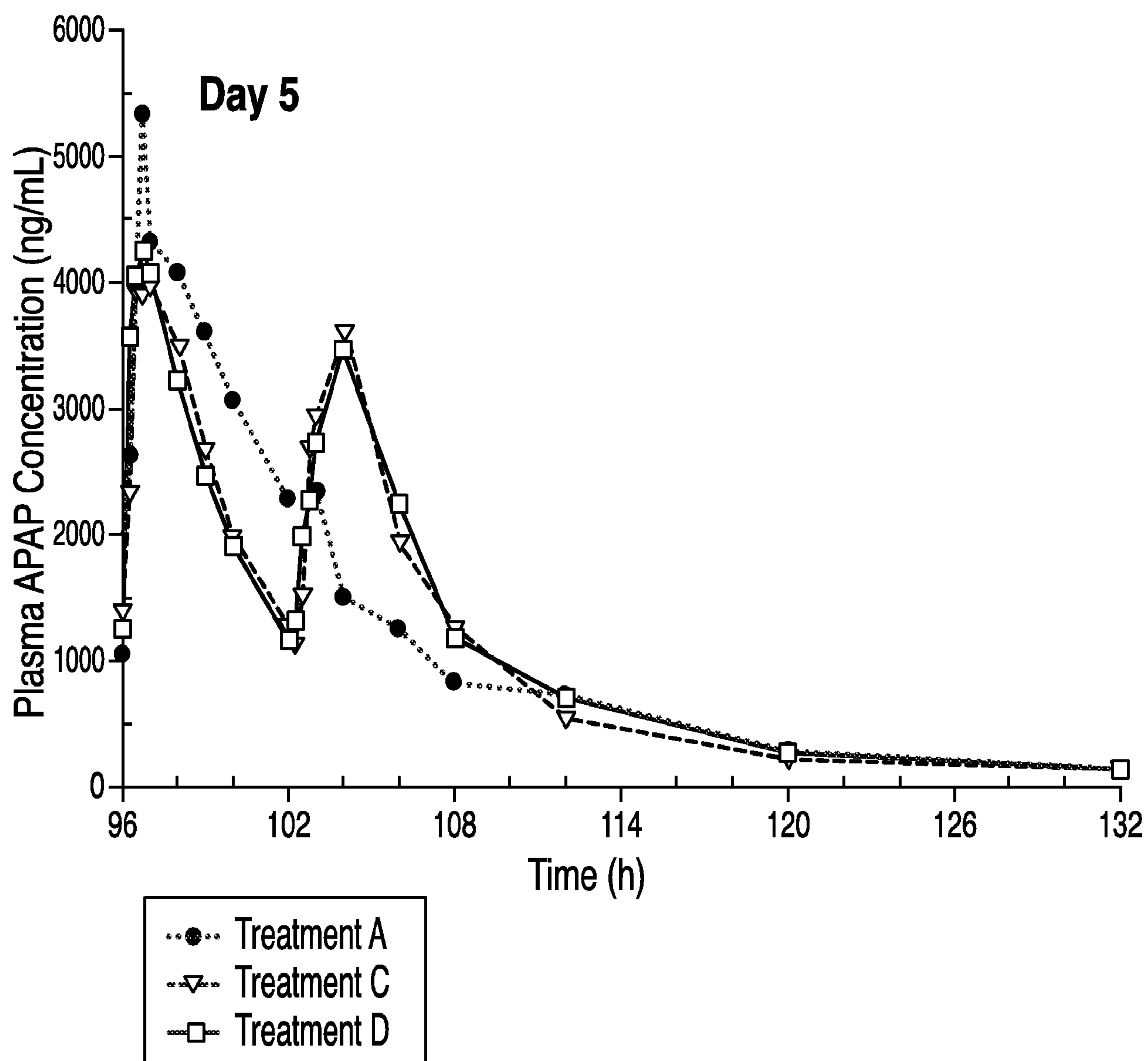


FIG. 51

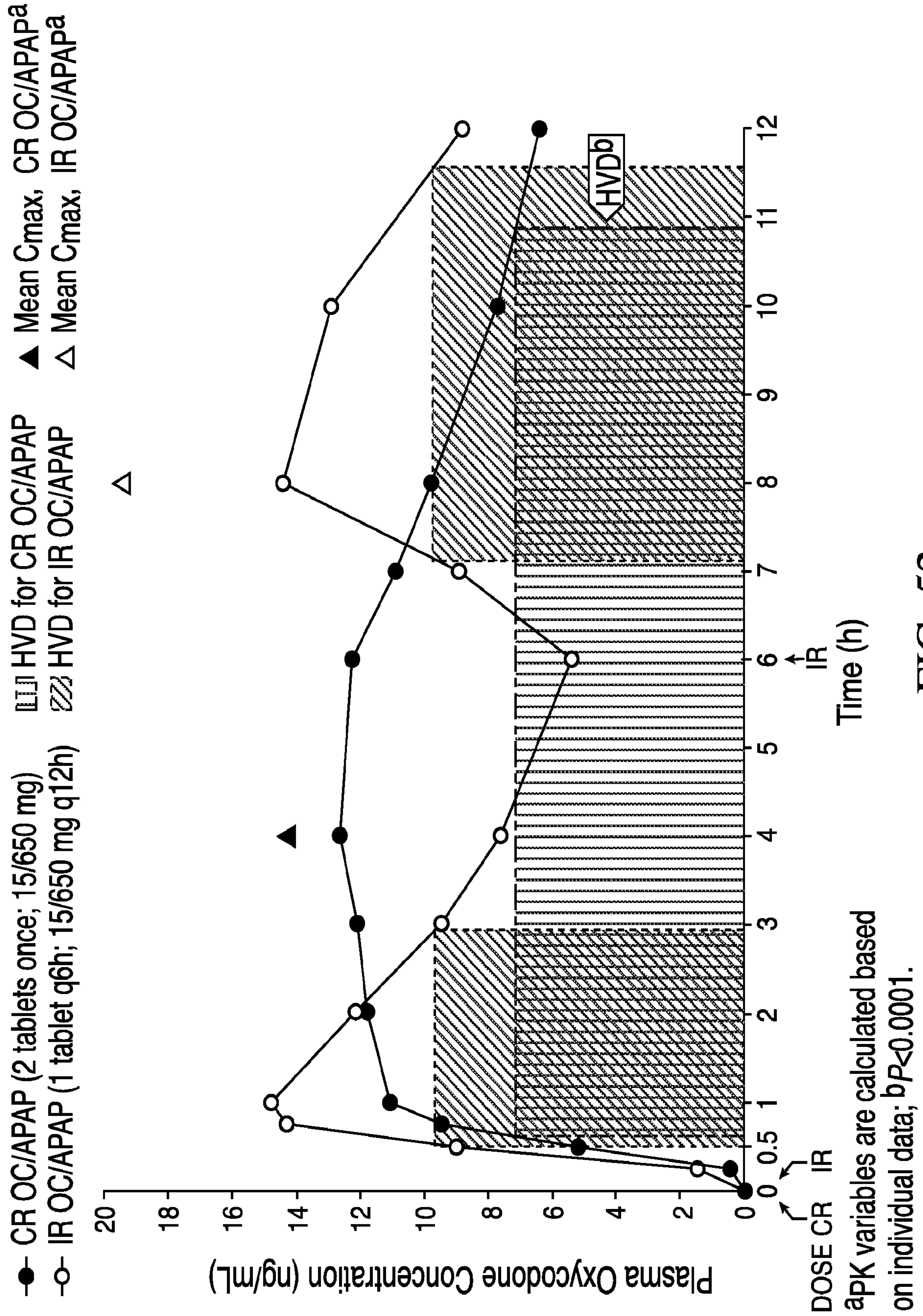


FIG. 52

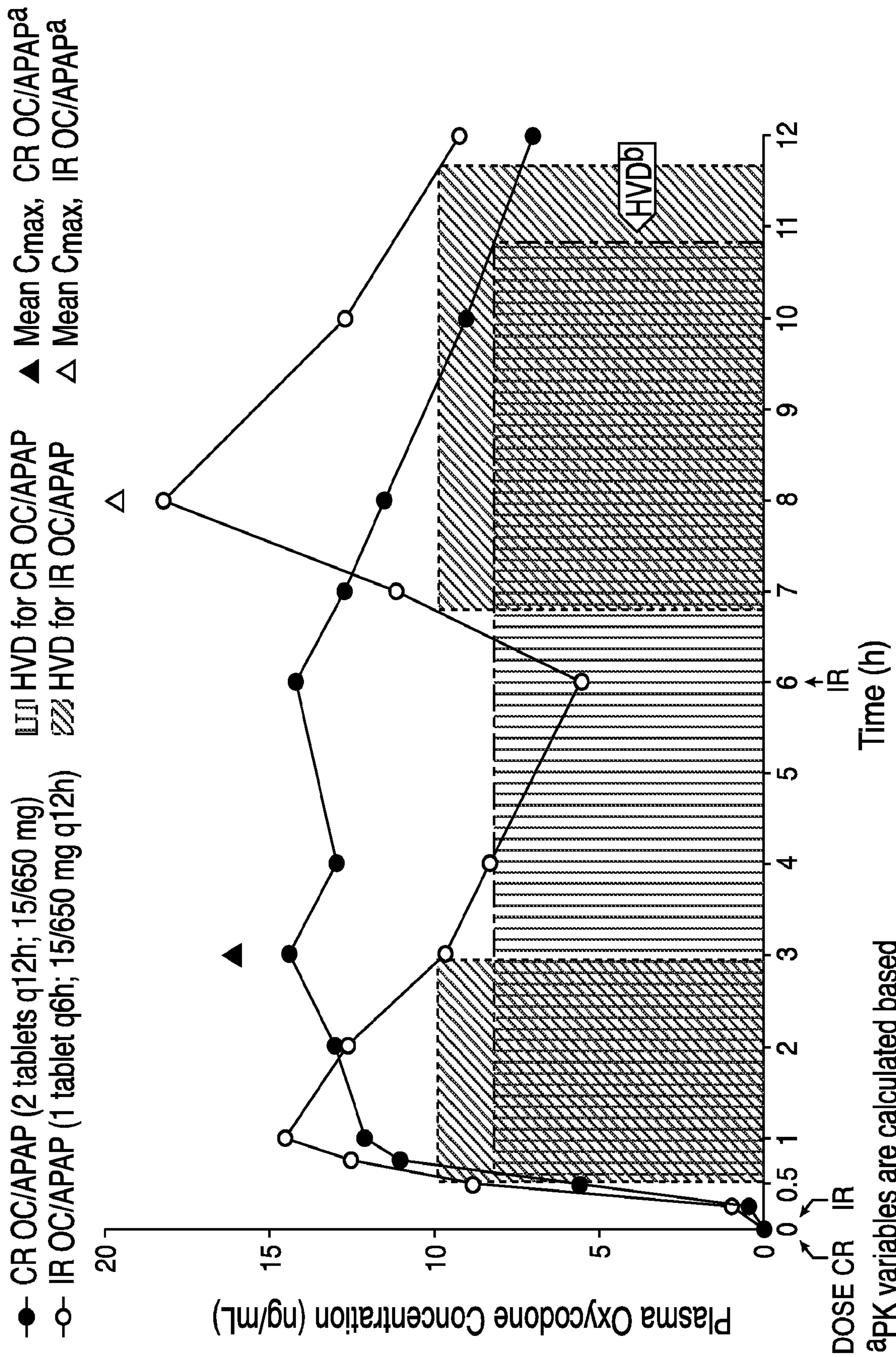


FIG. 53

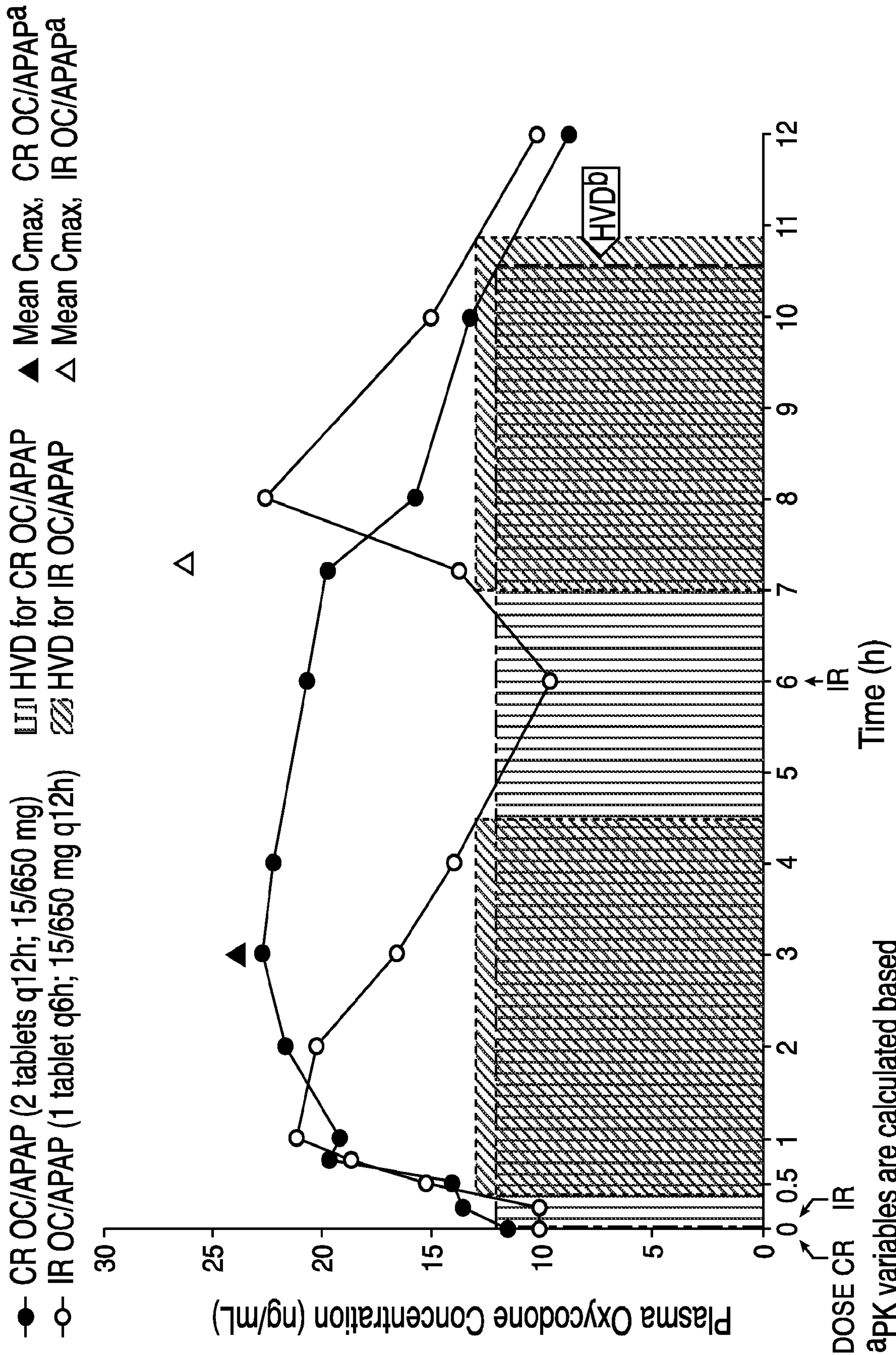


FIG. 54

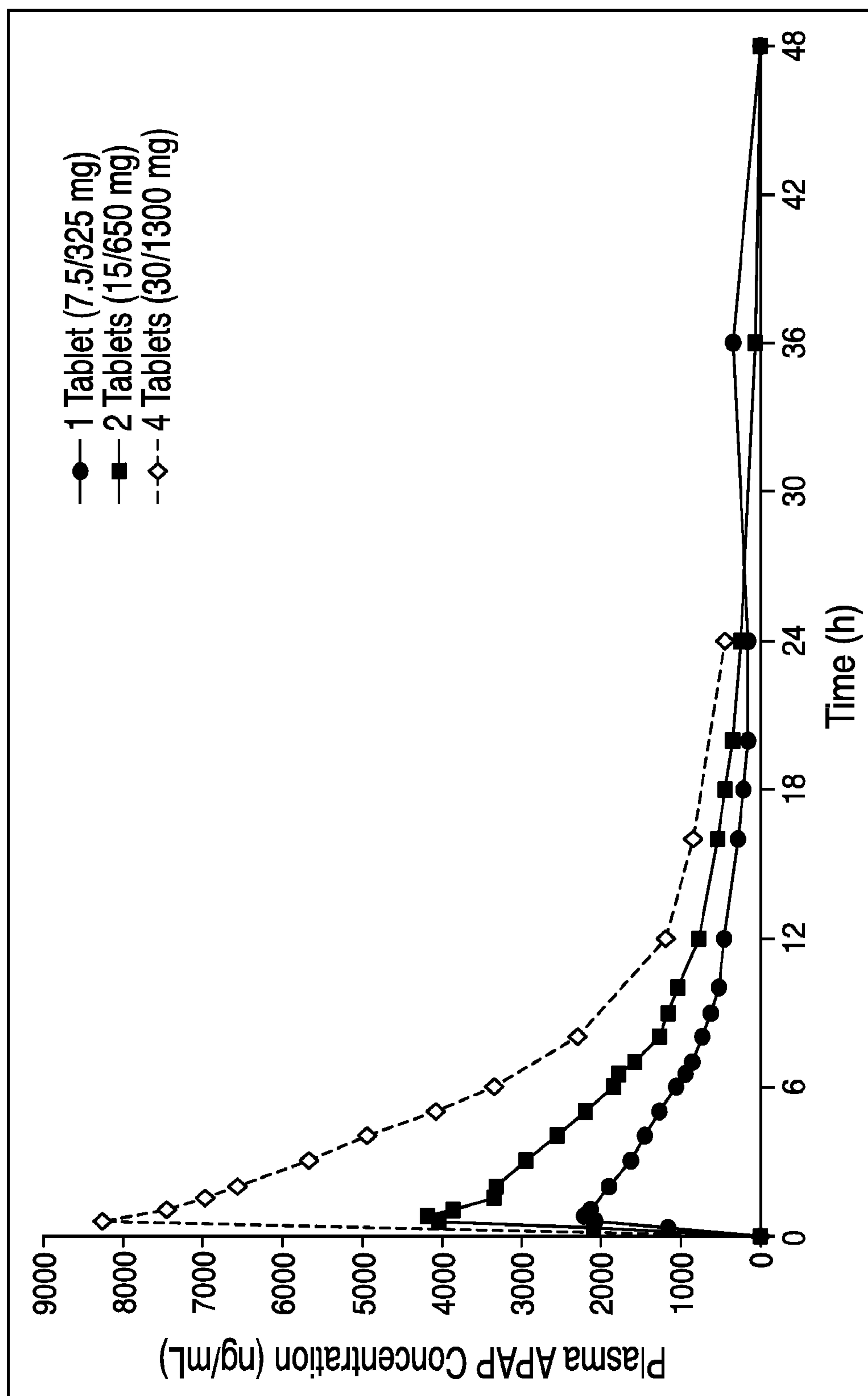
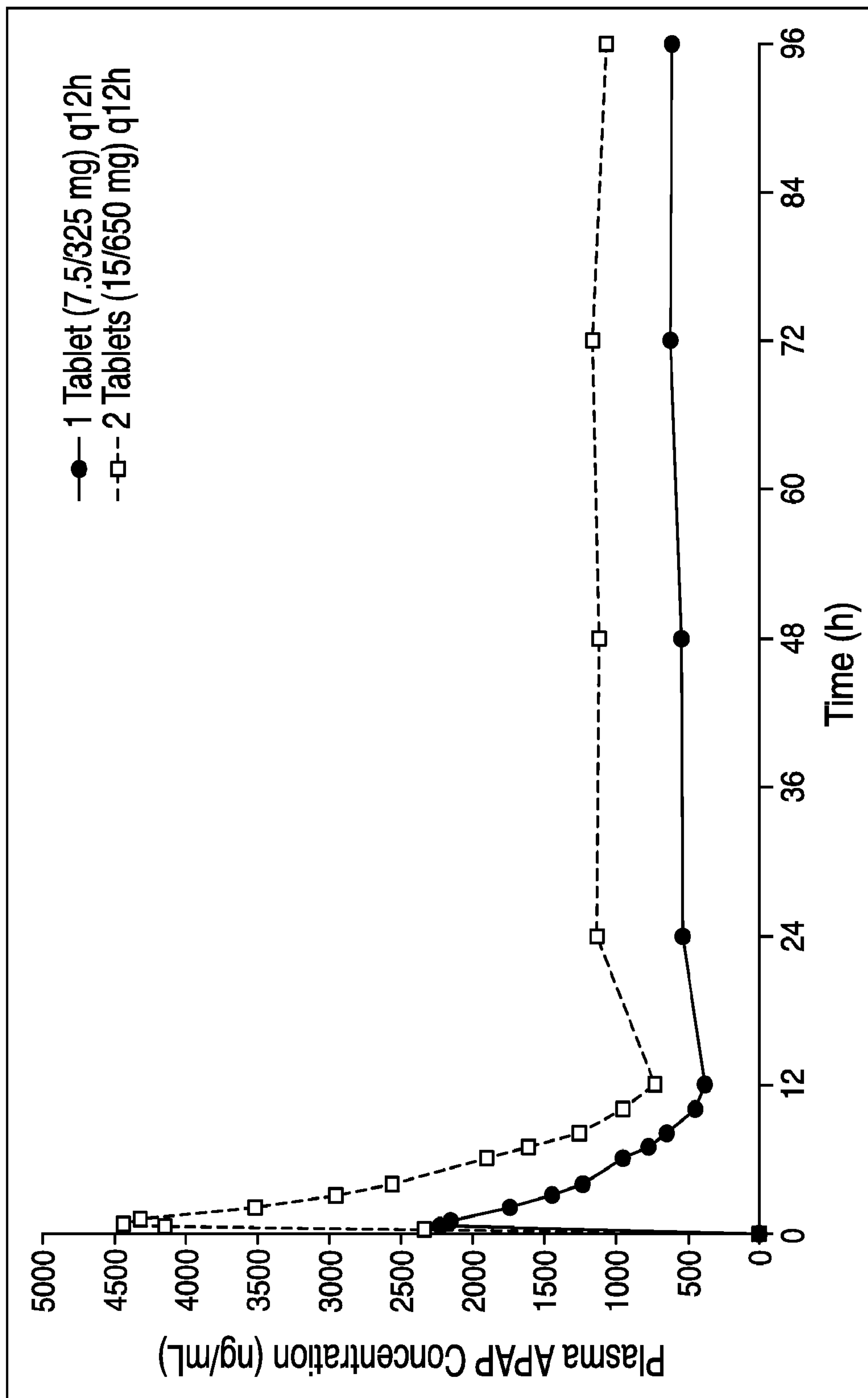


FIG. 55



aPlasma only collected prior to morning dose on days 2 to 4.

FIG. 56

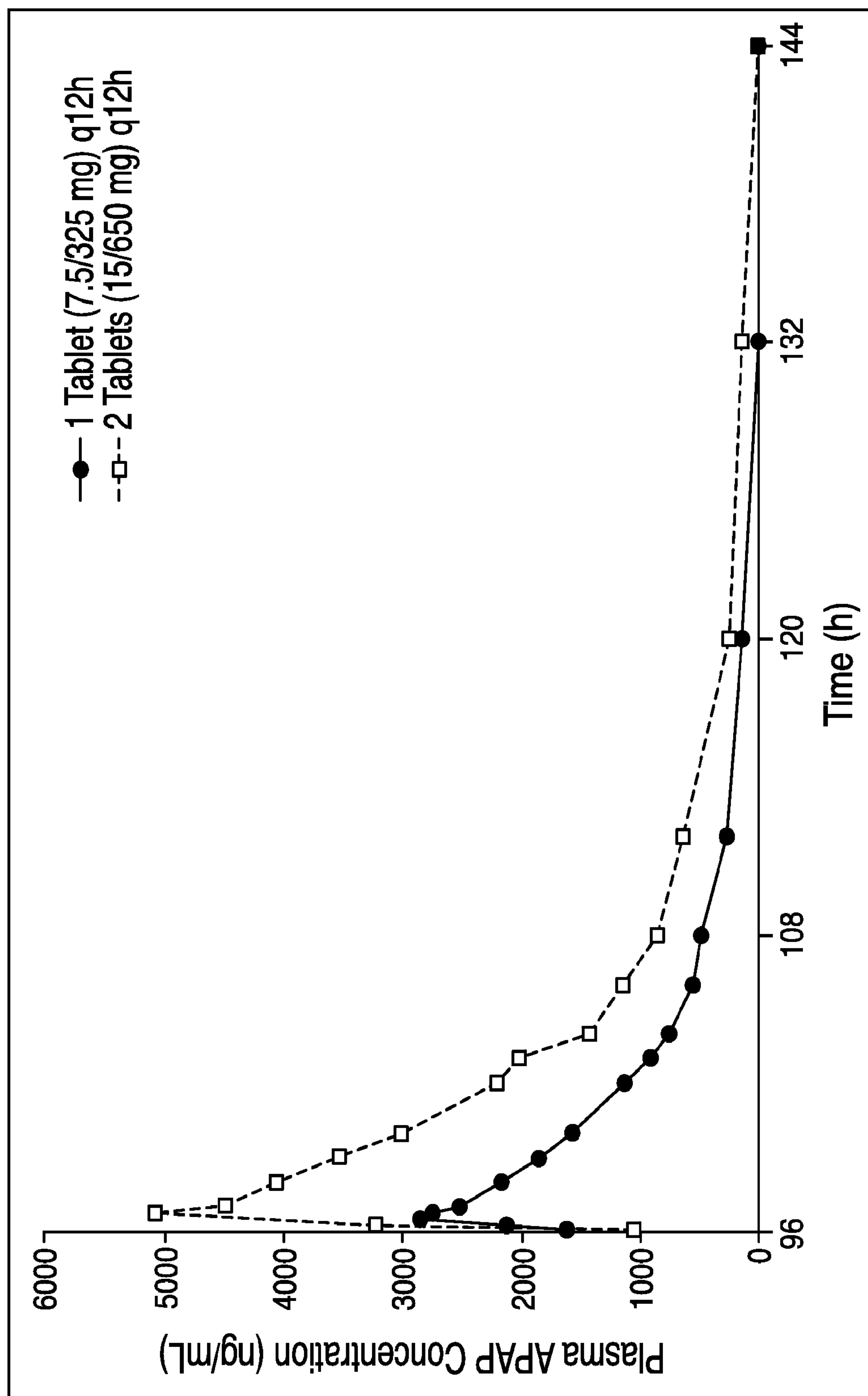


FIG. 57

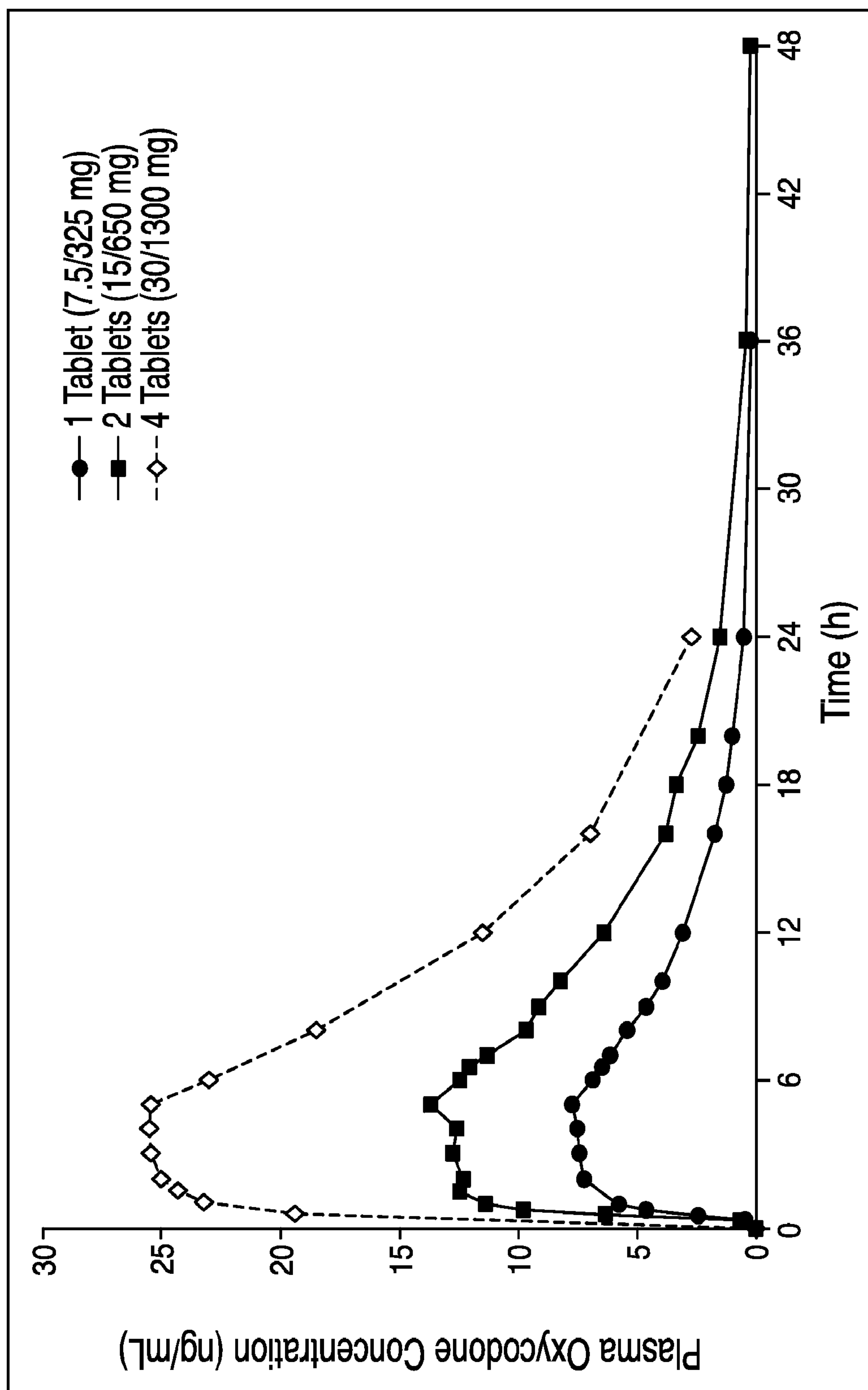
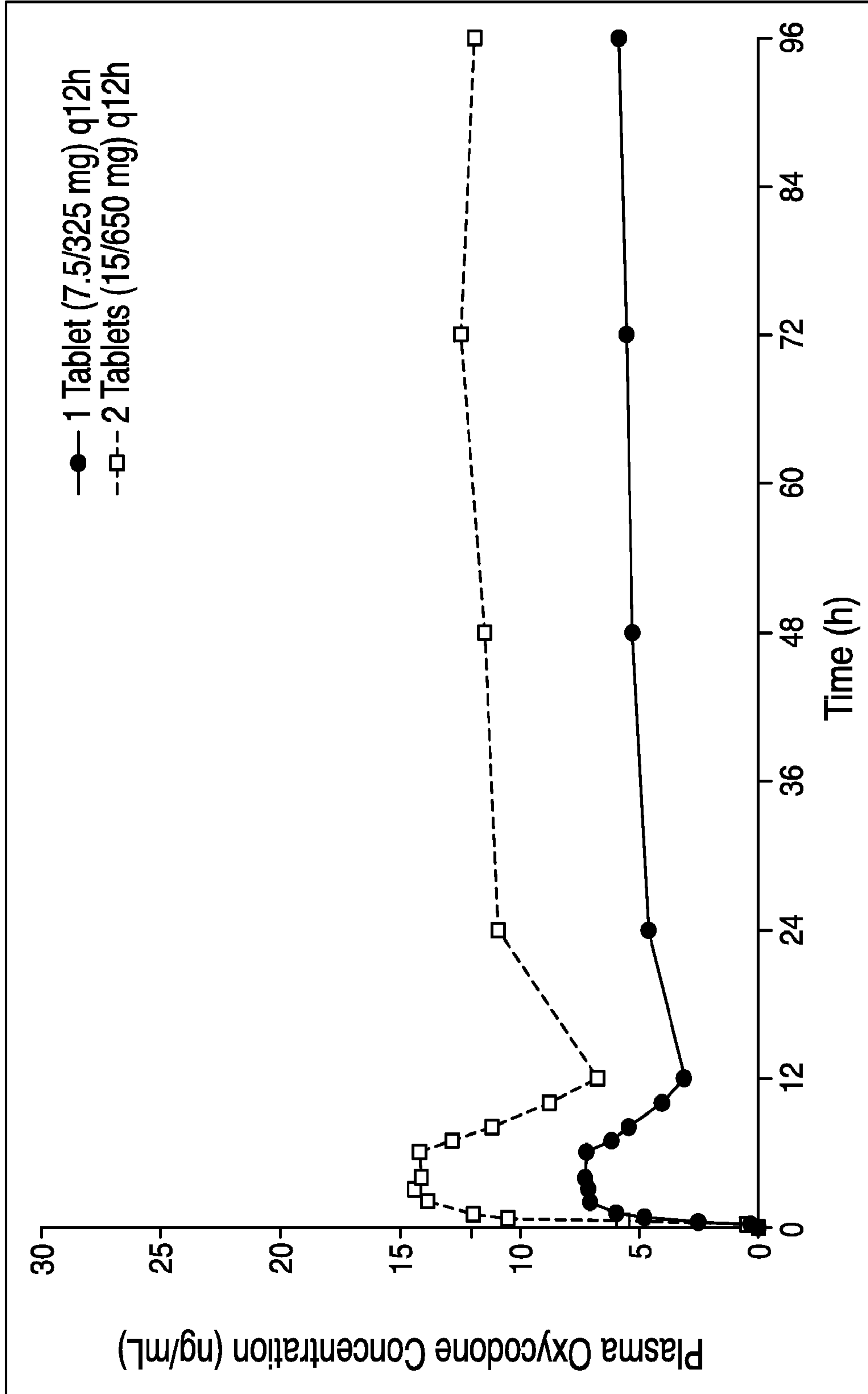


FIG. 58



^aPlasma only collected prior to morning dose on days 2 to 4.

FIG. 59

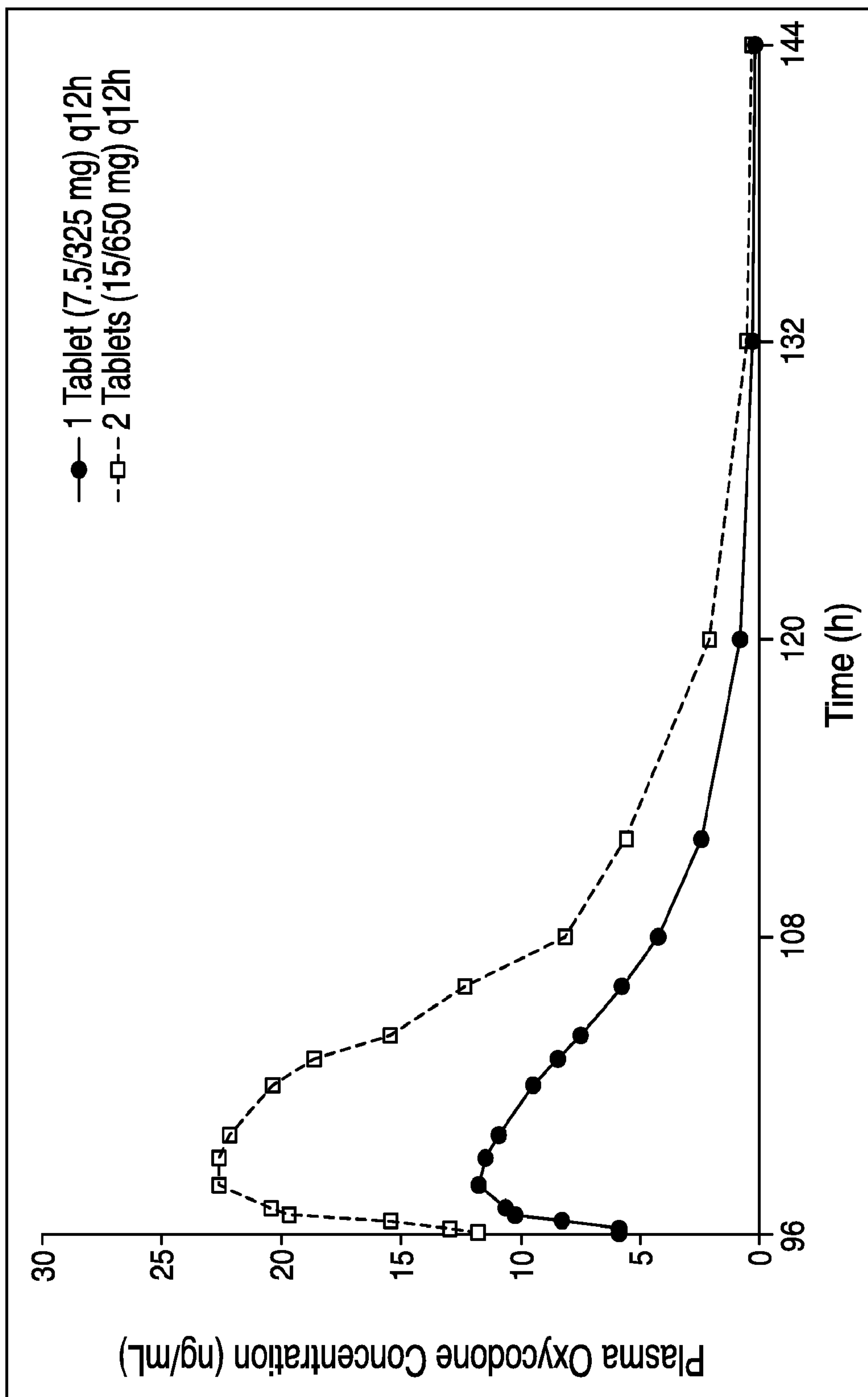
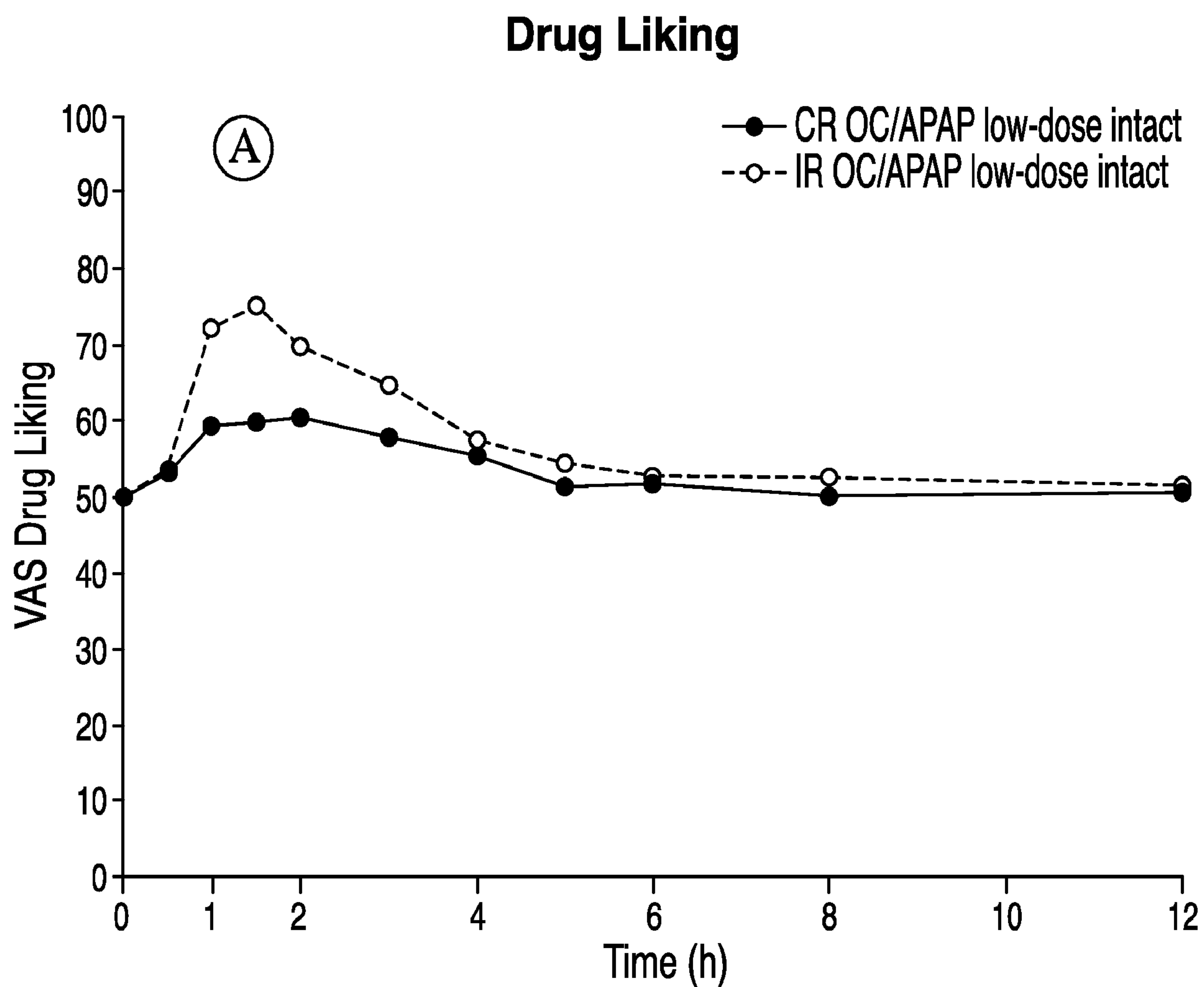
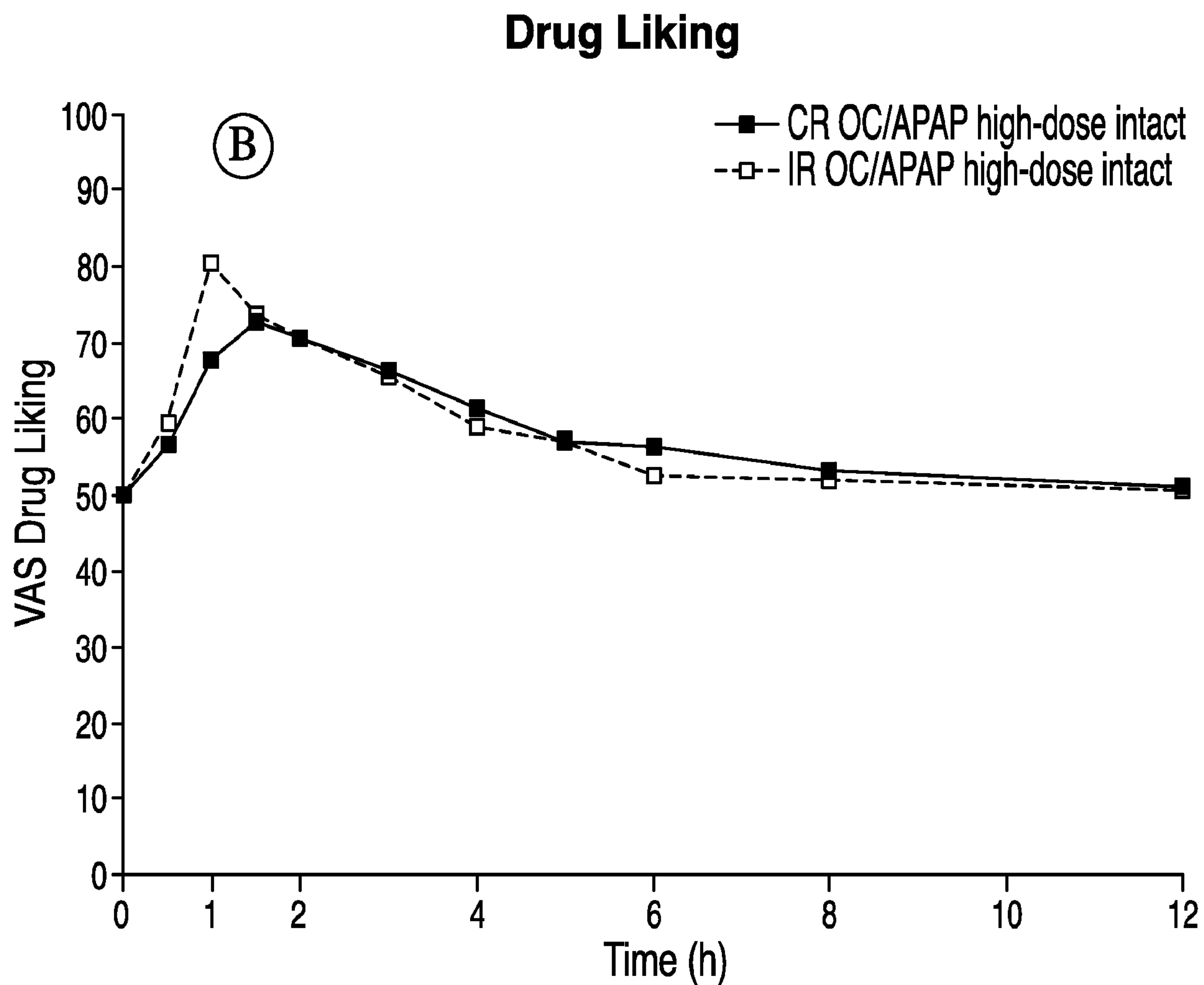


FIG. 60



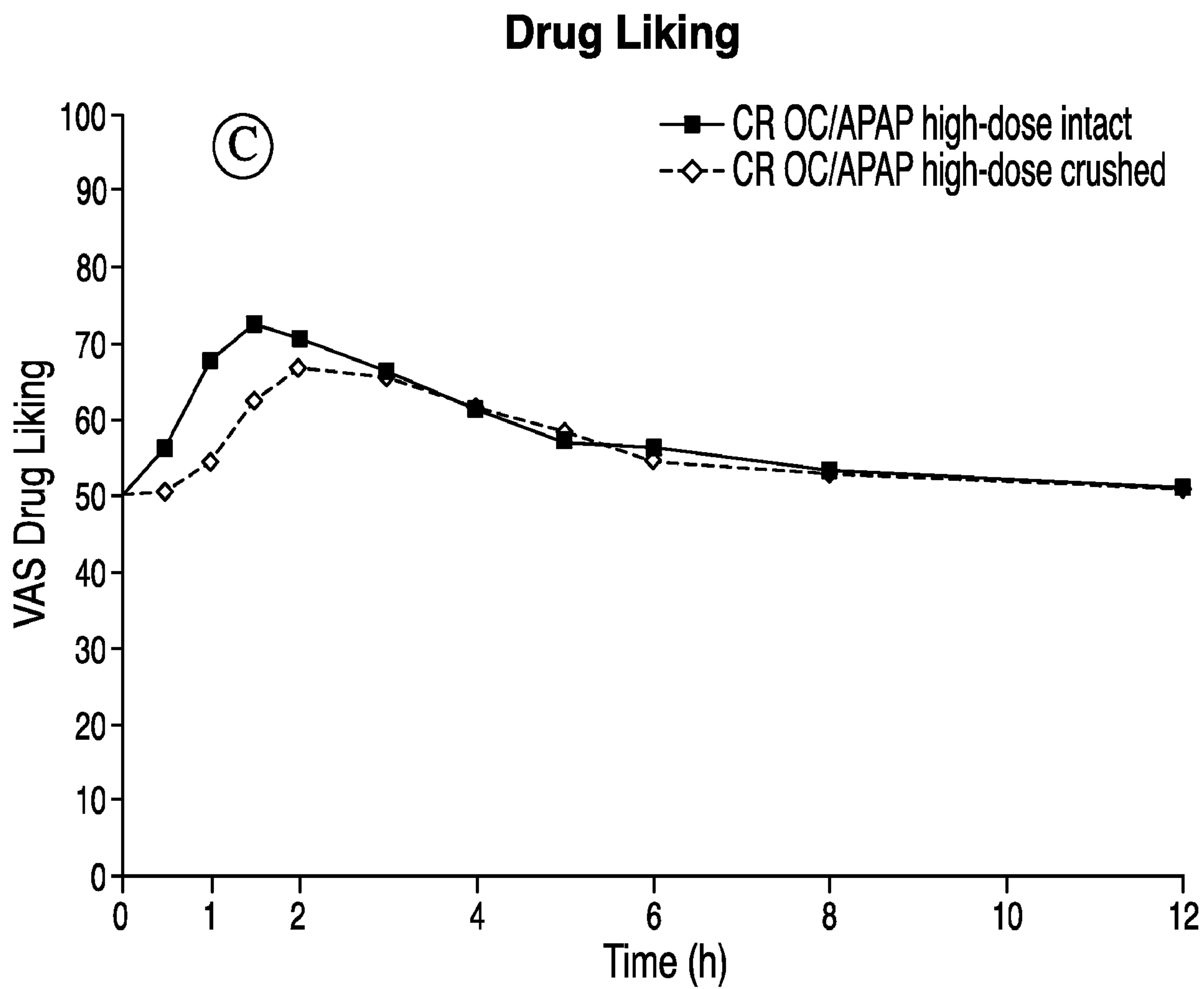
(A) CR OC/APAP low-dose intact vs. IR OC/APAP low-dose intact

FIG. 61



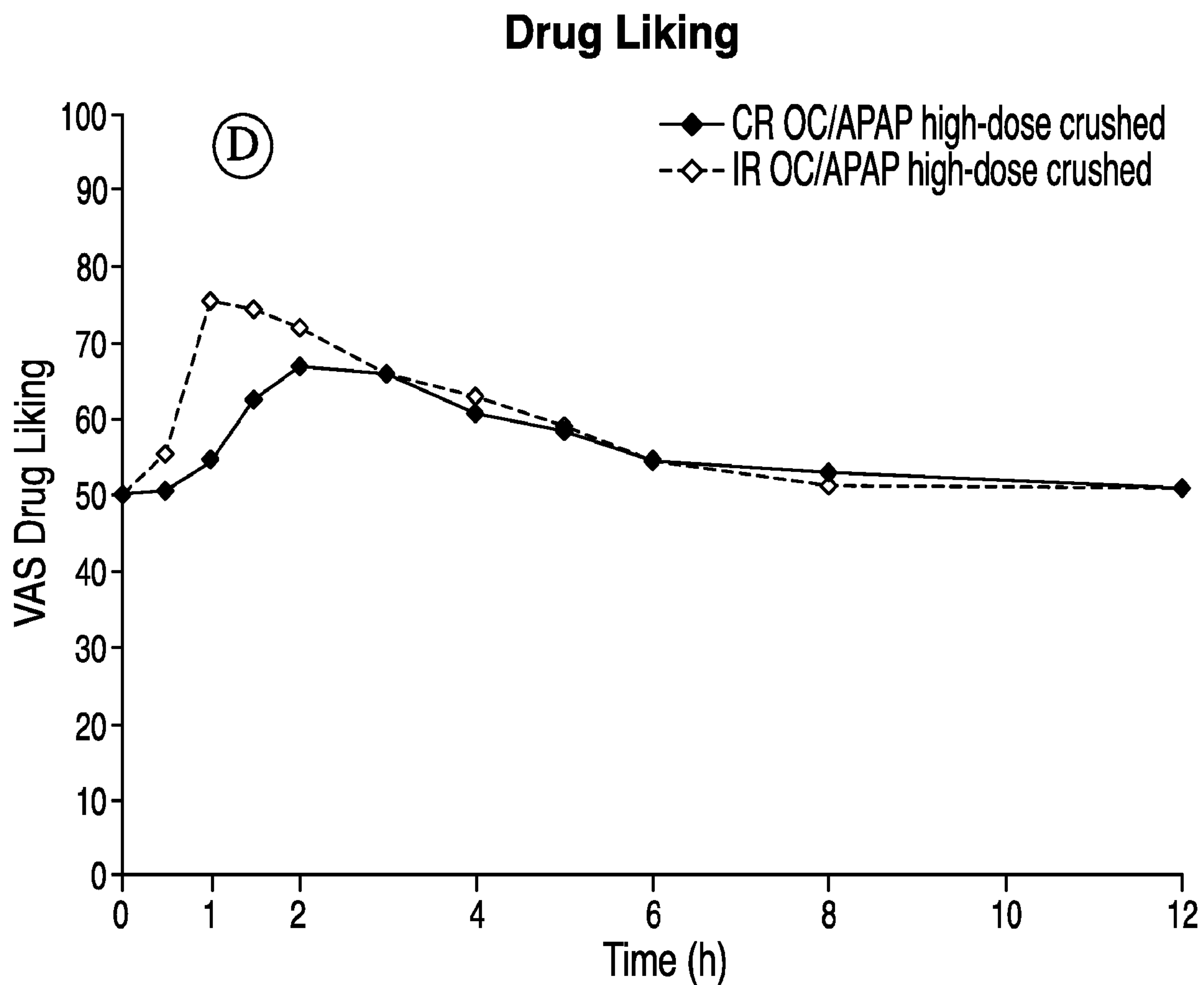
(B) CR OC/APAP high-dose intact vs. IR OC/APAP high-dose intact

FIG. 62



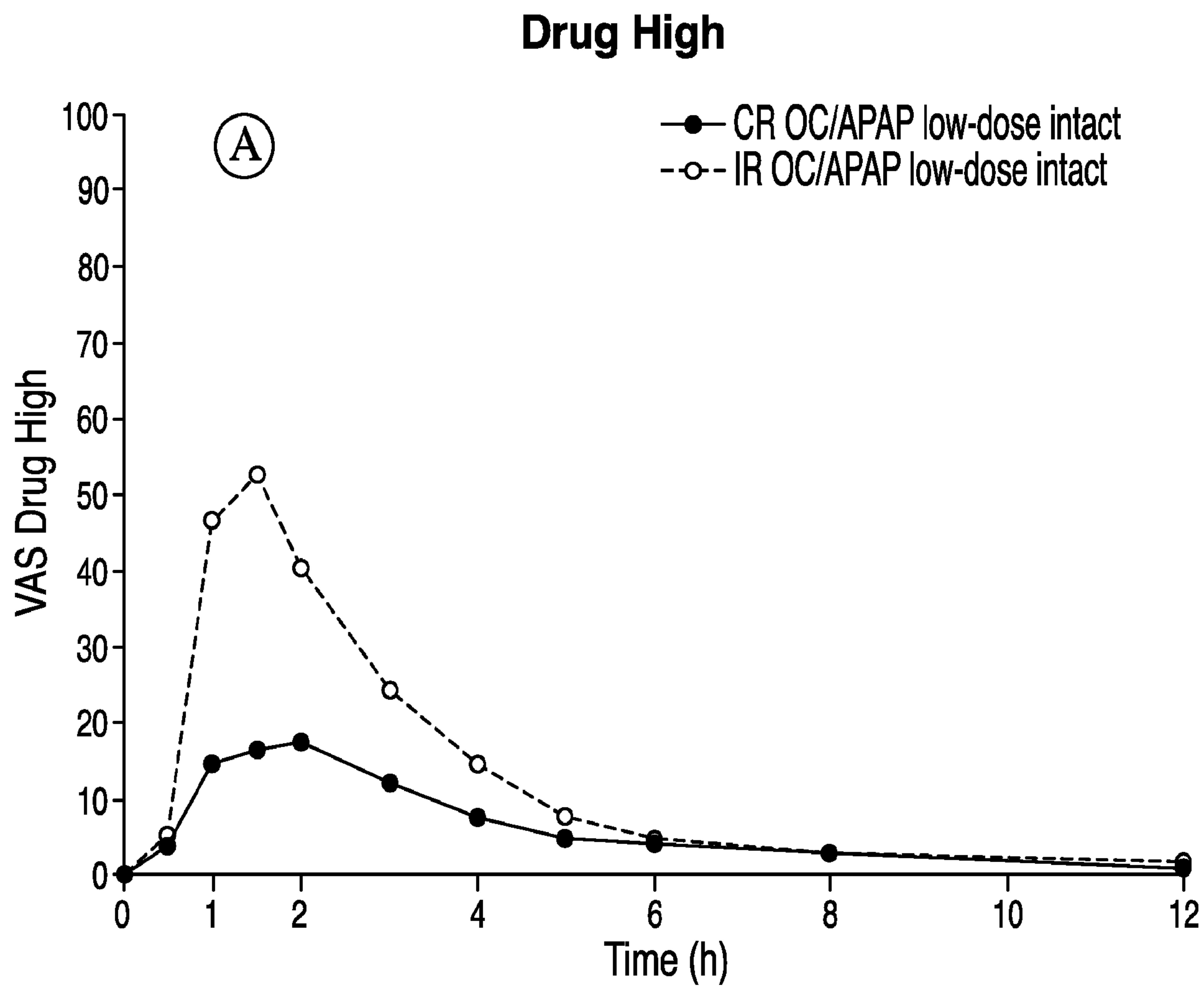
(C) CR OC/APAP high-dose intact vs. high-dose crushed

FIG. 63



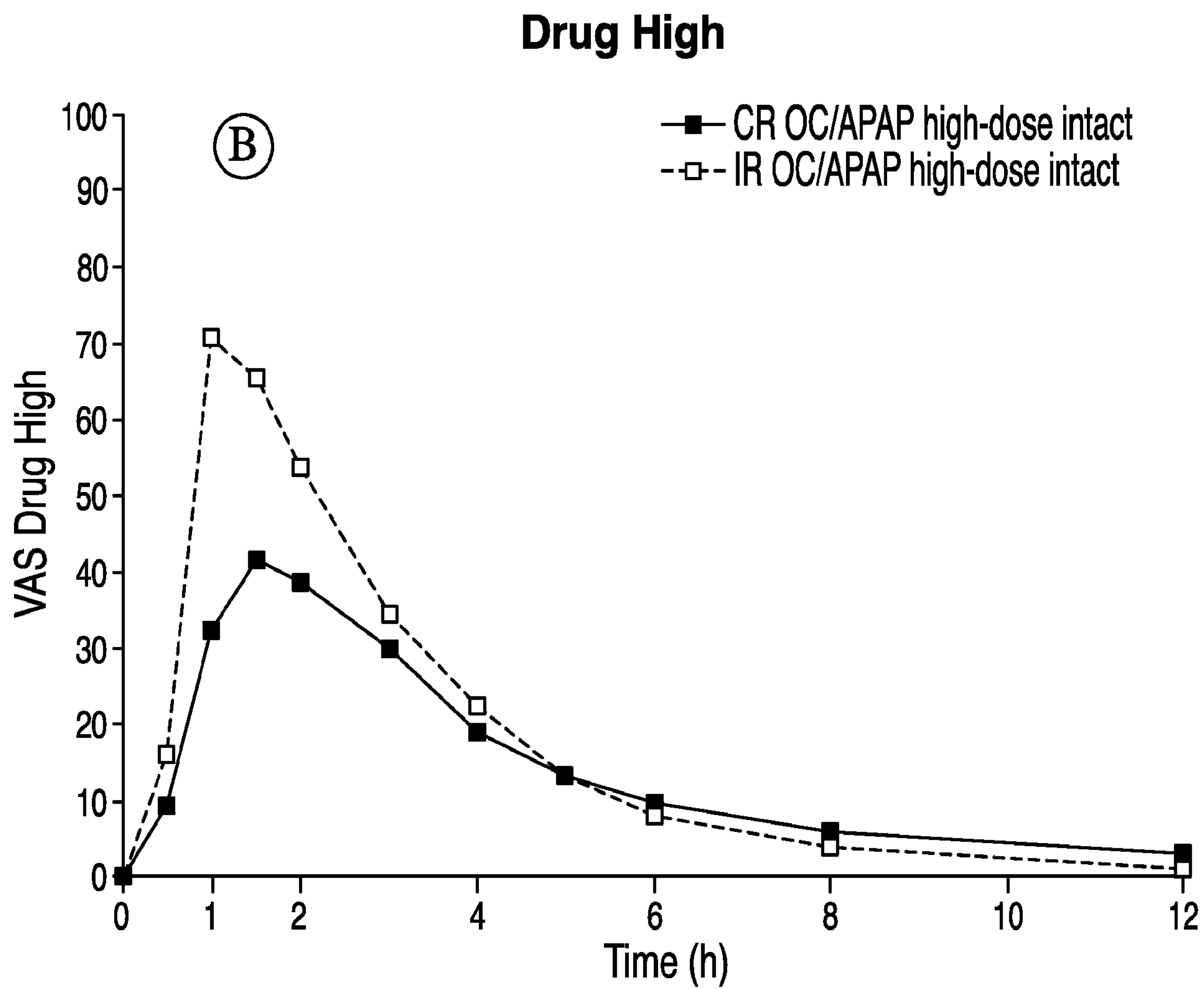
(D) CR OC/APAP high-dose crushed vs. IR OC/APAP high-dose crushed

FIG. 64



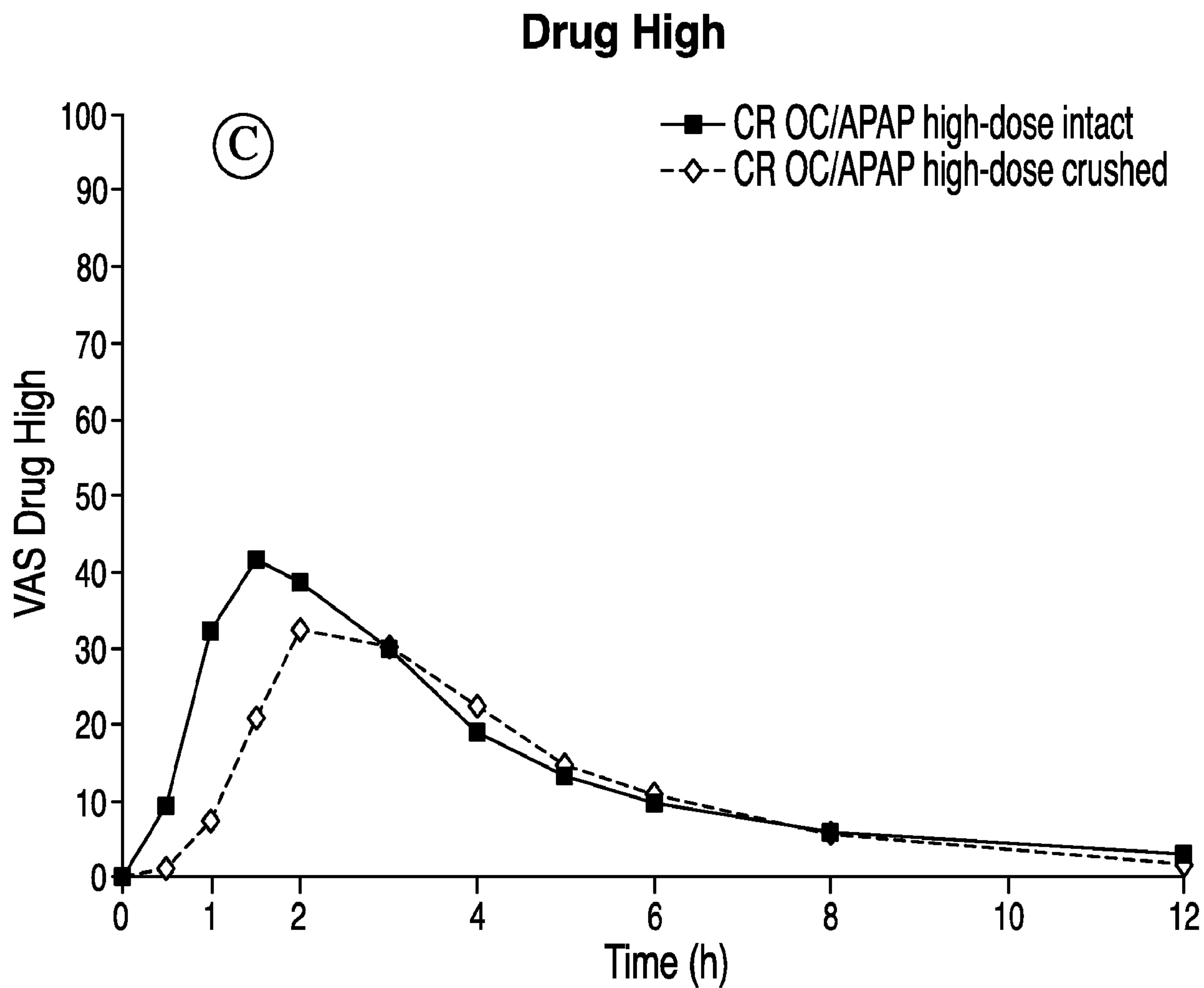
(A) CR OC/APAP low-dose intact vs. IR OC/APAP low-dose intact

FIG. 65



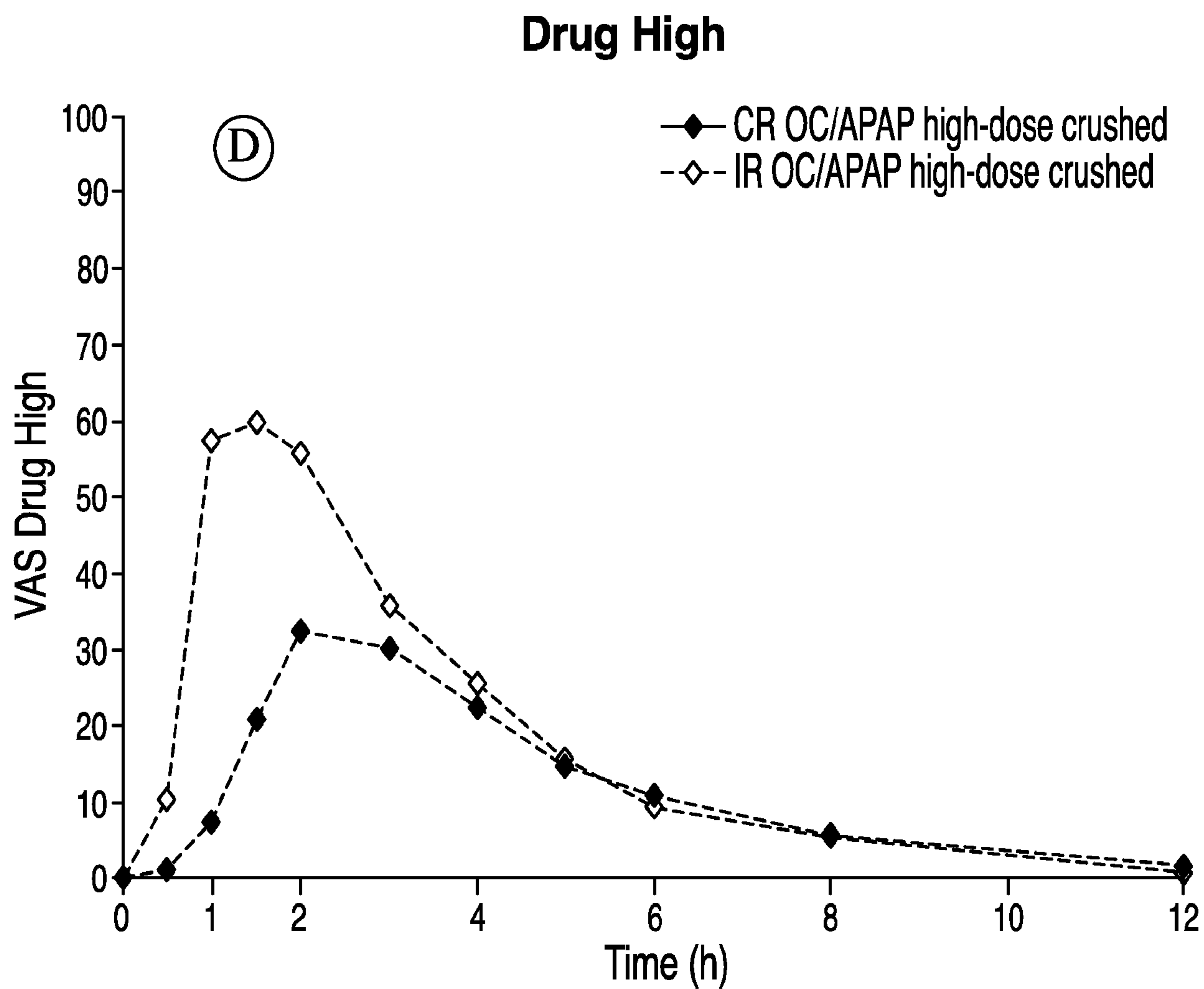
(B) CR OC/APAP high-dose intact vs. IR OC/APAP high-dose intact

FIG. 66



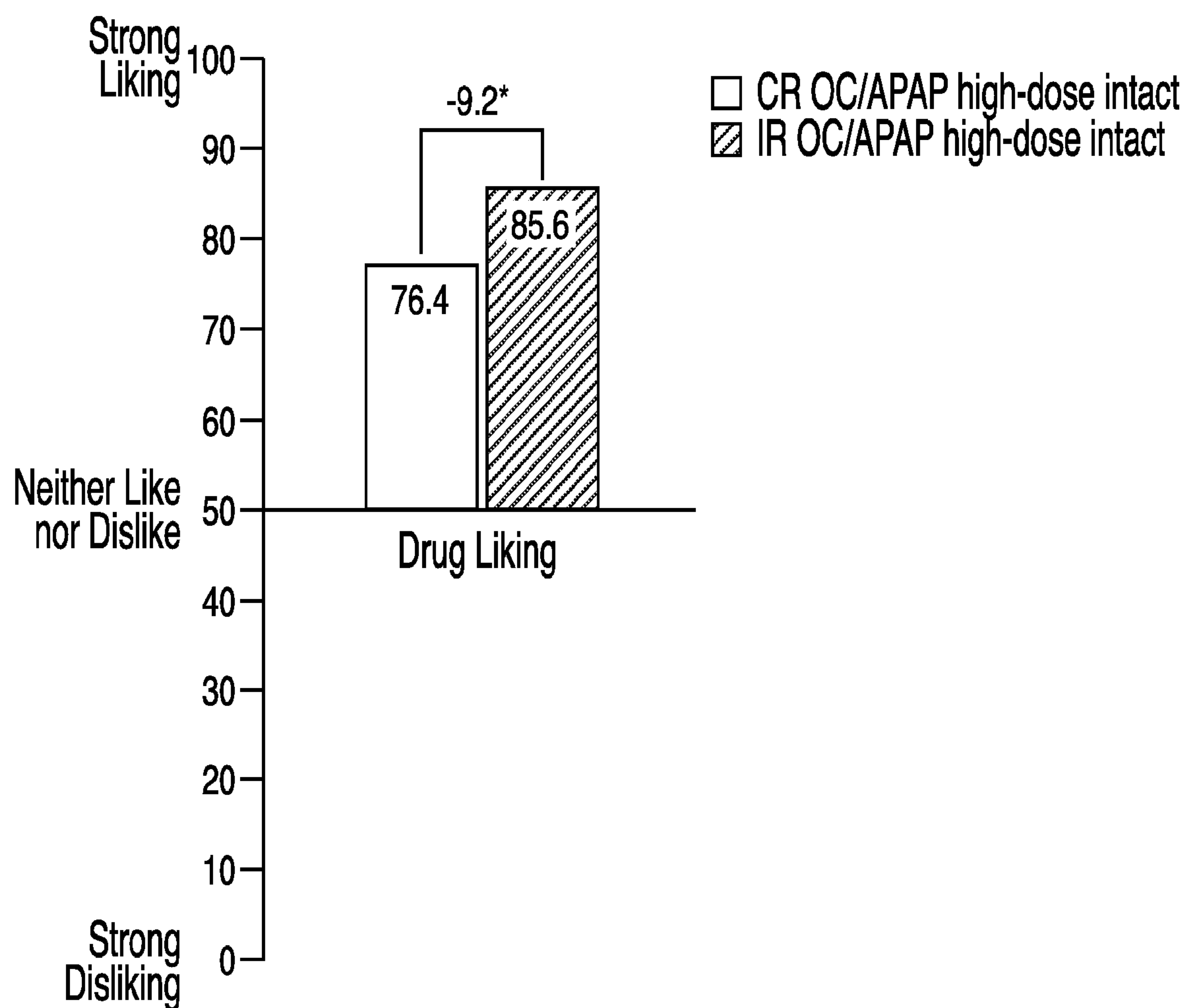
(C) CR OC/APAP high-dose intact vs. high-dose crushed

FIG. 67



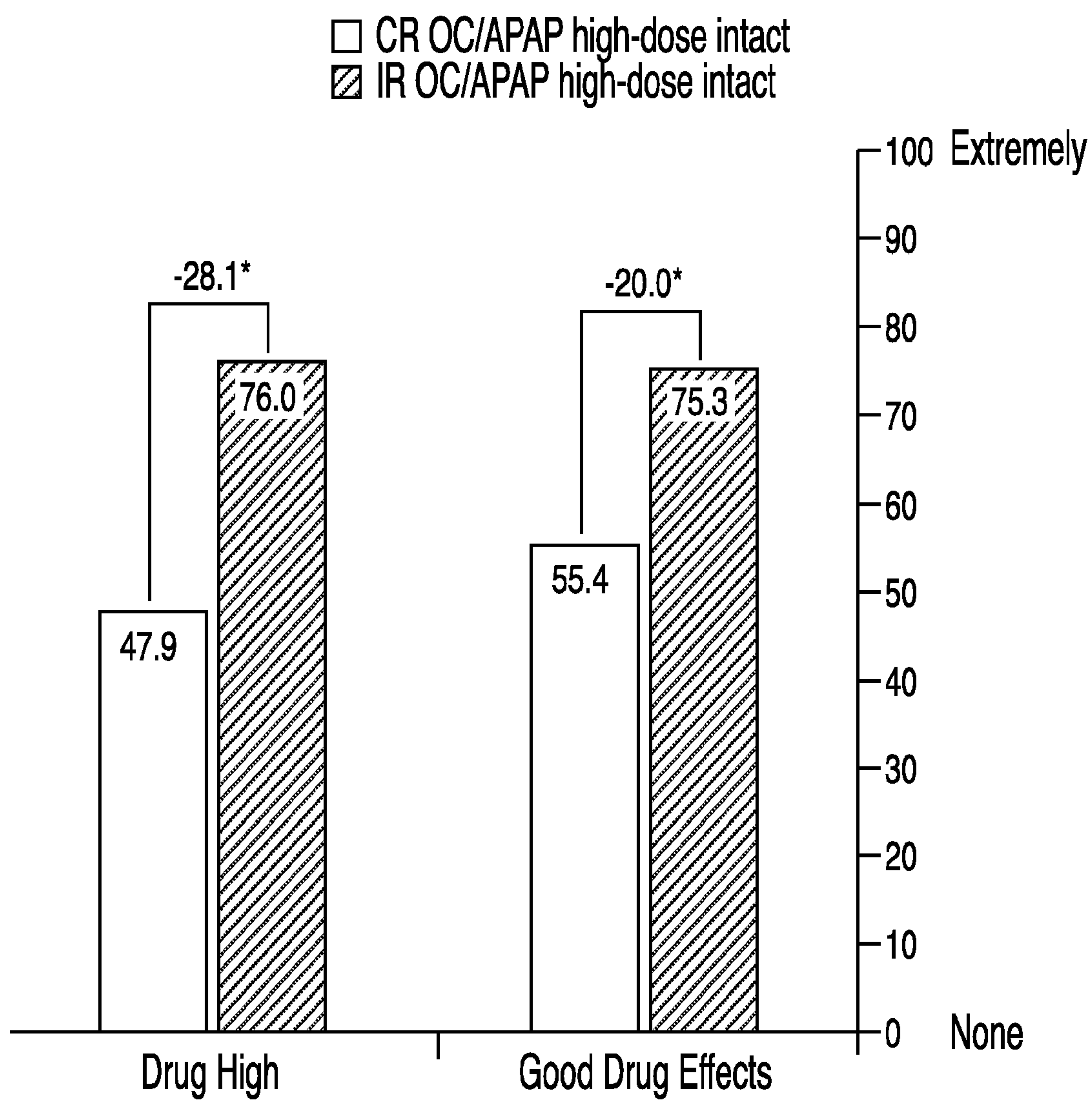
(D) CR OC/APAP high-dose crushed vs. IR OC/APAP high-dose crushed

FIG. 68



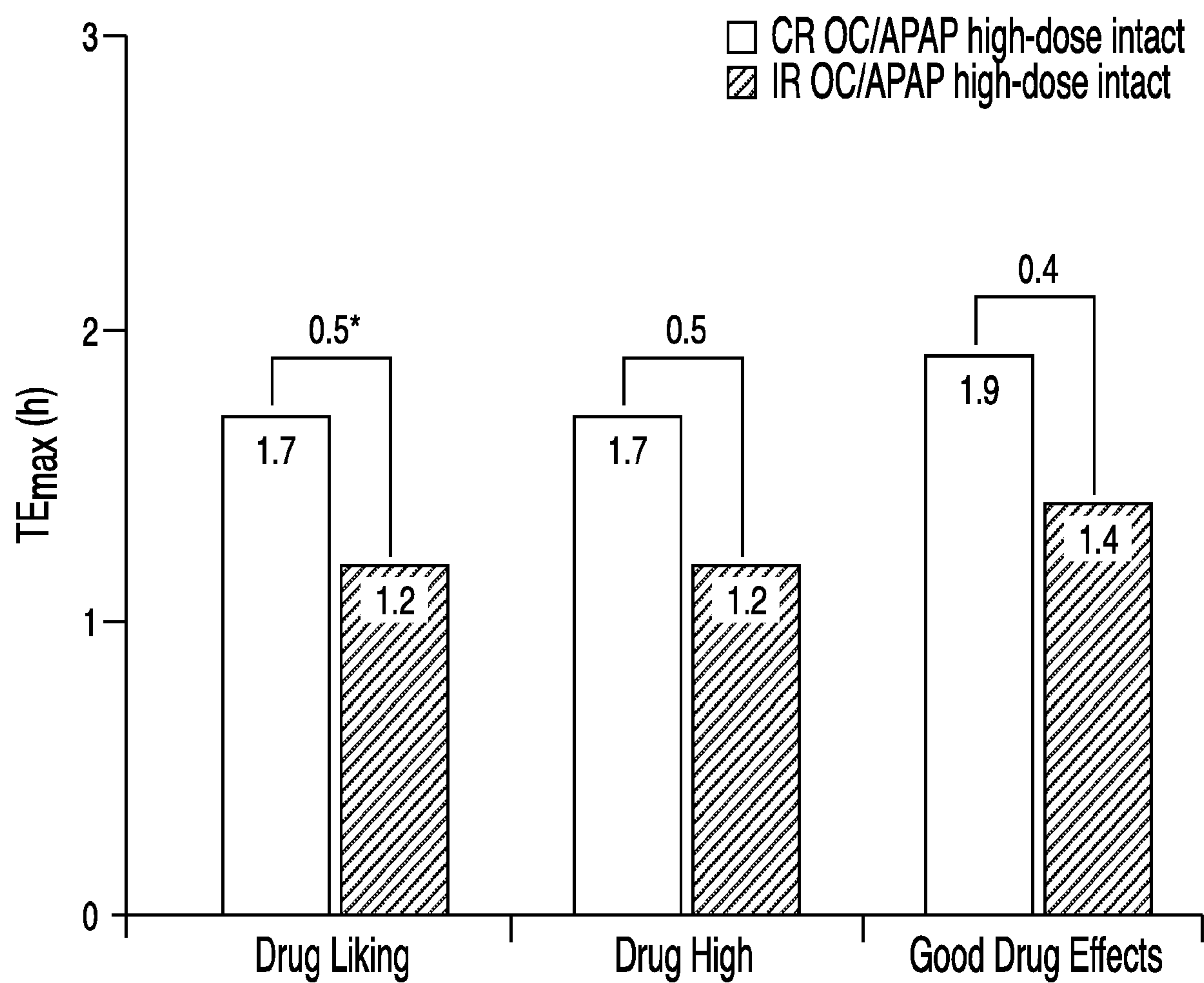
* $P < 0.001$ for difference between groups.

FIG. 69



* $P < 0.001$ for difference between groups.

FIG. 70



* $P < 0.05$ for difference between groups.

FIG. 71

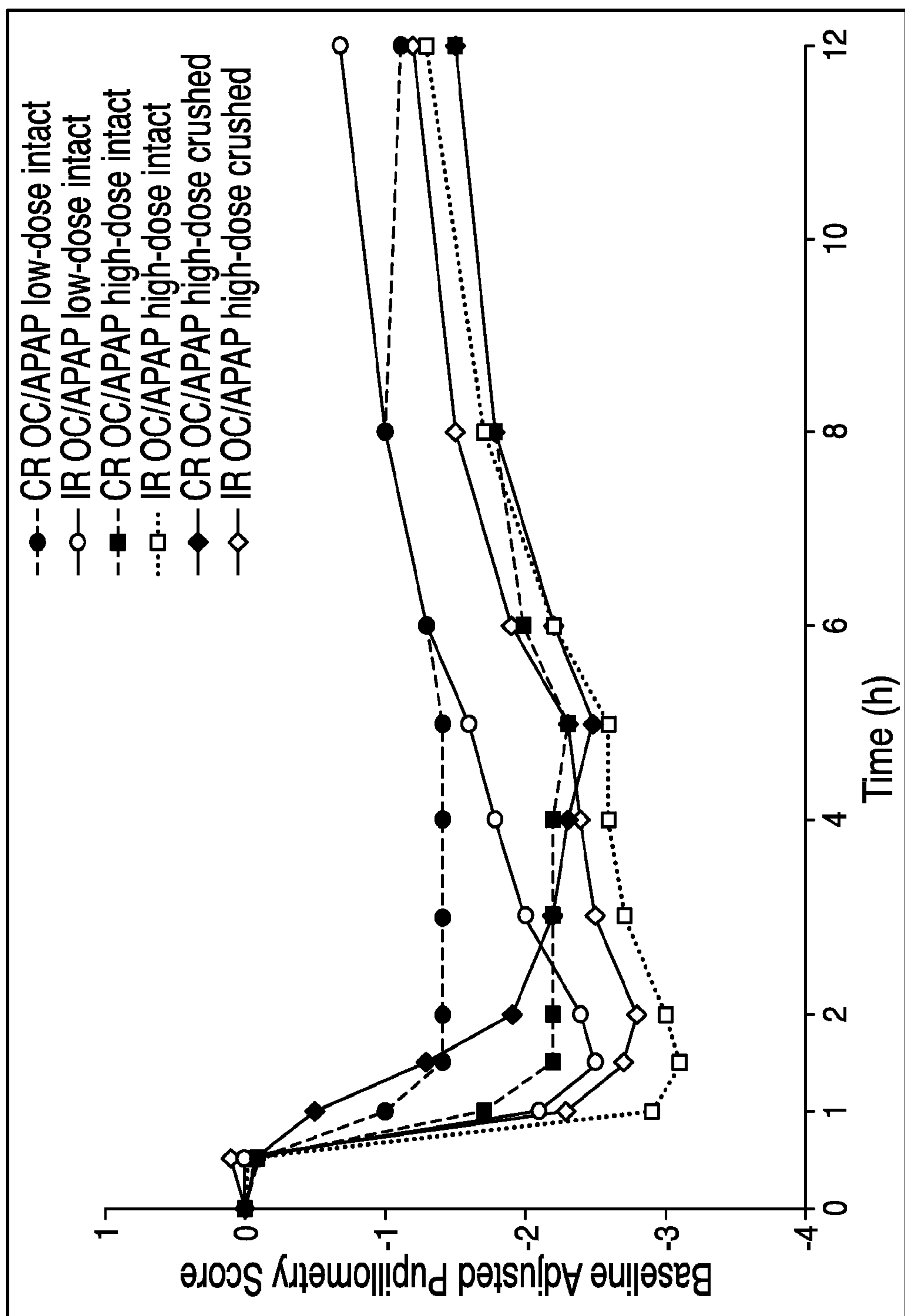


FIG. 72

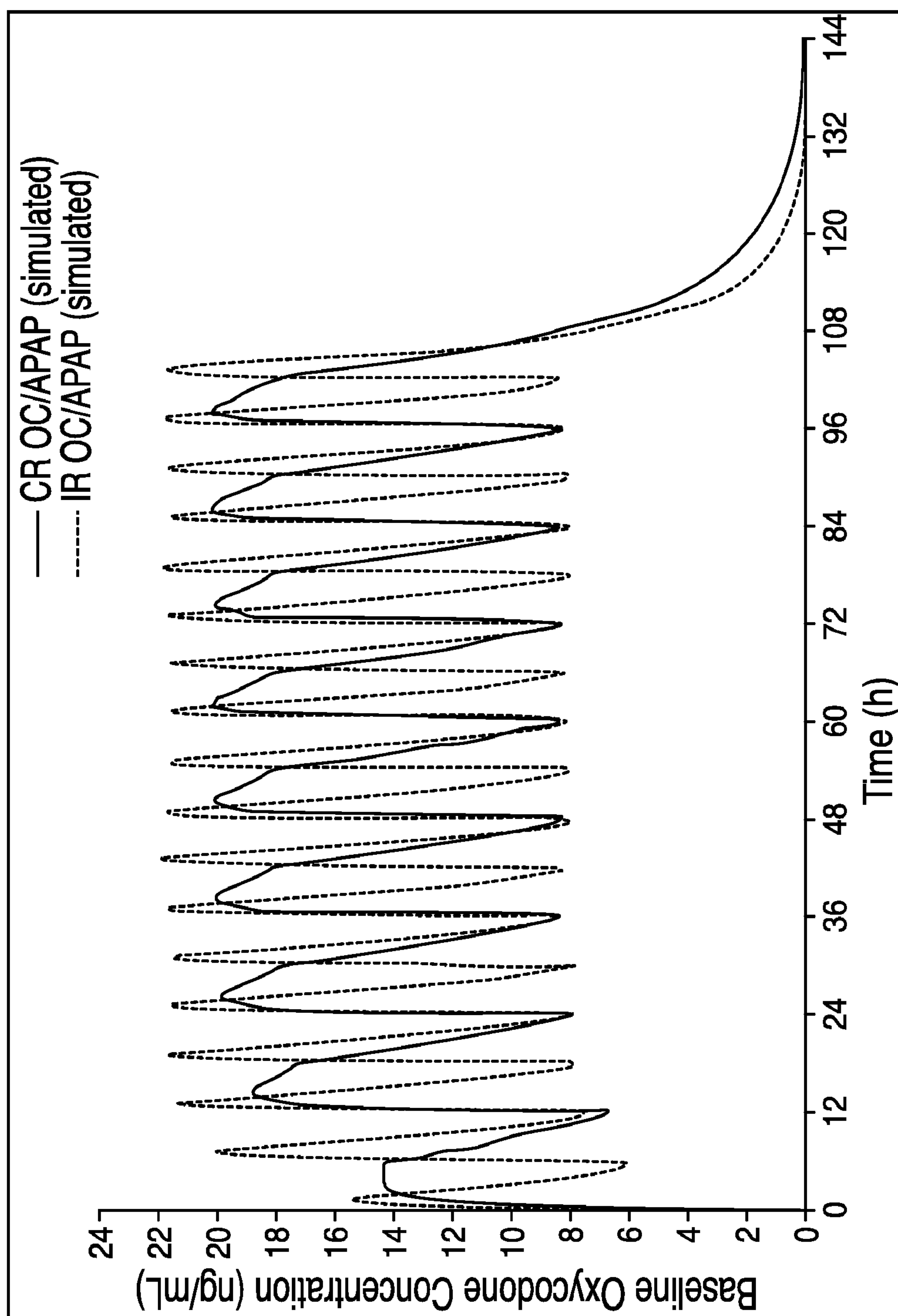


FIG. 73

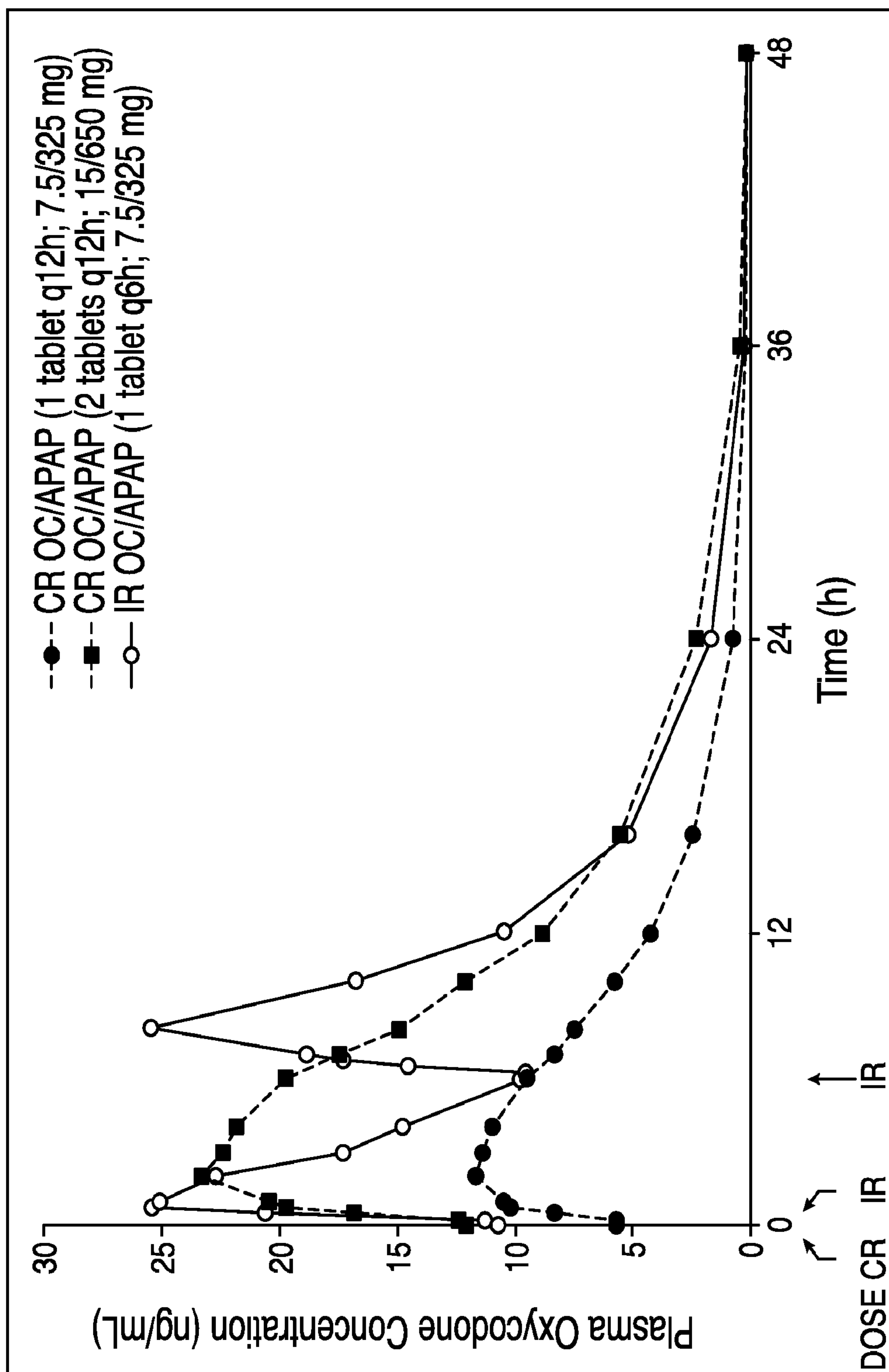


FIG. 74

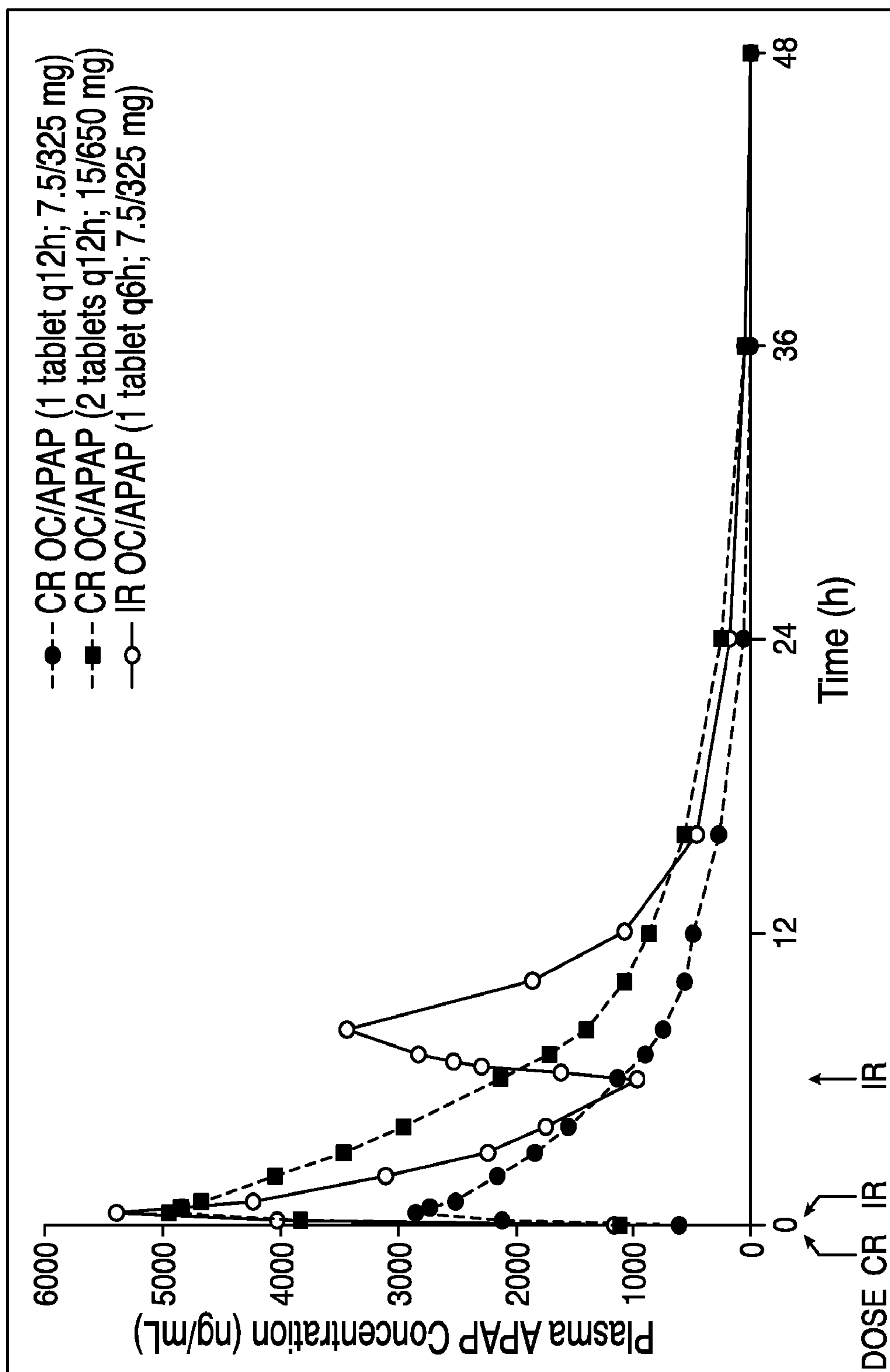
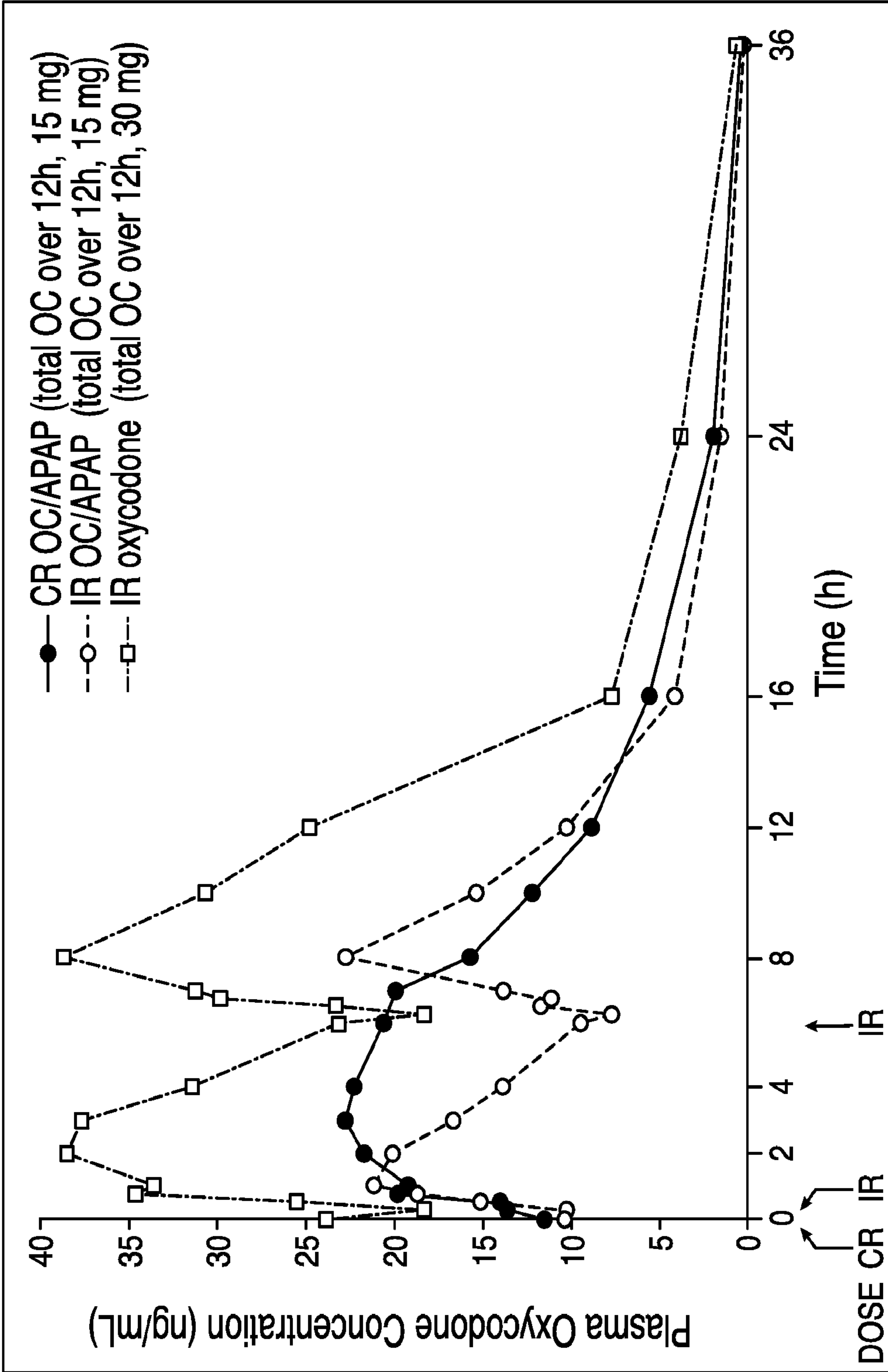
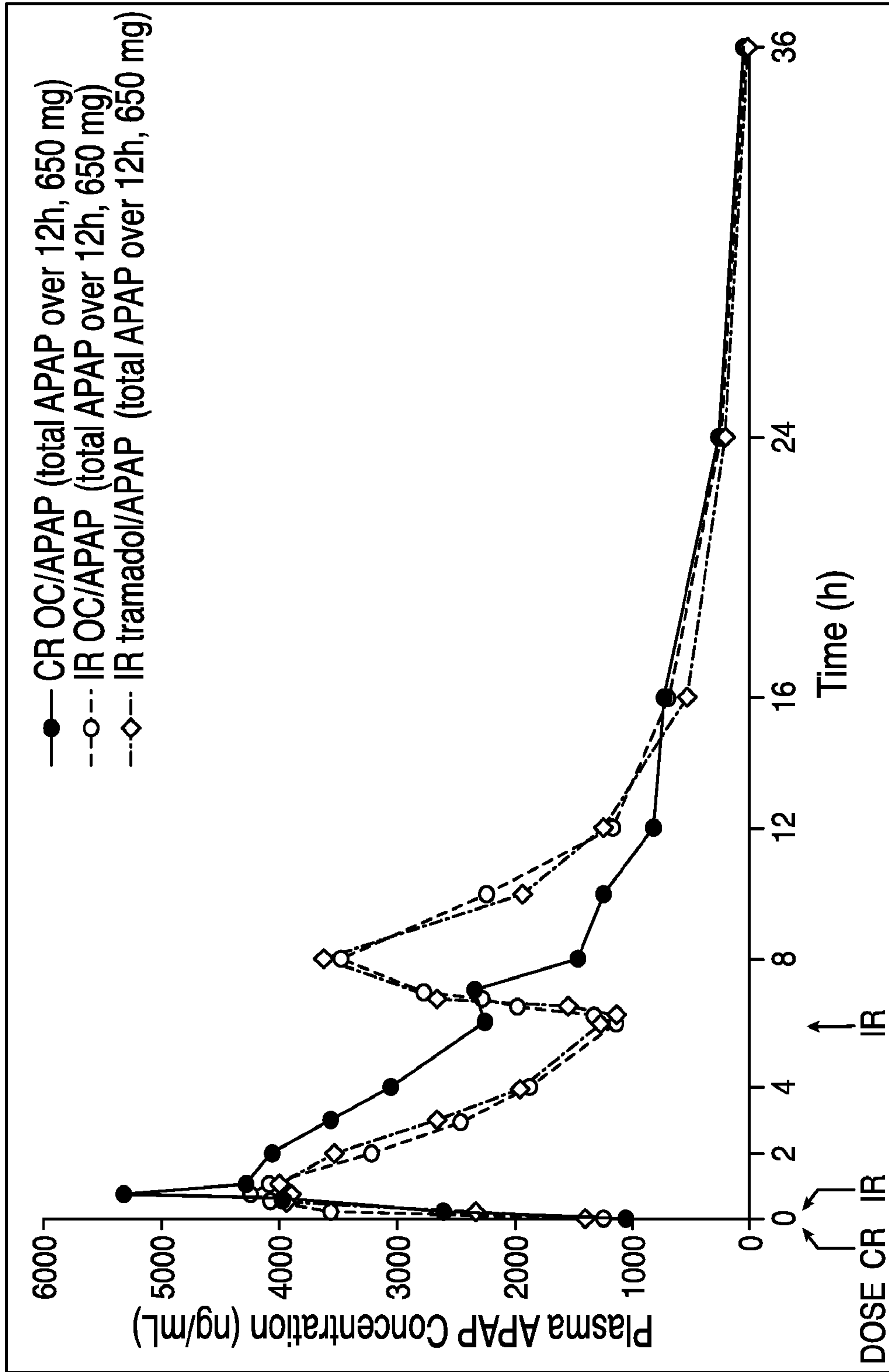


FIG. 75



^aData from 24 subjects who completed all study periods.

FIG. 76



^aData from 24 subjects who completed all study periods.

FIG. 77

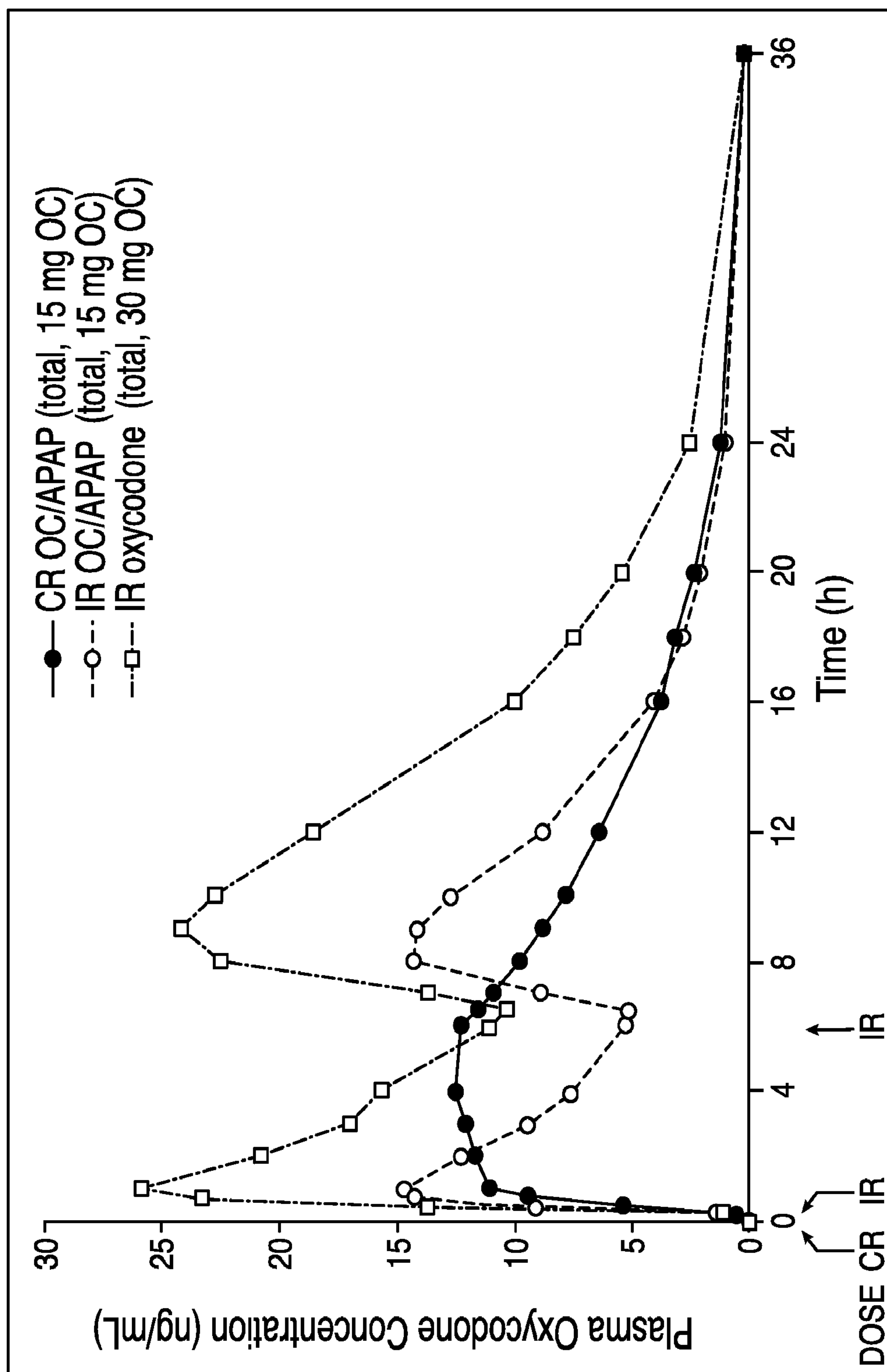
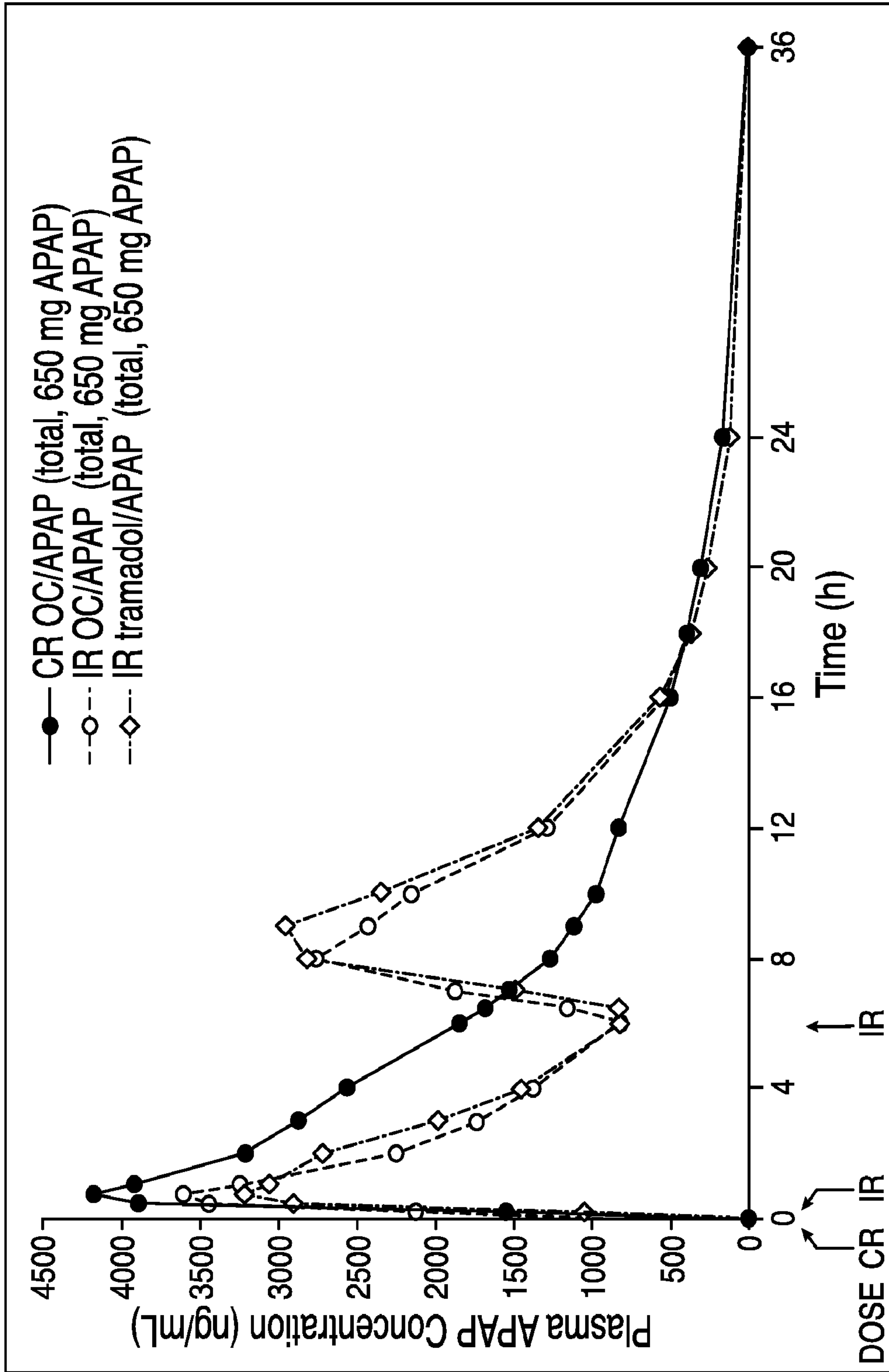
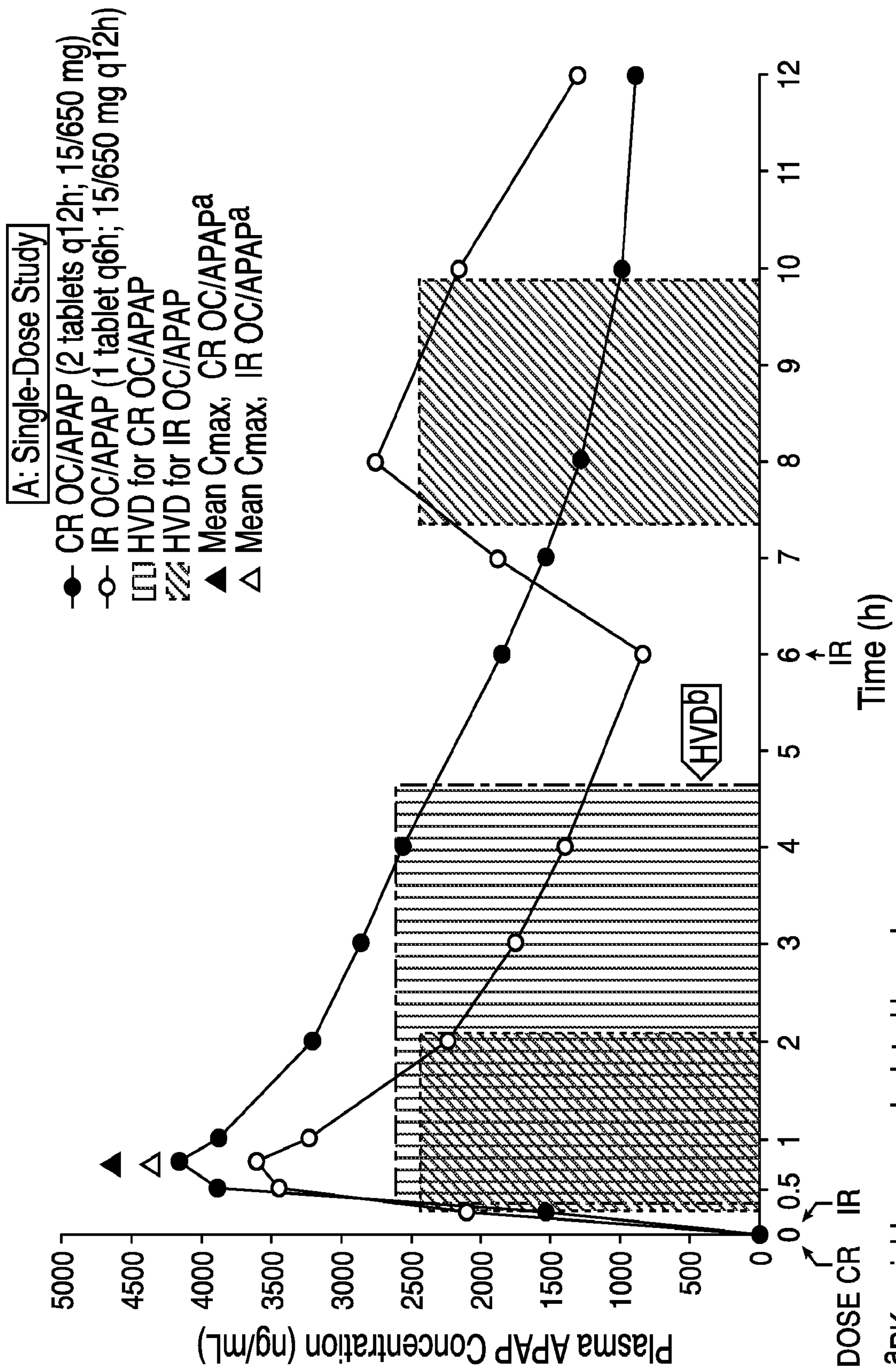


FIG. 78



^aData from 29 subjects who completed all study periods.

FIG. 79



^aPK variables are calculated based on individual data; ^bP = 0.133;

FIG. 80

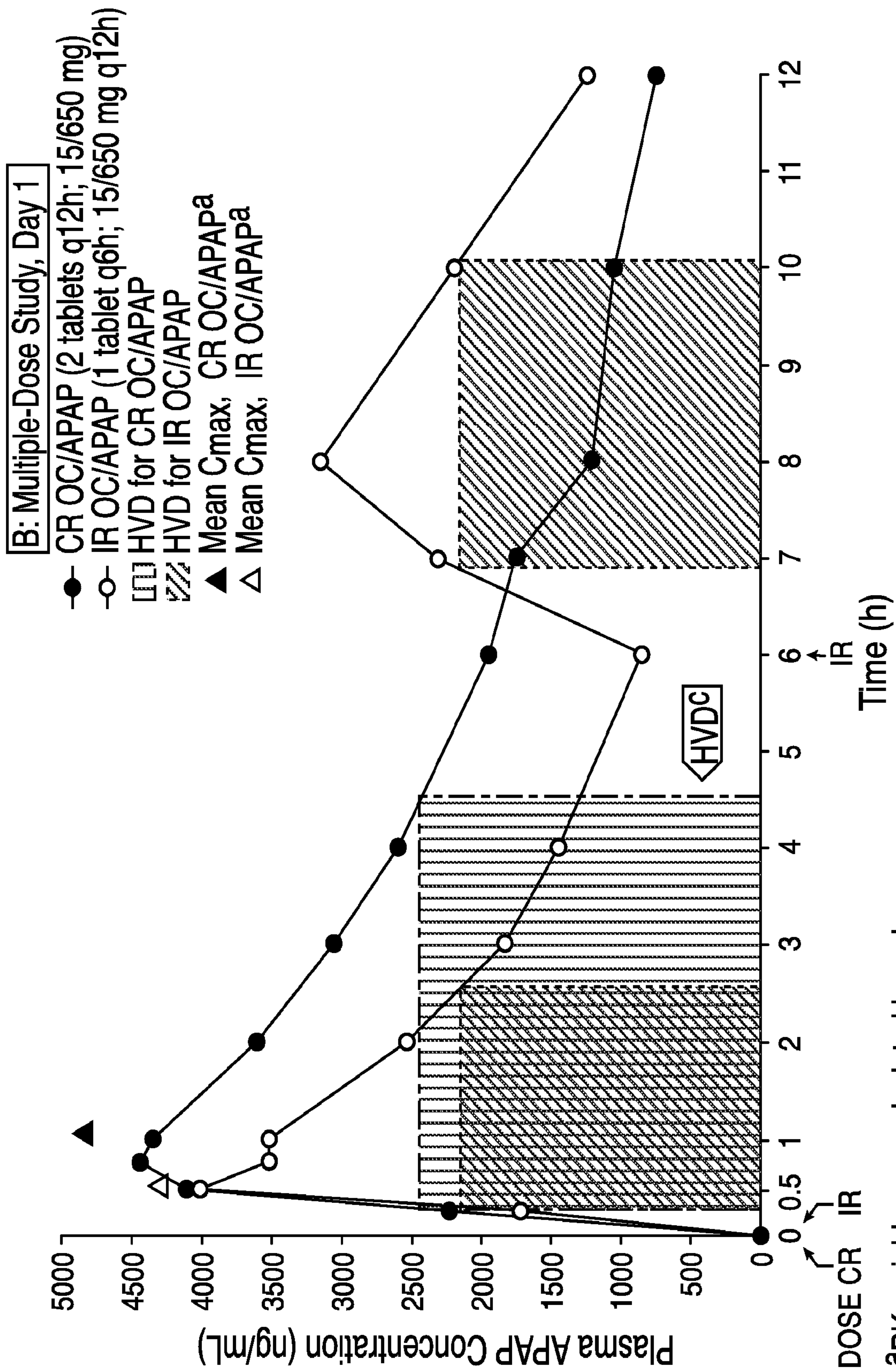


FIG. 81

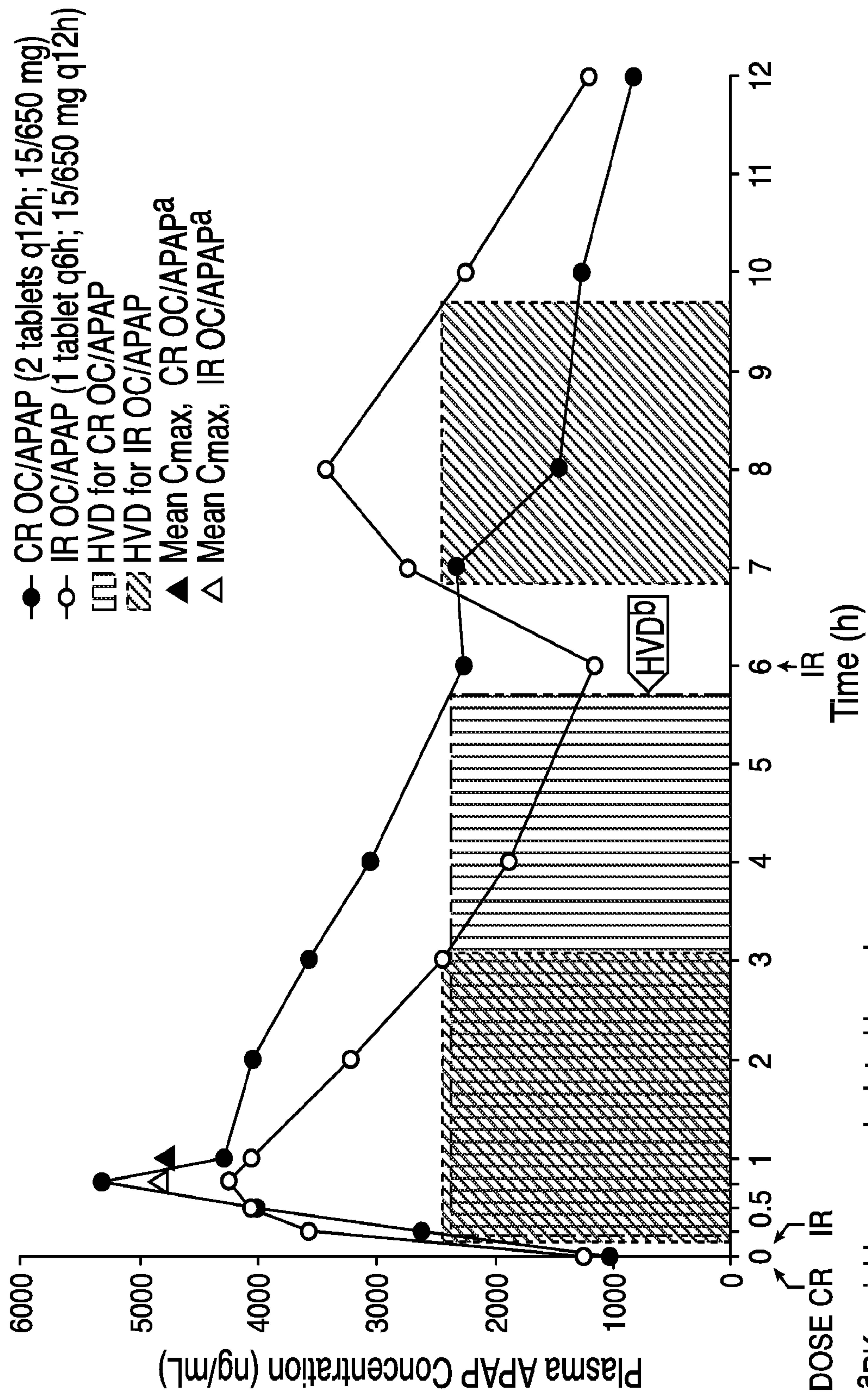


FIG. 82

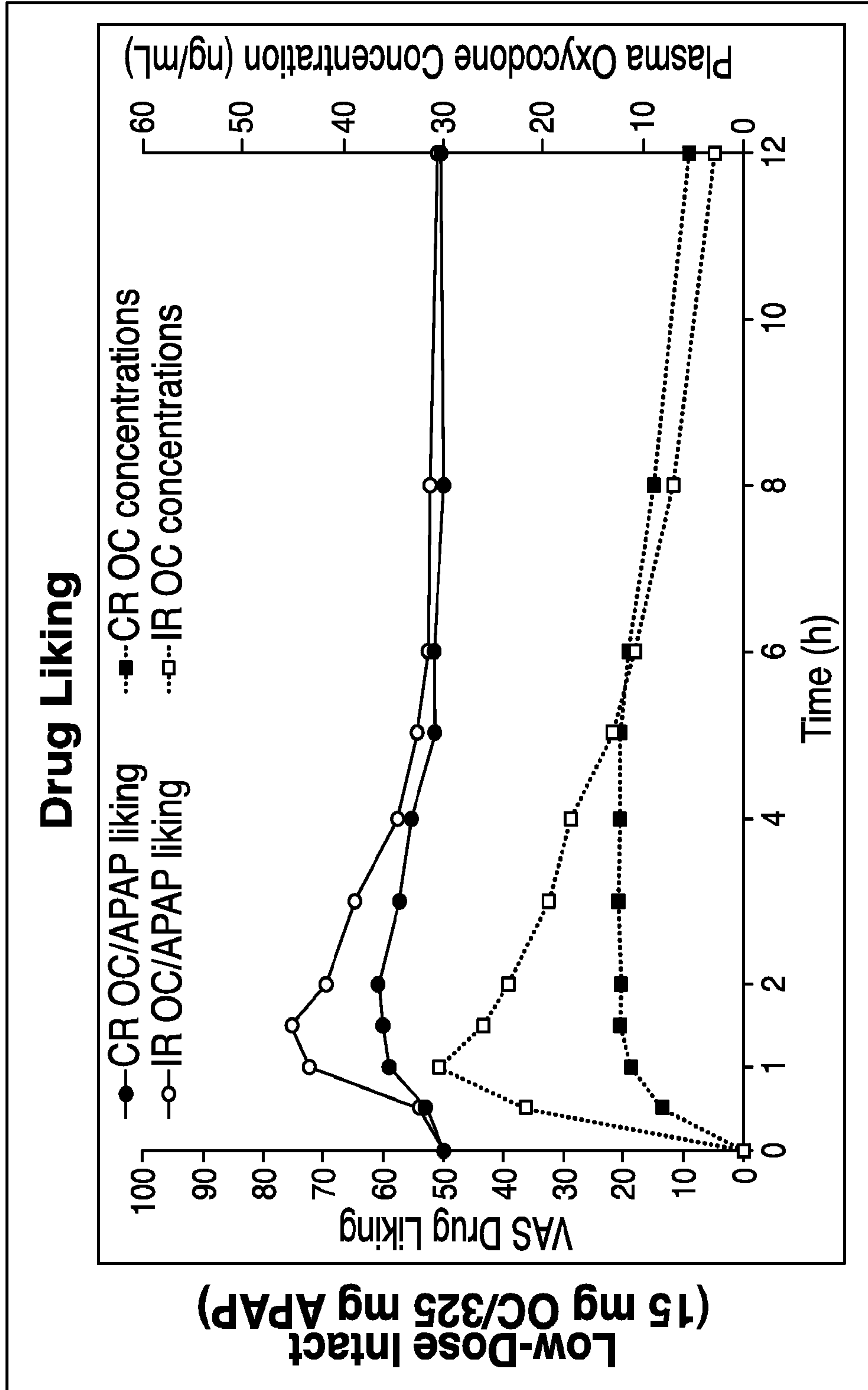


FIG. 83

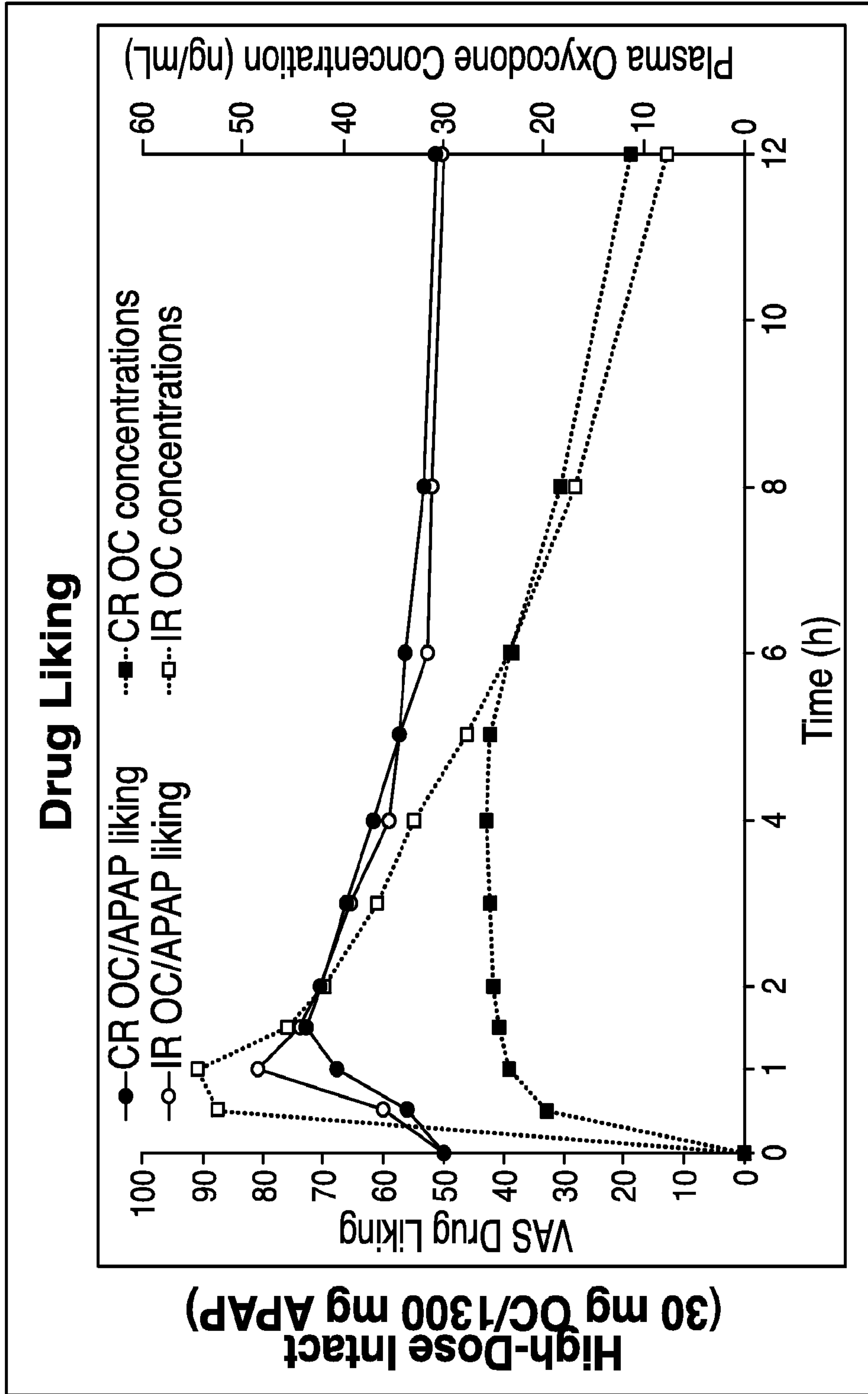


FIG. 84

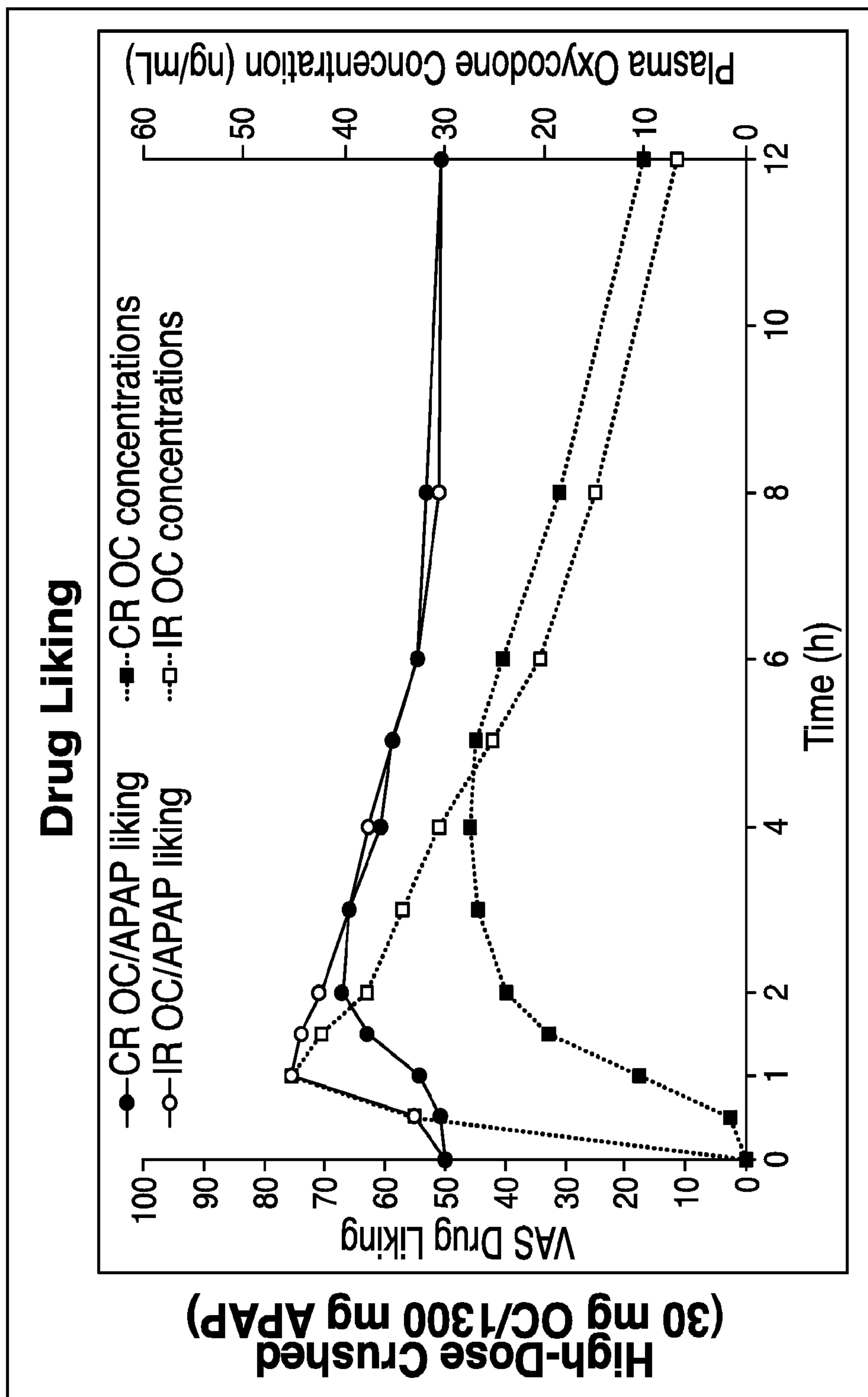


FIG. 85

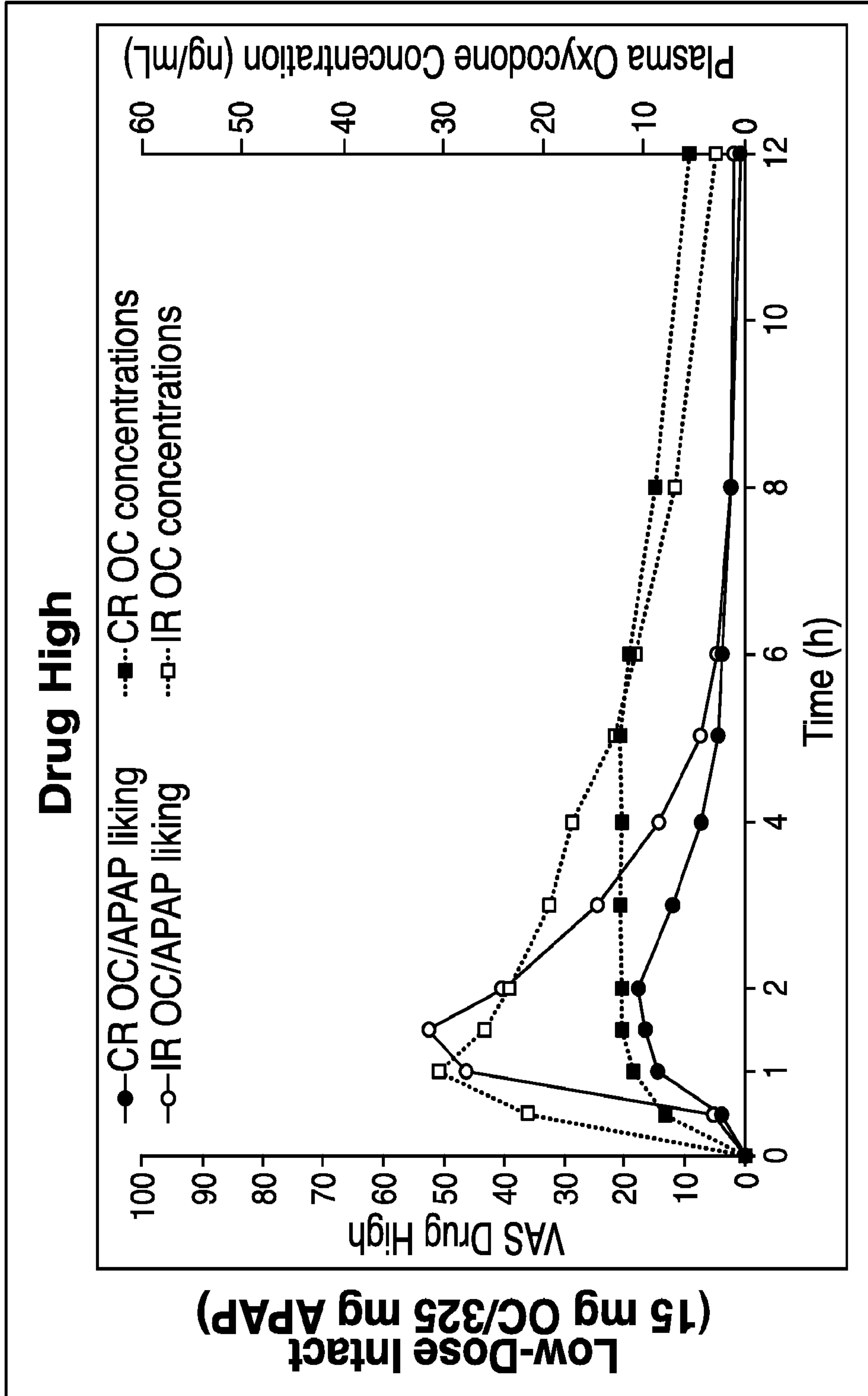


FIG. 86

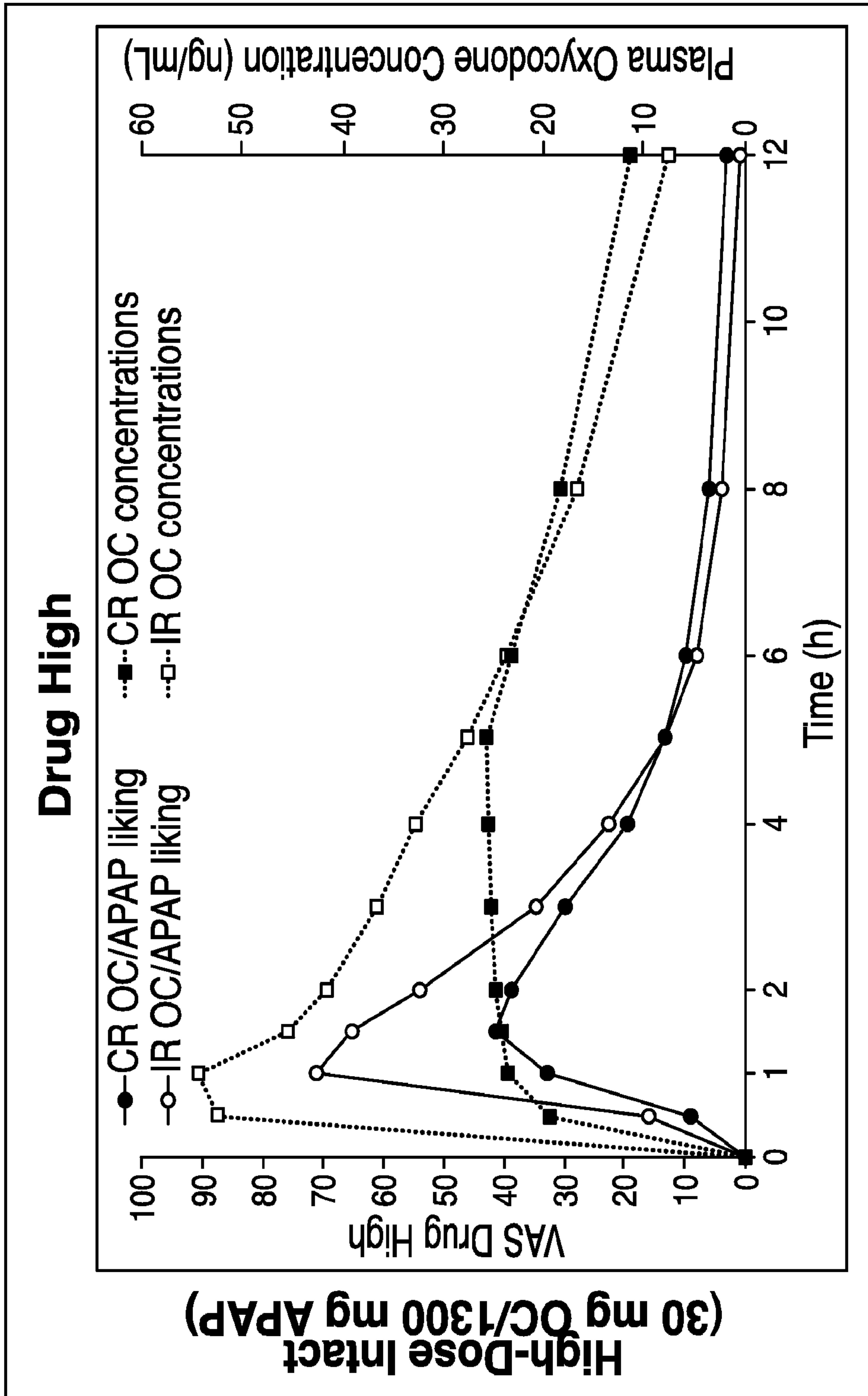


FIG. 87

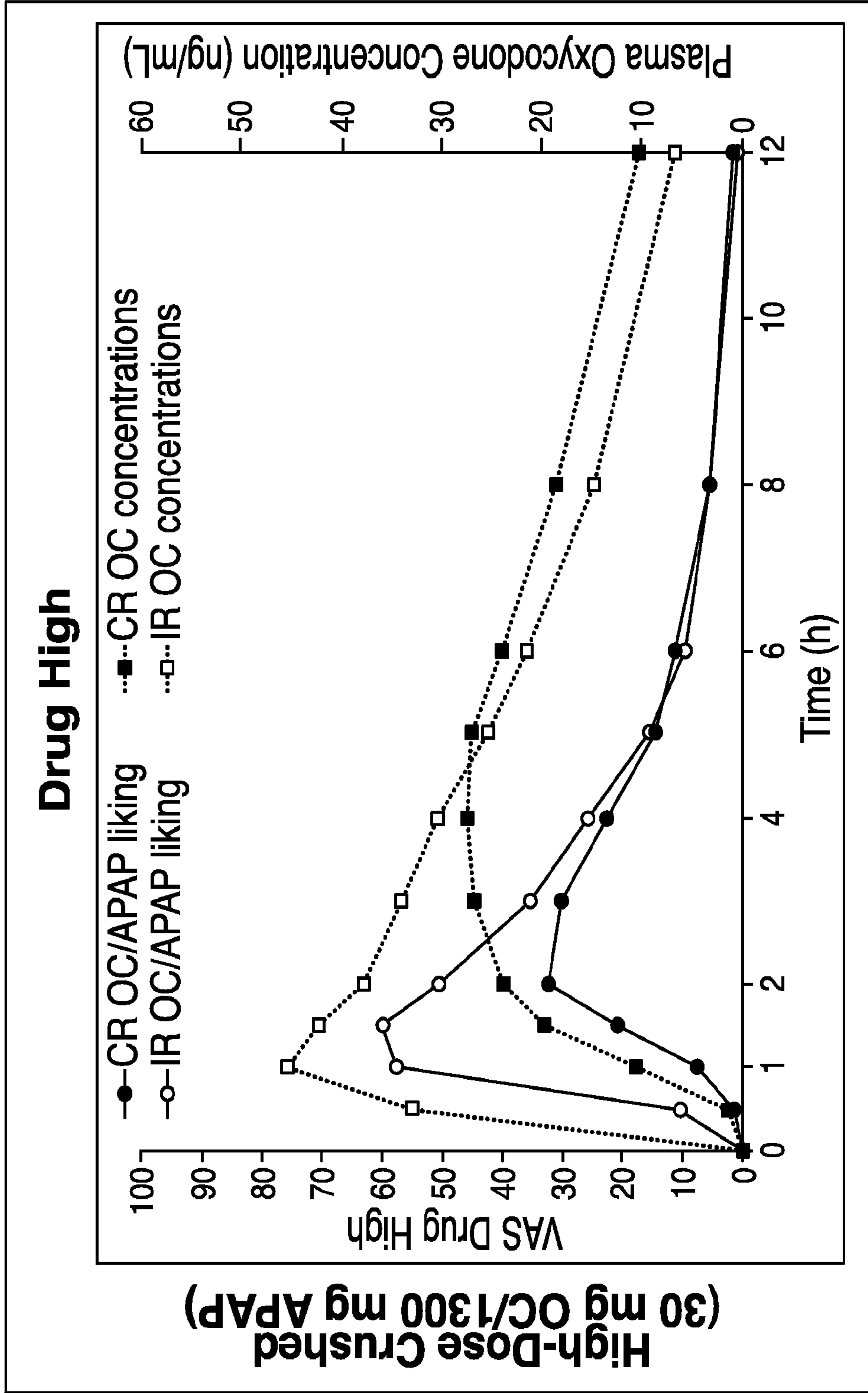
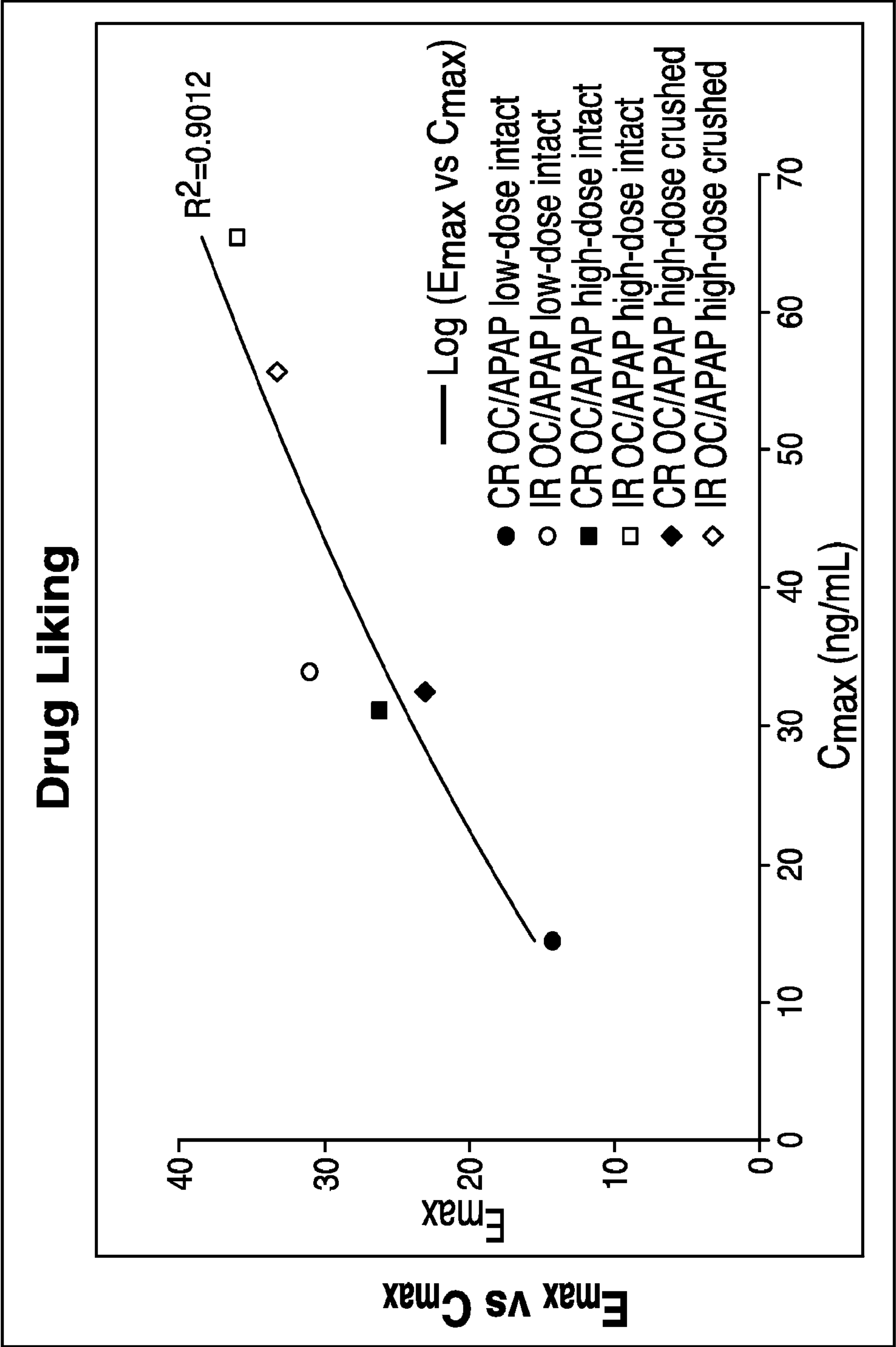
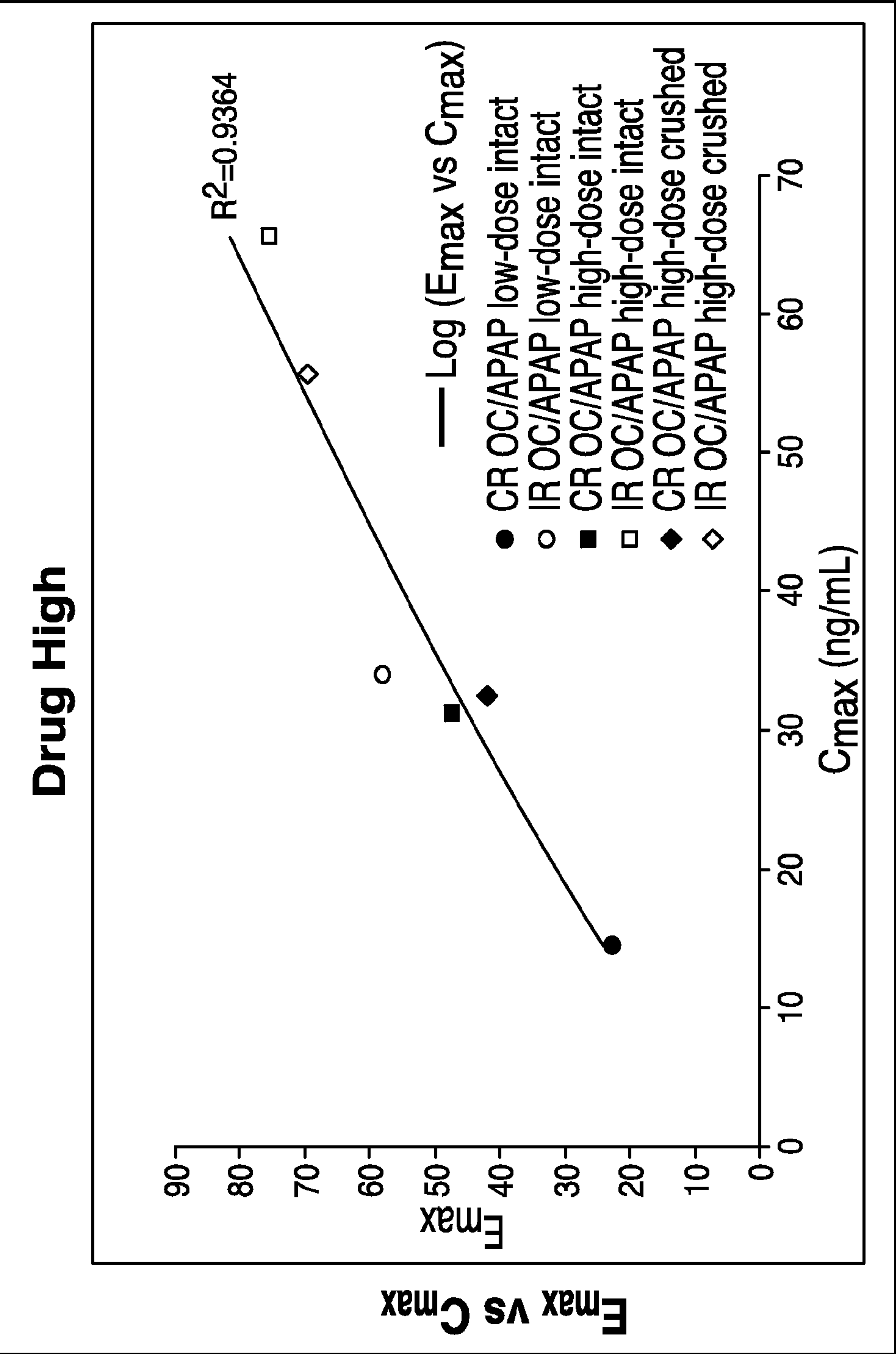


FIG. 88



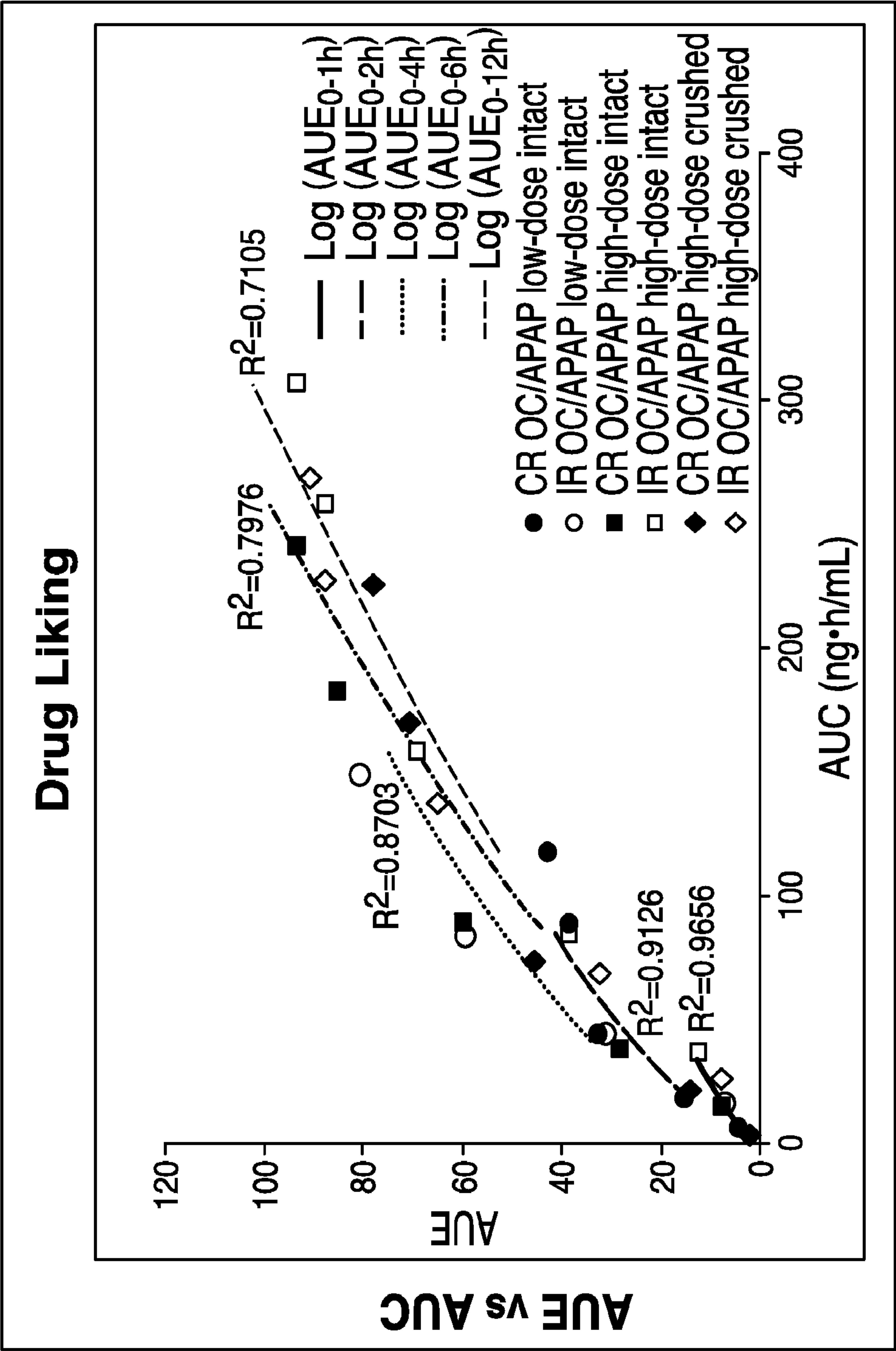
High-dose = 30 mg OC/1300 mg APAP; low-dose = 15 mg OC/1300 APAP.

FIG. 89



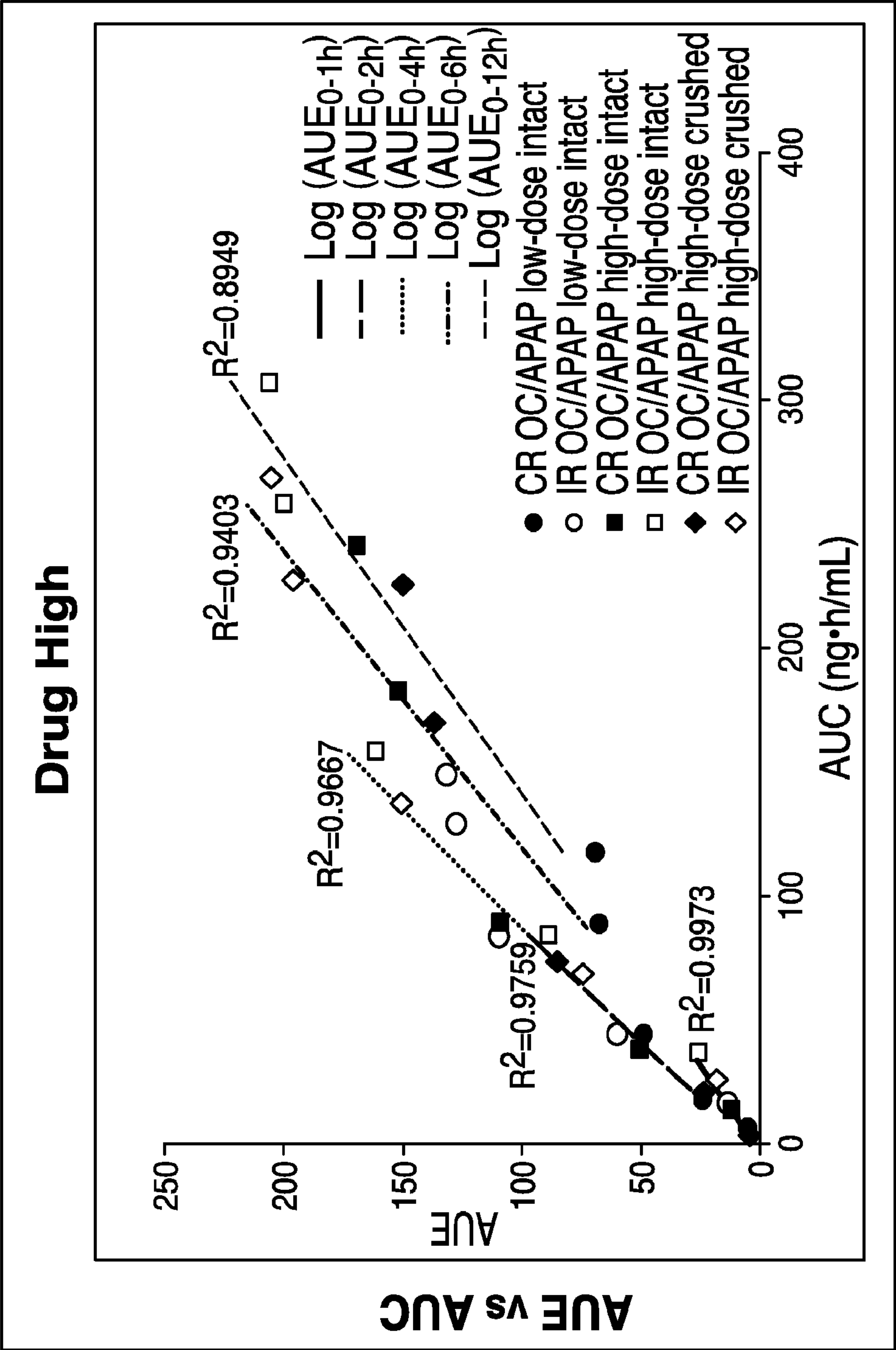
High-dose = 30 mg OC/1300 mg APAP; low-dose = 15 mg OC/1300 APAP.

FIG. 90



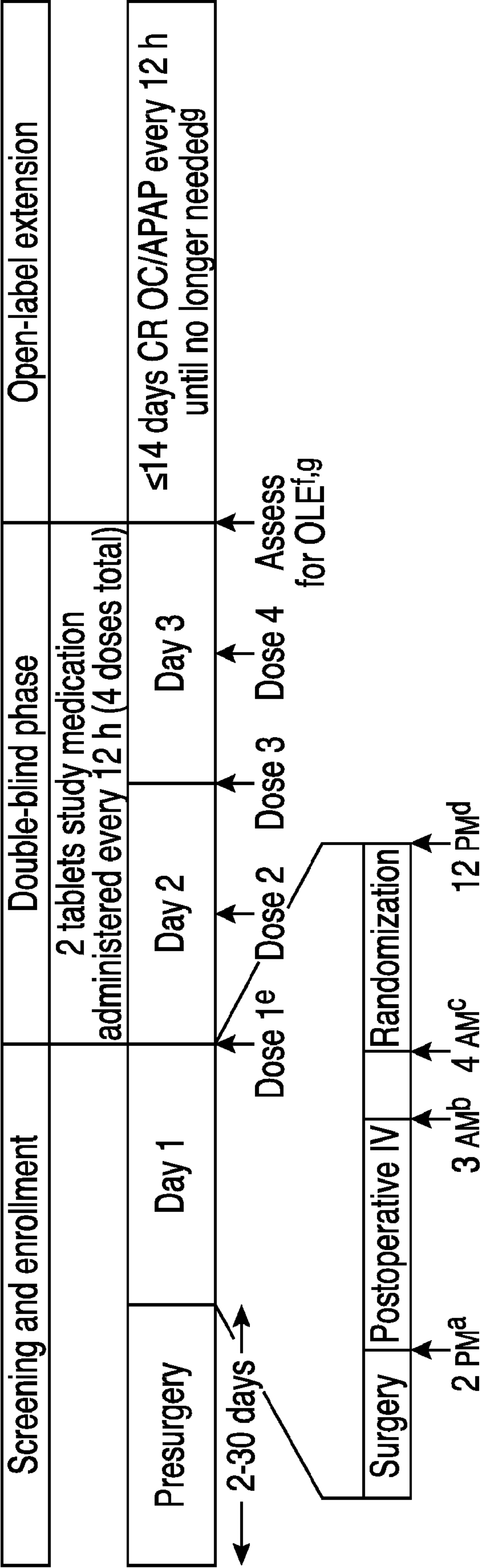
High-dose = 30 mg OC/1300 mg APAP; low-dose = 15 mg OC/1300 APAP.

FIG. 91



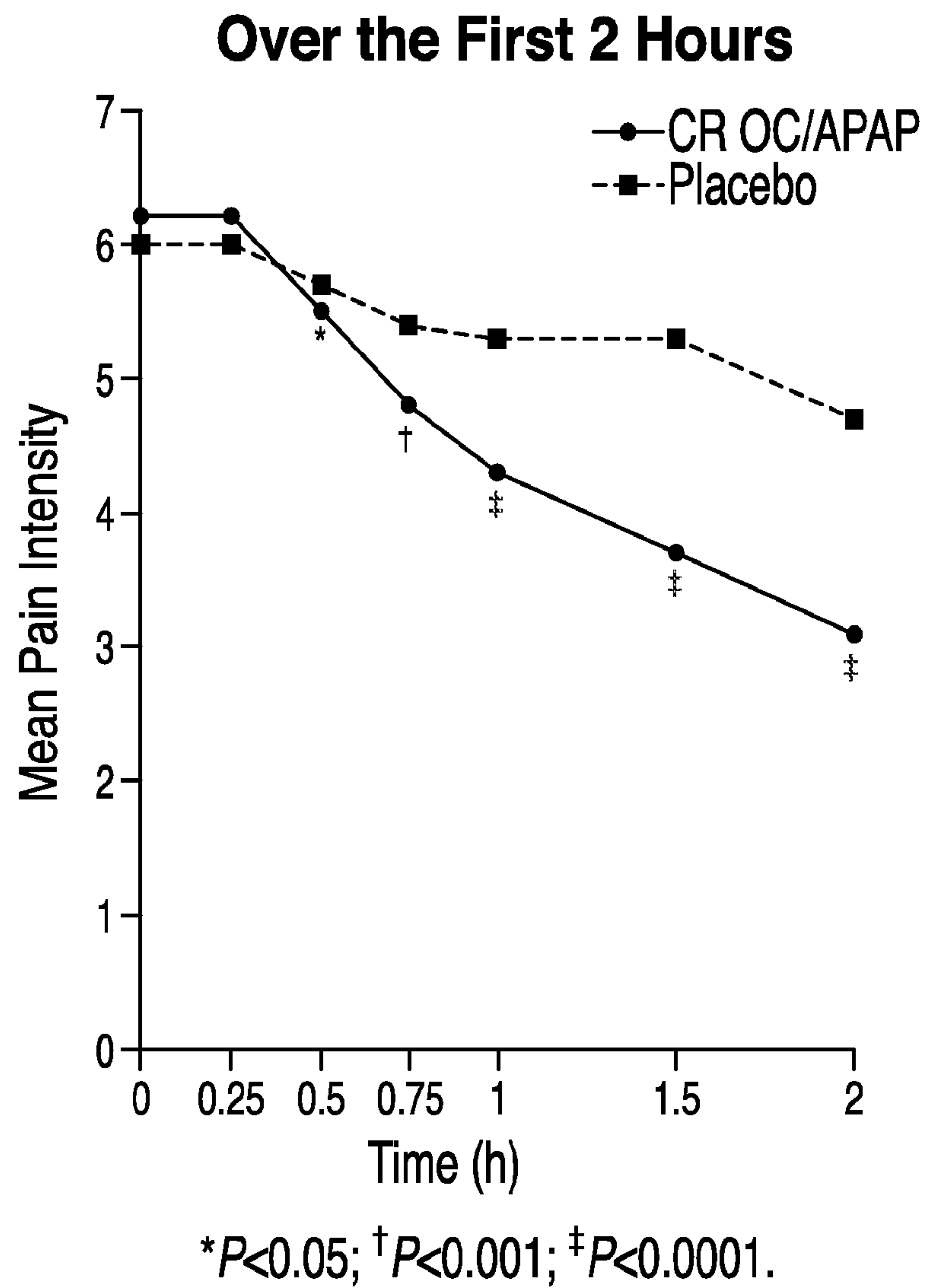
High-dose = 30 mg OC/1300 mg APAP; low-dose = 15 mg OC/1300 APAP.

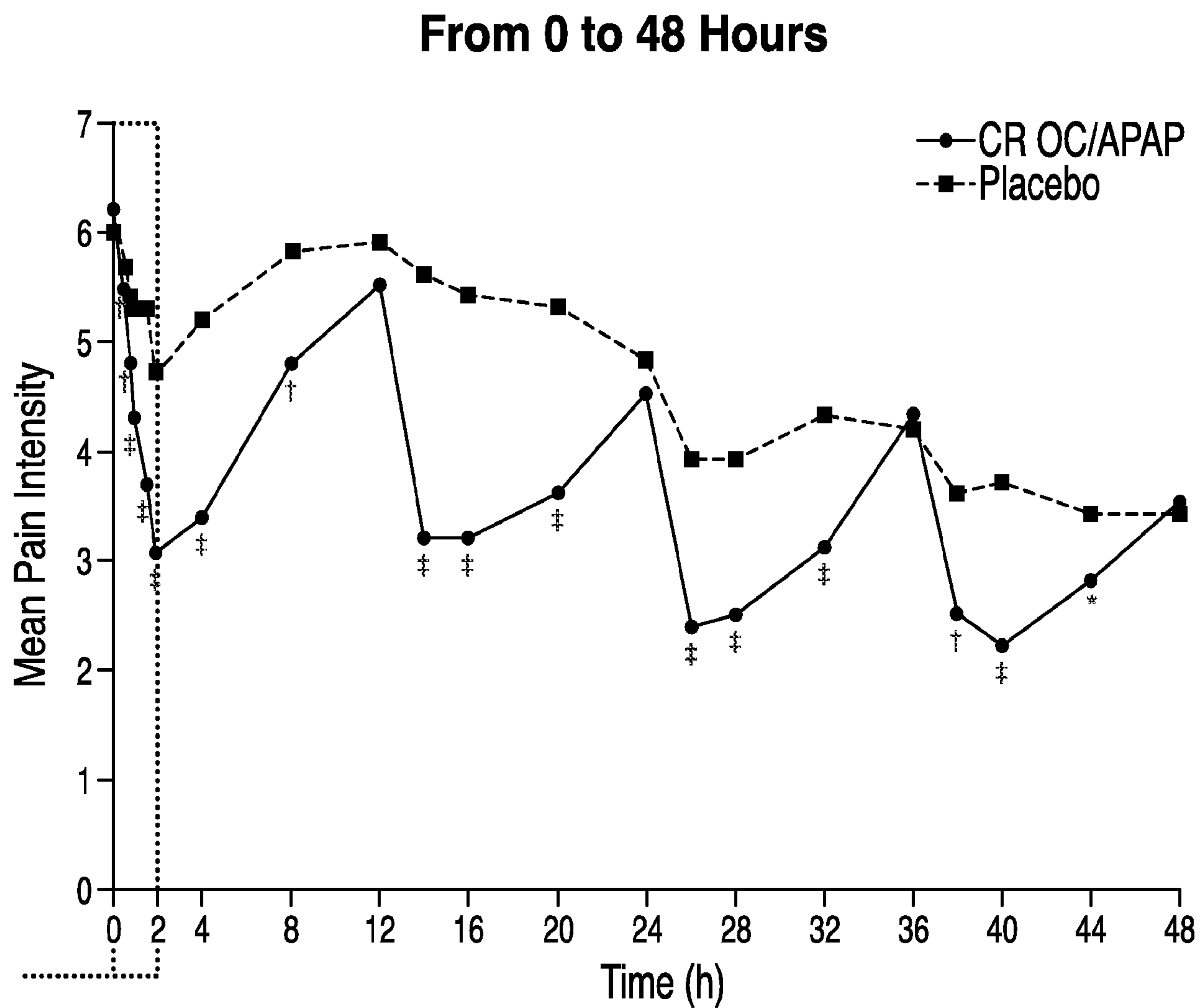
FIG. 92



^aSurgery completed; ^bNerve block stopped; ^cEarliest start for pain assessment and randomization; ^dLatest start for pain assessment and randomization; ^eStudy medication administered within 30 minutes of randomization; ^fPatients assessed for participation in open label extension within 48 to 52 hours of receiving first dose of study drug; ^gEnd-of-treatment evaluations performed within 3 days of receiving last dose of study drug; follow-up telephone call 7±2 days after receiving last dose of study drug (double-blind and open-label phases).

FIG. 93

**FIG. 94**



* $P < 0.05$; † $P, 0.001$; ‡ $P < 0.0001$.

FIG. 95

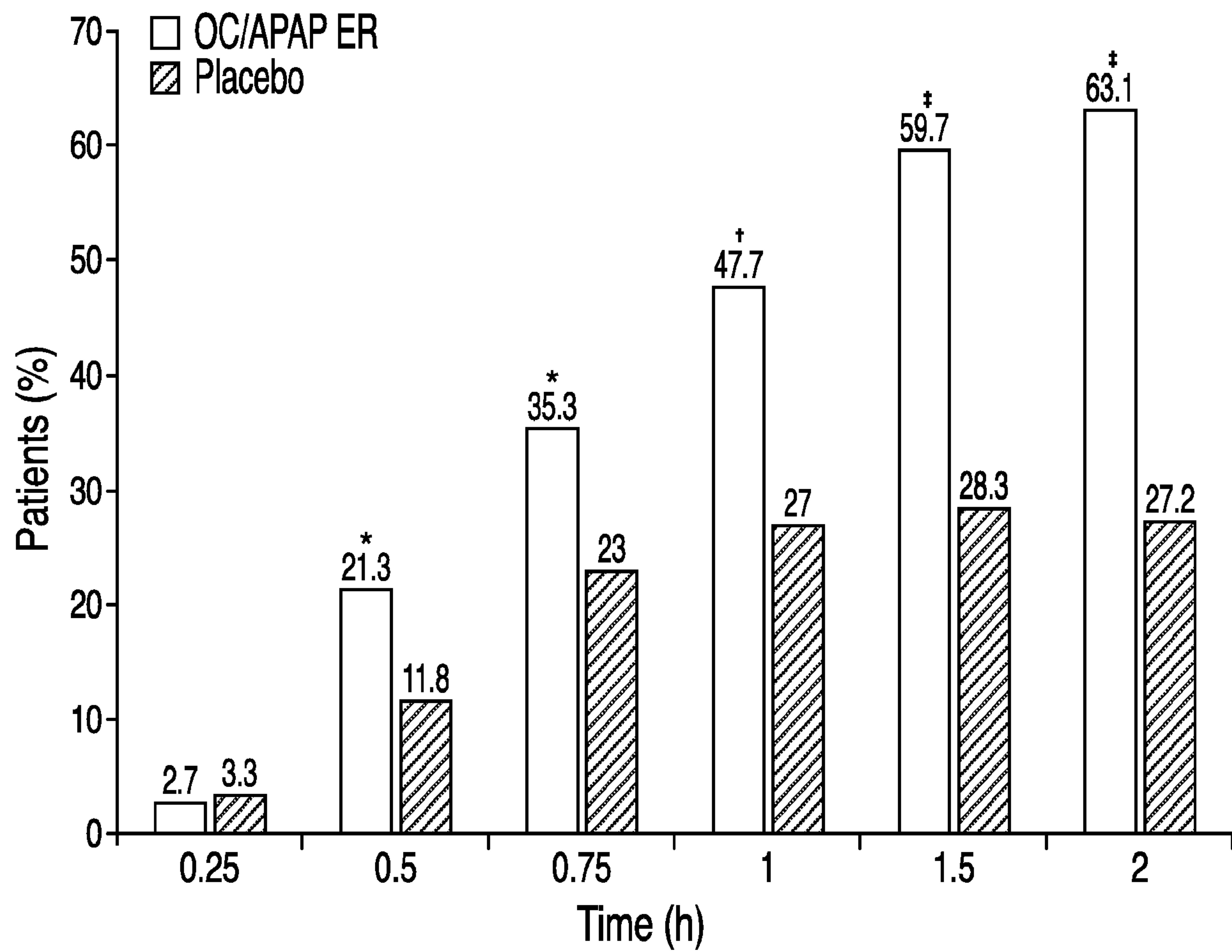
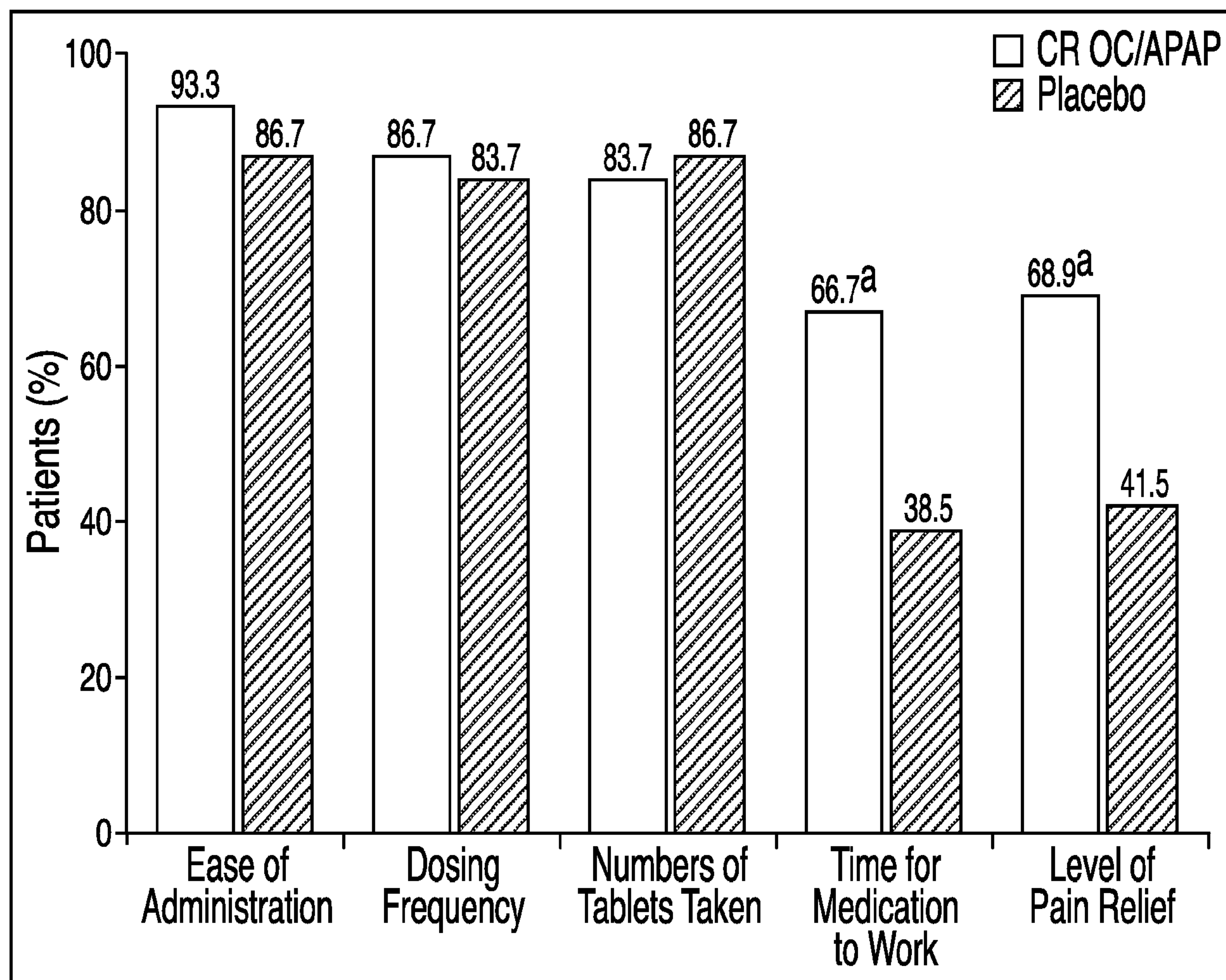


FIG. 96



^a $P < 0.001$.

FIG. 97

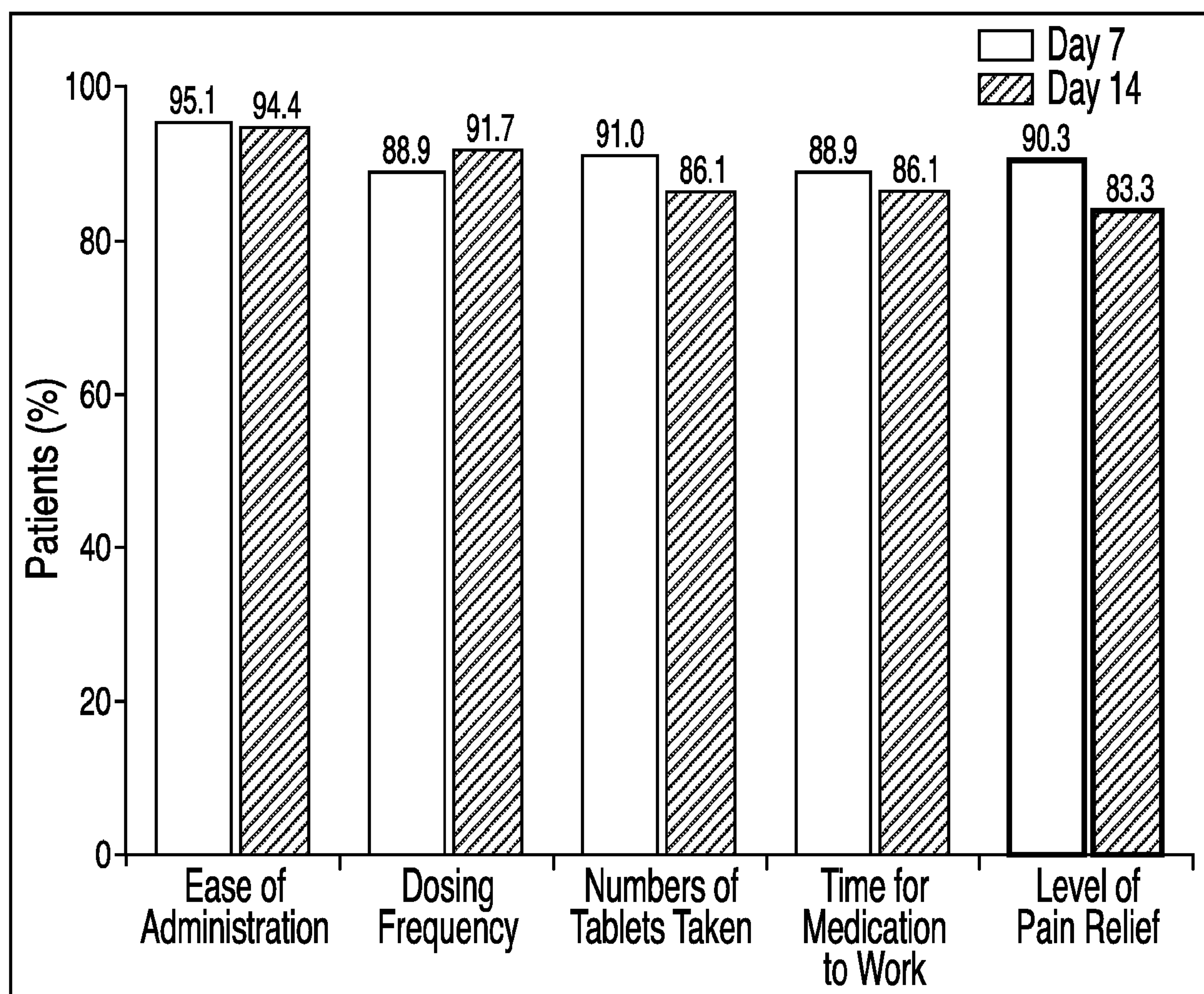


FIG. 98

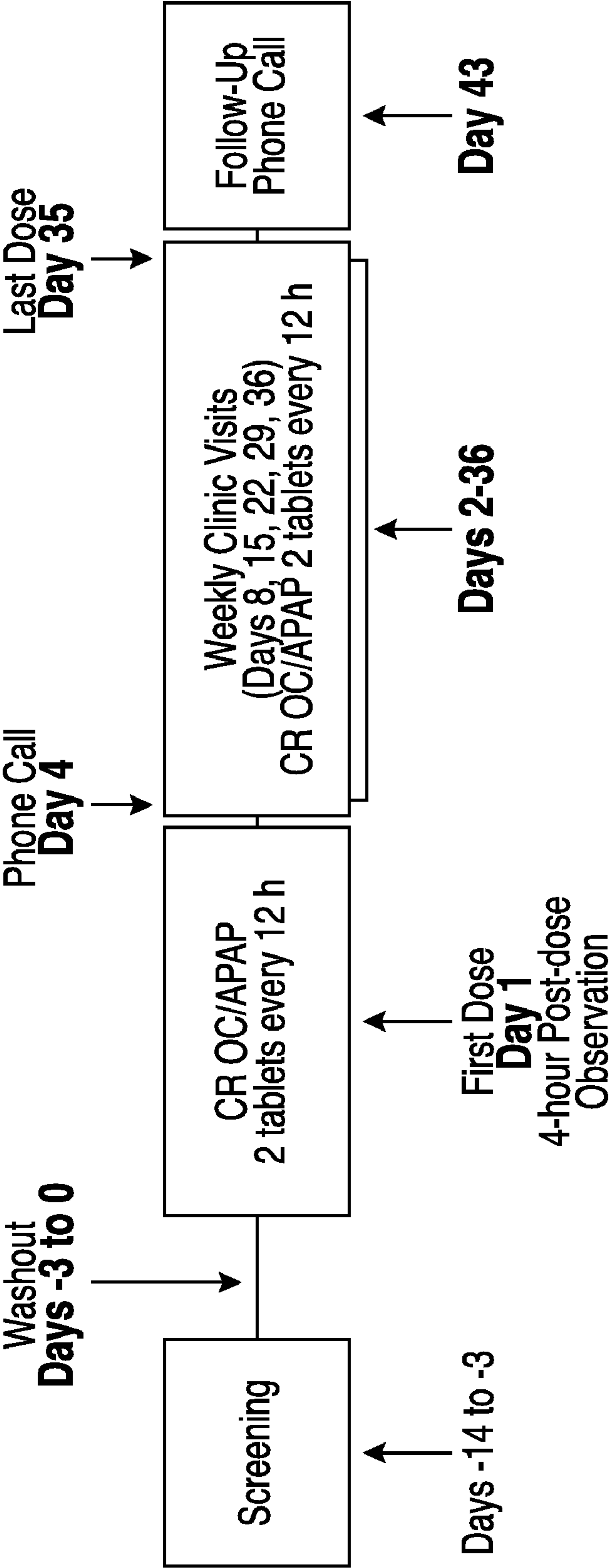
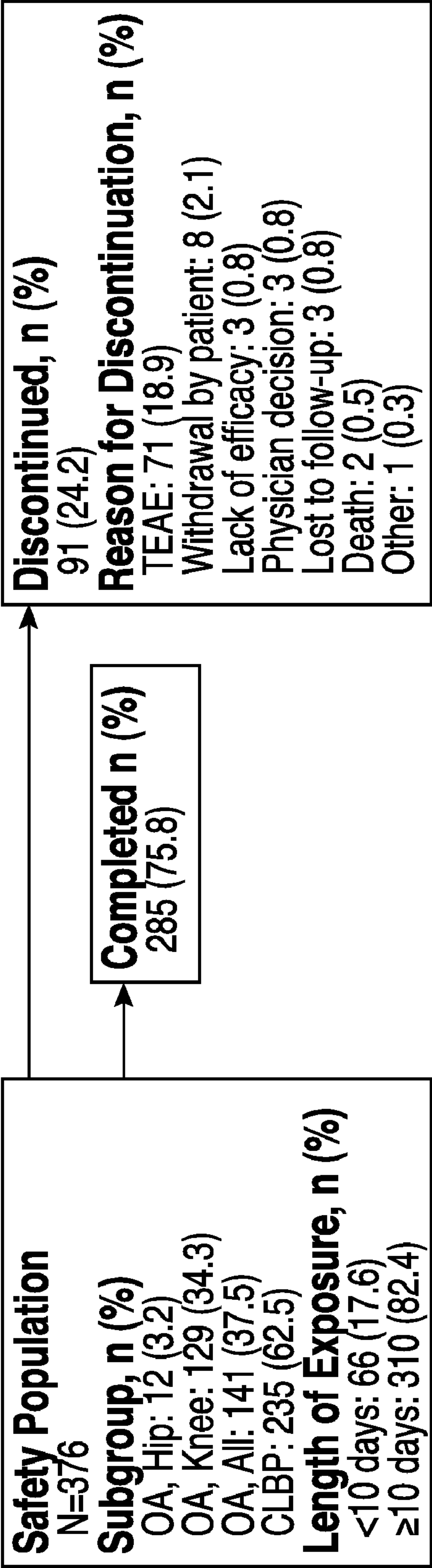
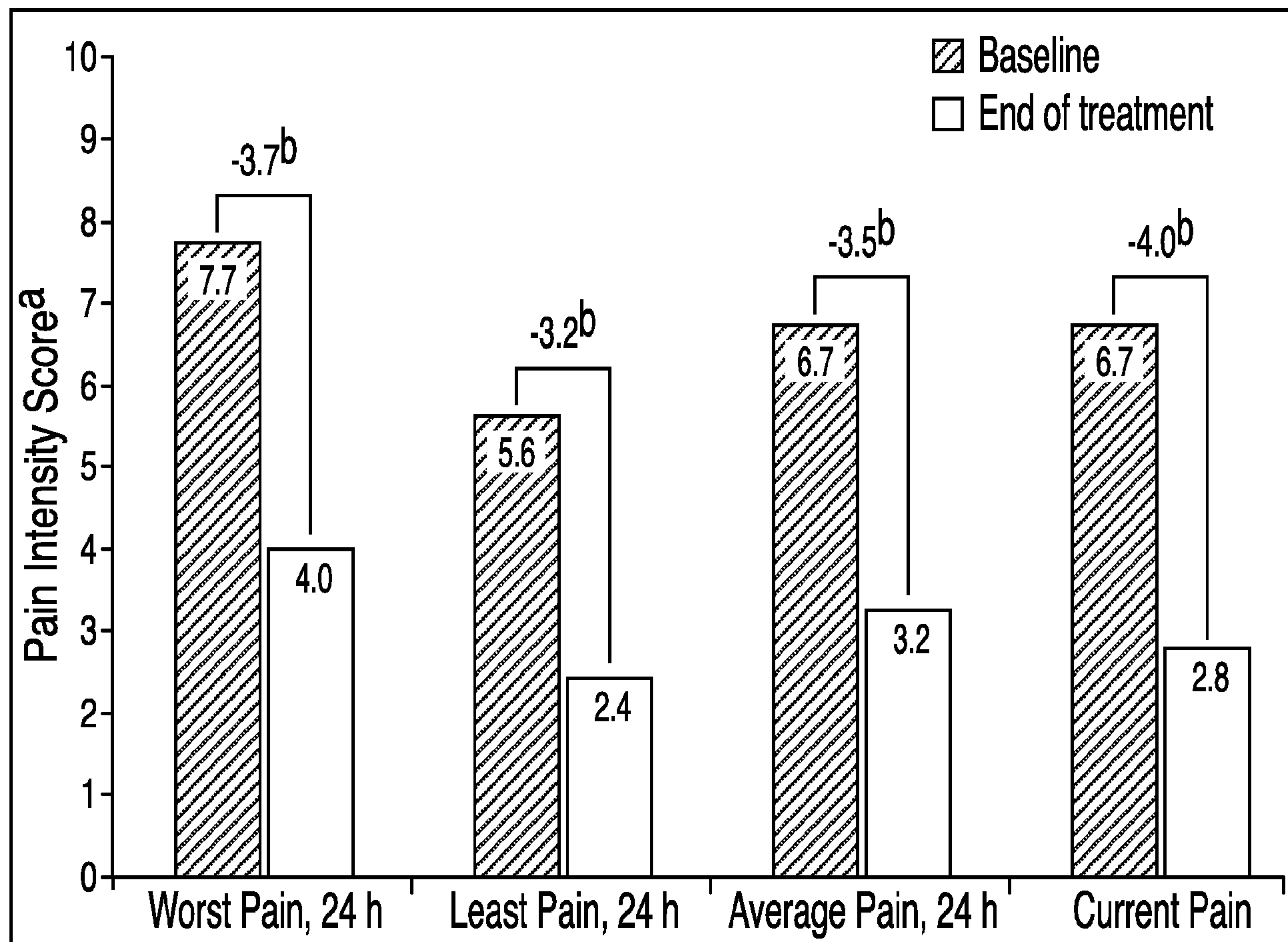


FIG. 99



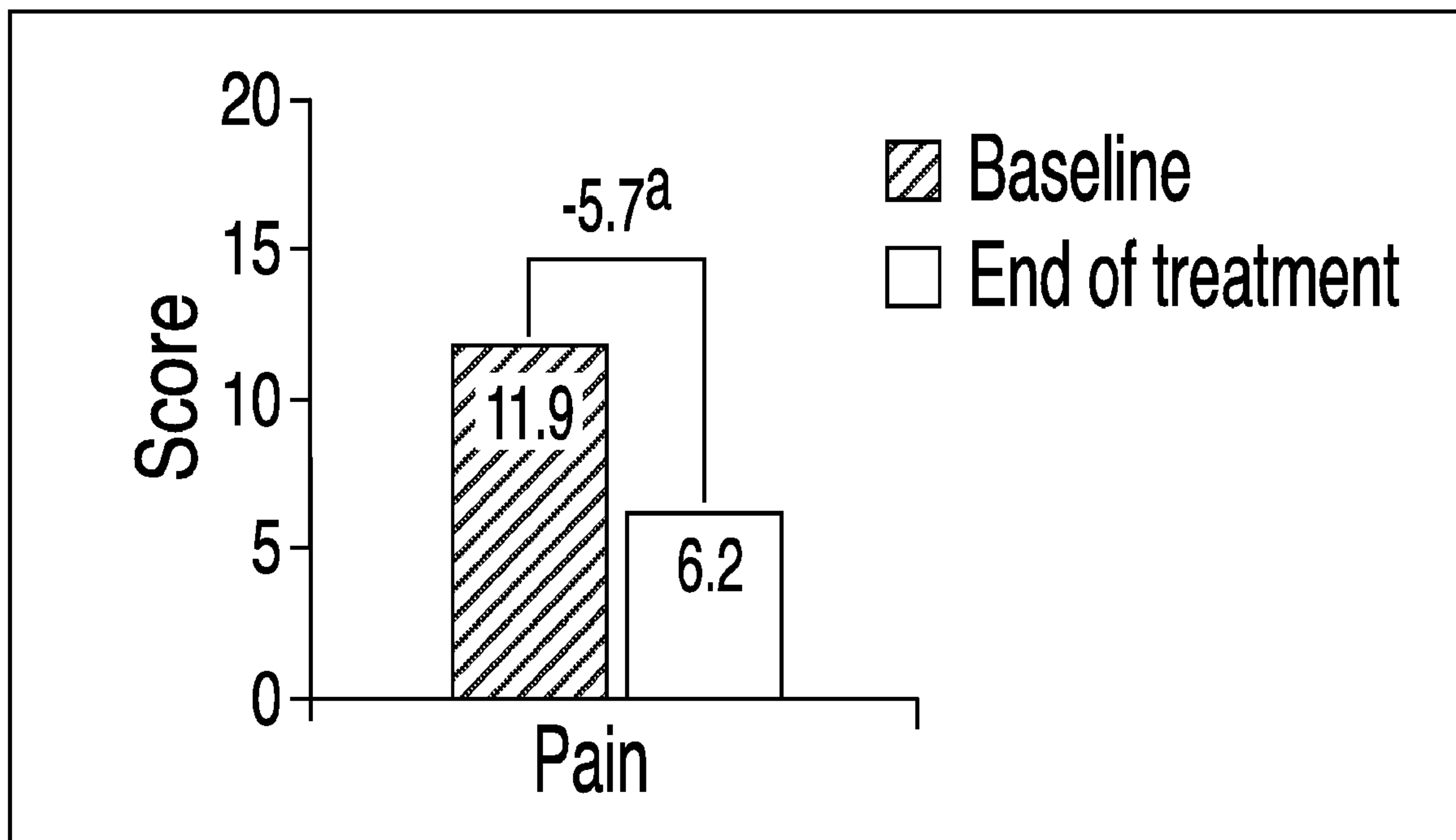
CLBP = chronic low back pain; OA = osteoarthritis; TEAE = treatment-emergent adverse event.

FIG. 100



^aScores range from 0 = no pain to 10 = pain as bad as you can imagine: ^b $P < 0.0001$.

FIG. 101



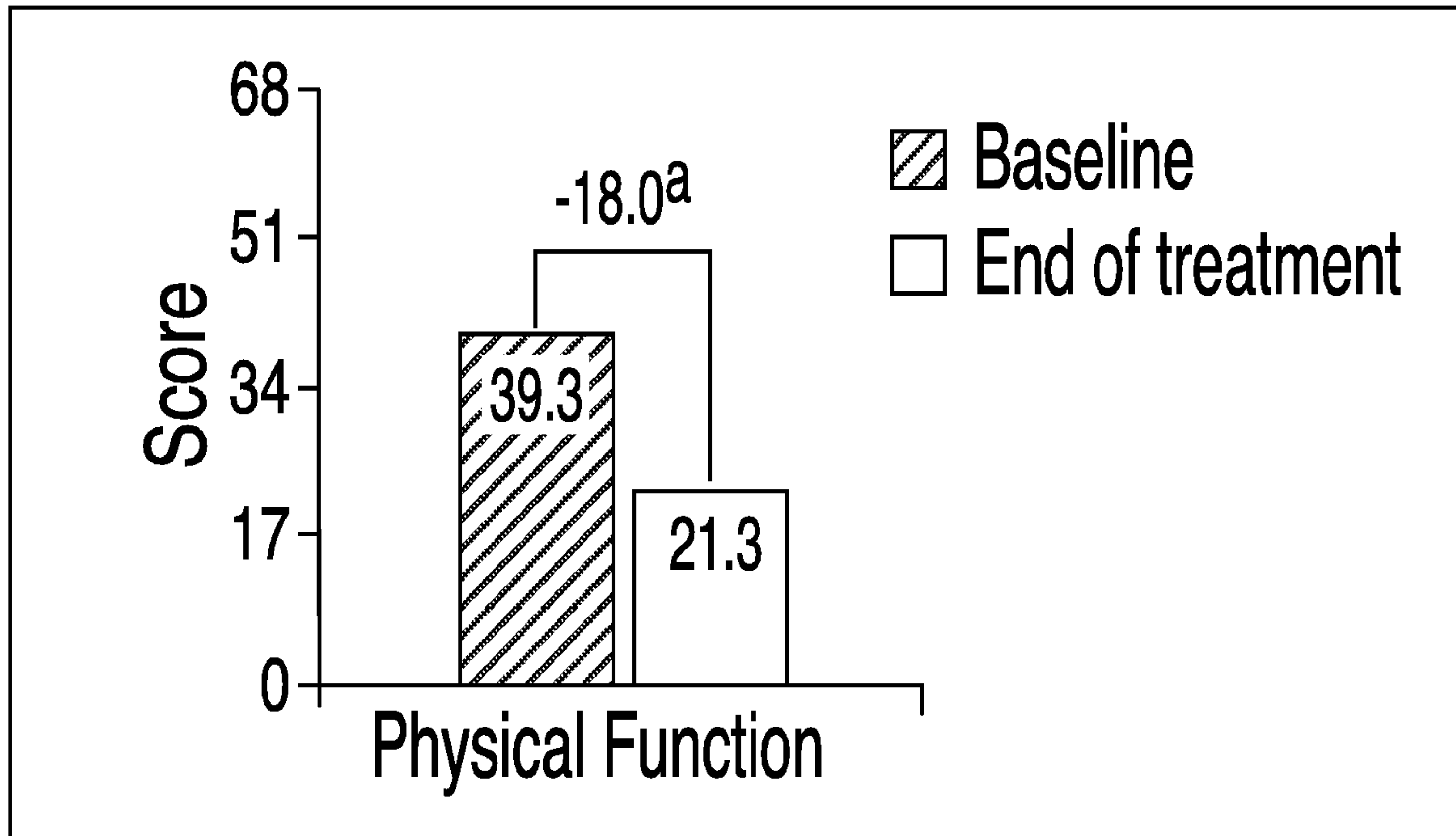
Higher scores represent worse pain/disability.
 $aP < 0.0001$.

FIG. 102



Higher scores represent worse pain/disability.
^a $P < 0.0001$.

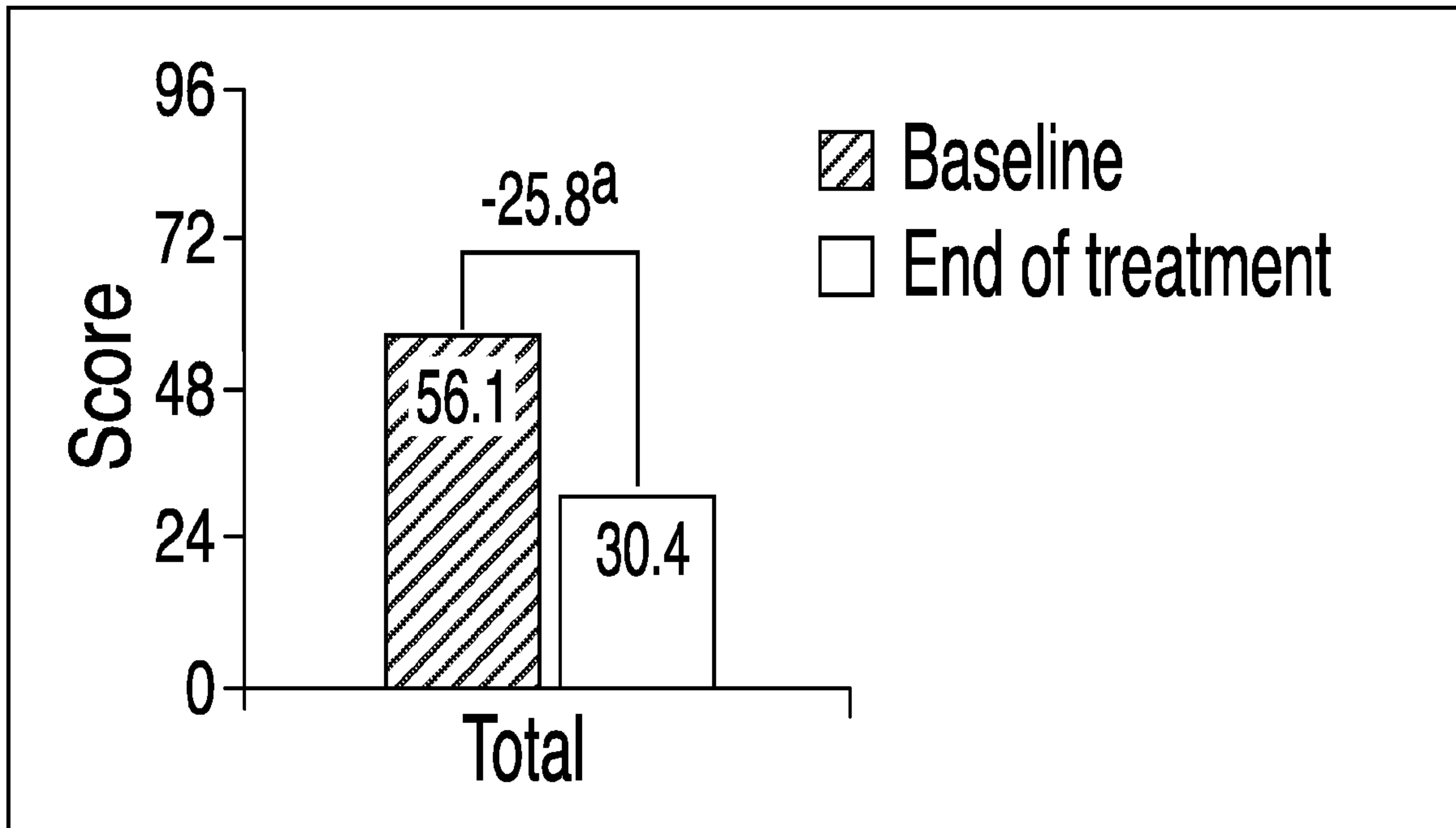
FIG. 103



Higher scores represent worse pain/disability.

^a $P < 0.0001$.

FIG. 104



Higher scores represent worse pain/disability.
 $aP < 0.0001$.

FIG. 105

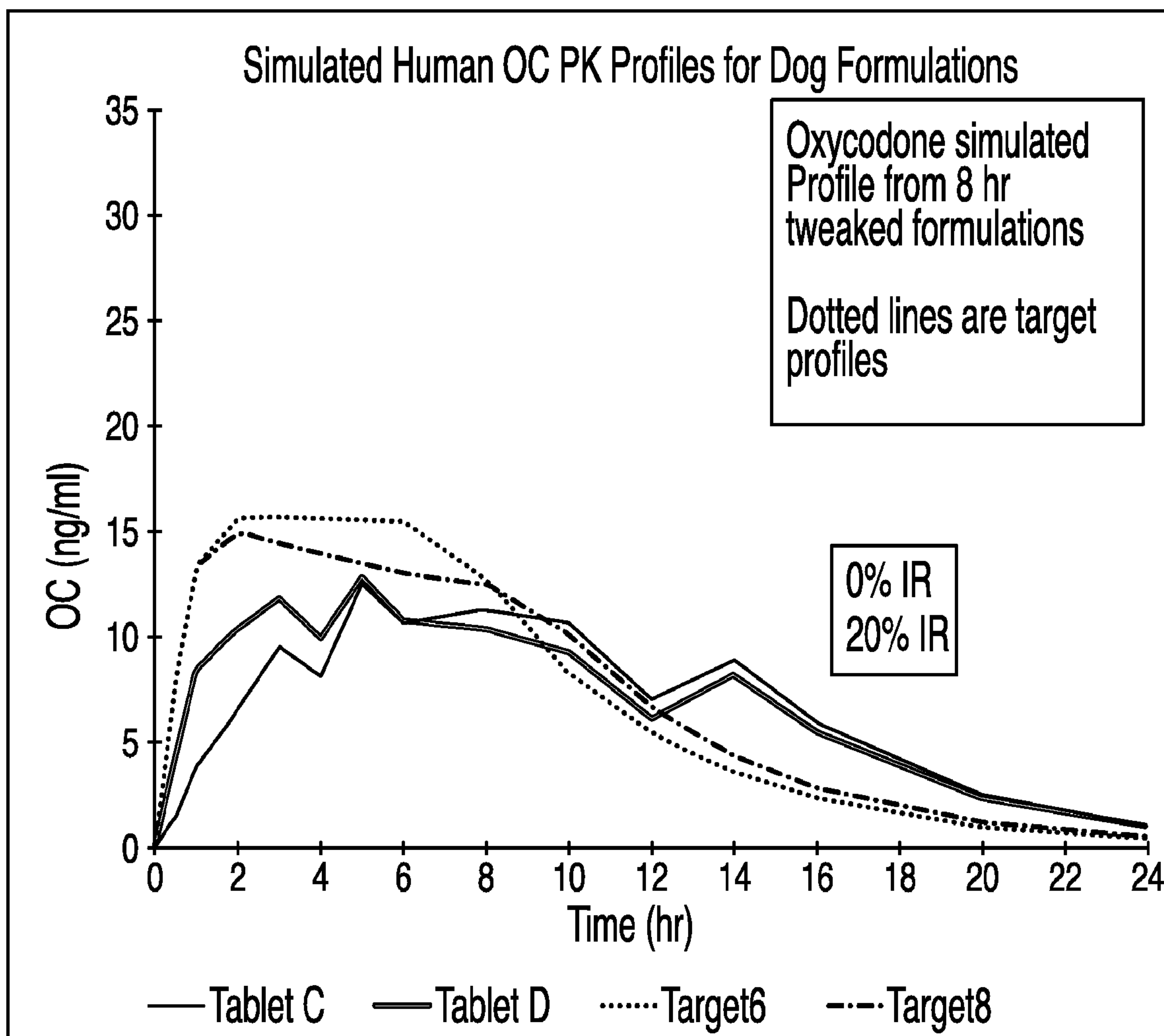


FIG. 106

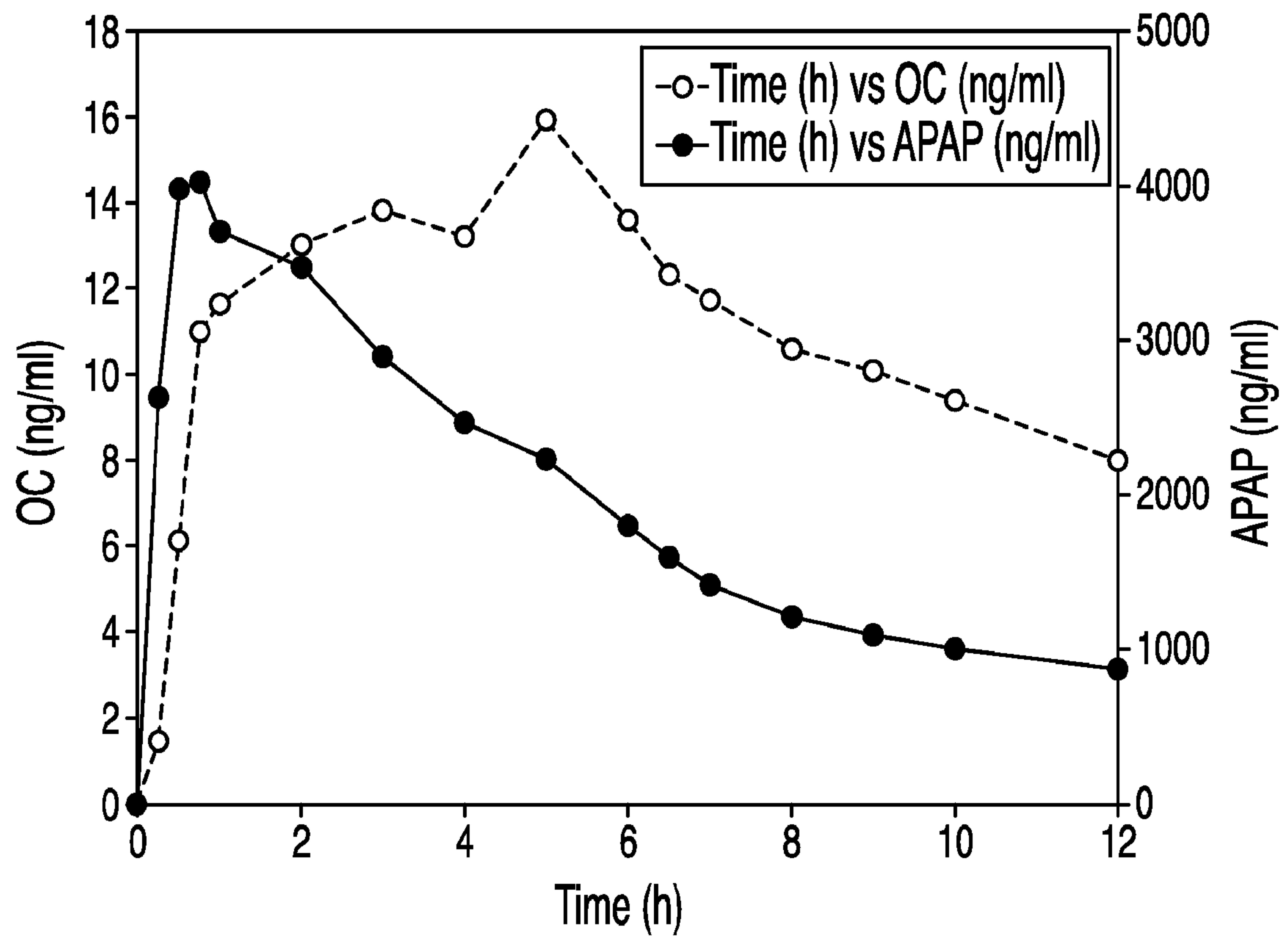


FIG. 107

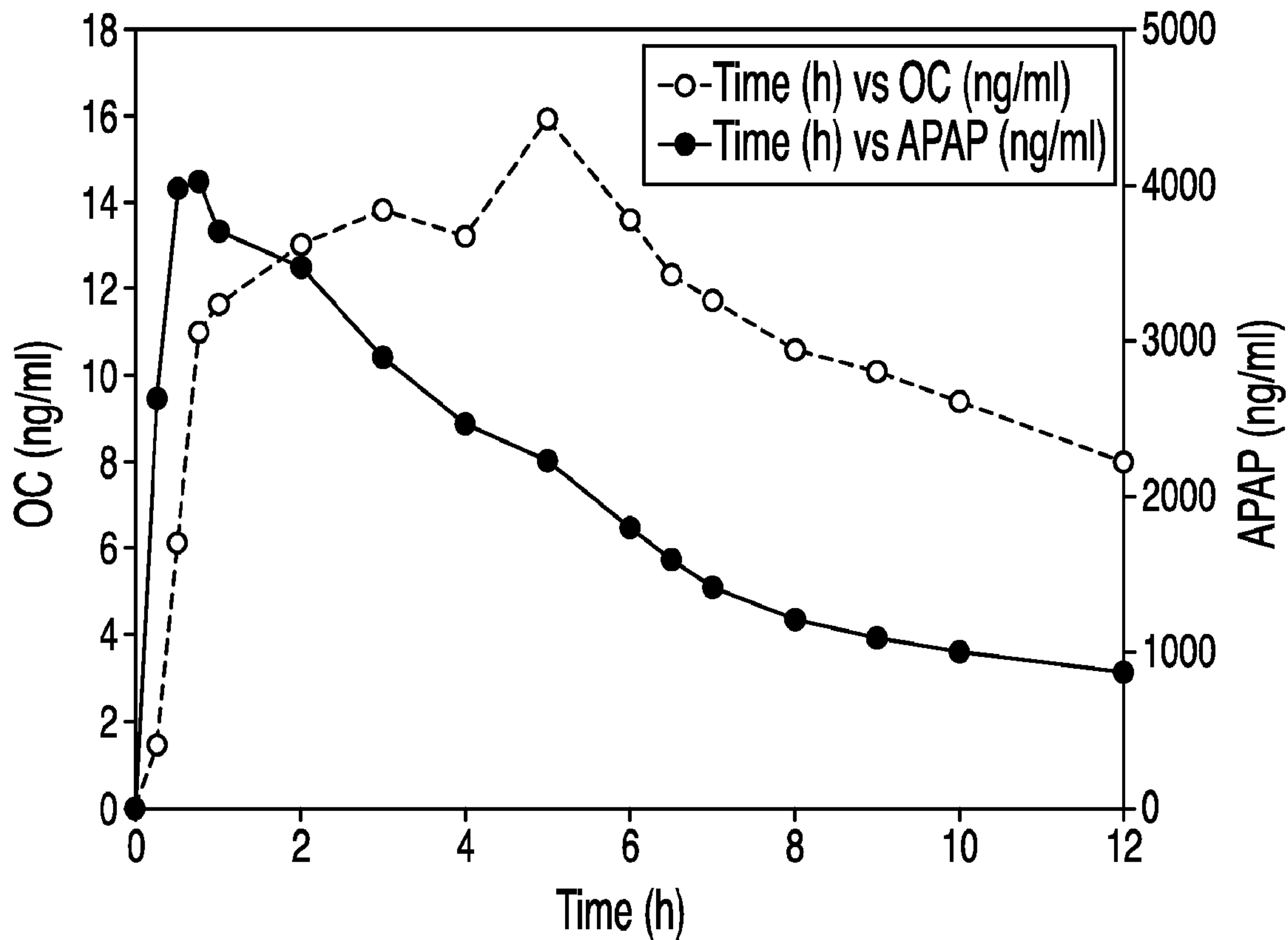


FIG. 107