(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 May 2015 (07.05.2015)

WIPO | PCT

(10) International Publication Number
WO 2015/066172 A1

(51) International Patent Classification:
A61K 9/20 (2006.01) *A61K 31/485* (2006.01)
A61P 25/04 (2006.01) *A61K 9/22* (2006.01)

(21) International Application Number:
PCT/US2014/062887

(22) International Filing Date:
29 October 2014 (29.10.2014)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/898,207 31 October 2013 (31.10.2013) US
14/333,986 17 July 2014 (17.07.2014) US
PCT/US2014/047014 17 July 2014 (17.07.2014) US
14/477,354 4 September 2014 (04.09.2014) US
PCT/US2014/054061 4 September 2014 (04.09.2014) US
14/484,793 12 September 2014 (12.09.2014) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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(54) Title: IMMEDIATE RELEASE ABUSE-DETERRENT GRANULATED DOSAGE FORMS

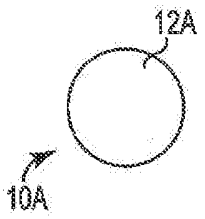

Fig. 1A

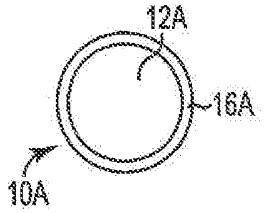

Fig. 1B

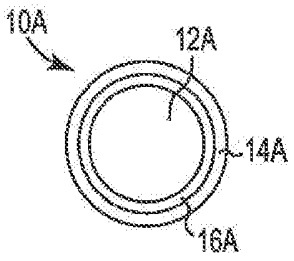

Fig. 1C

(57) Abstract: Described are immediate release oral dosage forms that contain abuse-deterrent features. In particular, the disclosed dosage forms provide deterrence of abuse by ingestion of multiple individual doses. In addition, the disclosed dosage forms provide protection from overdose in the event of accidental or intentional ingestion of multiple individual doses.

WO 2015/066172 A1

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

IMMEDIATE RELEASE ABUSE-DETERRENT GRANULATED DOSAGE FORMS

Cross Reference to Related Applications

This application is a continuation-in-part of U.S. application Serial No. 14/484,793, filed September 12, 2014, which is a continuation U.S. application Serial No. 14/477,354, filed September 4, 2014, which is a continuation-in-part of U.S. application Serial No. 14/333,986, filed July 17, 2014; and of PCT application Serial No. PCT/US2014/054061, filed September 4, 2014, which is a continuation-in-part of PCT application Serial No. PCT/US2014/047014, filed July 17, 2014, both of which claim the benefit of U.S. Provisional Application No. 61/898,207, filed October 31, 2013, the disclosures of which are incorporated herein by reference in their entirety.

Field of the Invention

The present invention relates to the field of oral dosage forms that contain abuse-deterrent features, in particular including immediate release dosage forms that contain a drug that is commonly susceptible to abuse.

Background

Pharmaceutical products, including both prescription and over-the-counter pharmaceutical products, while useful for improving health of a person in need, are also susceptible to intentional and unintentional abuse and overdosing. Examples of commonly abused active pharmaceutical ingredients include psychoactive drugs, anxiolytics, sedative hypnotics, stimulants, depressants, and analgesics such as narcotic analgesics, among others. A complete list of specific drug compounds that are commonly abused would be lengthy; a short listing of some classes of drugs commonly abused includes opioids and morphine derivatives, barbiturates, amphetamines, ketamine, and other drugs that can cause psychological or physical dependence.

Some common techniques for intentionally abusing a drug begin with an abuser obtaining a solid dosage form such as an orally administered tablet or capsule, and crushing the solid dosage form into a powder. The powder may be administered by an abuser by nasal insufflation (i.e., "snorting") to introduce the drug to the abuser's bloodstream intranasally. Alternately, the crushed dosage form may be combined with a

solvent that is capable of dissolving the drug (active pharmaceutical ingredient, or "API"), and the solvent with the dissolved drug may be injected directly into an abuser's bloodstream.

Alternatively, with immediate release oral dosage forms, an abuser might simply ingest multiple units (e.g., tablets) of the dosage form together, e.g., simultaneously. Each one of the multiple dosage form units -immediately releases an amount of drug to produce a short-term concentration spike of the drug in the user's bloodstream and a desired "high" in the user.

The pharmaceutical industry has identified various mechanisms of adapting drug compositions and oral dosage forms that can be useful to discourage abuse of oral dosage forms. Pharmaceutical companies have studied dosage forms that contain a nasal irritant or an effervescent agent, which can cause irritation or pain in a nasal passage if the dosage form is crushed and then snorted, thus discouraging abuse by nasal insufflation. Pharmaceutical companies studied adding gelling polymers to dosage forms to prevent abuse by injection. If the dosage form is crushed to a powder and combined with a small amount of solvent, the gelling polymer can cause the combination to take the form of a highly viscous liquid or gel that cannot be administered by injection. Another possible abuse deterrent may be addition of an emetic agent which can deter abuse by causing emesis on ingestion of multiple doses. Another abuse deterrent involves adding an antagonist of an API to a dosage form that will substantially block the effect of the drug.

Although the pharmaceutical industry has identified of a variety of abuse deterrent (sometimes referred to as "abuse-resistant") features useful with oral dosage forms, there is continuing need to improve and identify new abuse deterrent features to inhibit or prevent abuse or overdosing of active pharmaceutical ingredients.

Summary

The following description relates to oral dosage forms that are useful for immediate release of an active pharmaceutical ingredient or "API."

The dosage form can be designed to release the API as desired in an immediate release dosage form, and can also include one or a combination of feature that will prevent or deter abuse of the API. The abuse deterrent features described herein can be included singly or in any combination in an immediate release dosage form.

As a first type of abuse deterrent feature, a dosage form as described can include a gelling polymer to prevent or compromise abuse practices wherein the dosage form is crushed and then combined with a small amount of a solvent to produce a liquid composition that contains a concentrated amount of API and that can be delivered to an abuser using a syringe. The gelling polymer can be any polymer useful to achieve this functionality, and can be placed in the dosage form at any location to allow the gelling polymer to perform as described and still allow immediate release of the API. A gelling polymer can be included in a core of a coated of core-shell particle or in a matrix of a dosage form that suspends the core-shell particles. The core may contain any amount of gelling polymer, such as from 0 to 100 percent gelling polymer based on a total weight of the core. Alternately, the core in a core-shell particle may comprise a filler, e.g., up to 100 percent filler, such as a sugar sphere or microcrystalline cellulose sphere (up to 100 percent microcrystalline cellulose spheres such as those available under the trade name Celphere®).

Another type of abuse deterrent feature can be a wax that alone or with other ingredients, e.g., the gelling polymer, is effective in compromising abuse practices wherein a dosage form is crushed and combined with a solvent to produce a liquid composition that can be abused by nasal insufflation or delivered to an abuser using a syringe. The wax can additionally inhibit or prevent an abuser from grinding the dosage form into a powder because upon grinding the wax will smear as opposed to fracturing or powdering. Similar to the gelling polymer, wax can be included in a dosage form at any location that allows the wax to function as an abuse deterrent feature while not interfering with an immediate release profile of the API. For example, a wax can be included in a core of a coated particle. A core may contain any amount of wax, such as from 0 to 100 percent wax based on a total weight of the core, such as up to 50, 75, or 80 weight percent wax based on a total weight of the core.

Still another type of abuse deterrent feature can be a filler or binder that alone or in combination with other ingredients can compromise abuse practices wherein a dosage form is being crushed and combined with a small amount of a solvent to produce a liquid composition that can be delivered to an abuser using a syringe. The filler or binder can inhibit or prevent an abuser from grinding the dosage form into a powder because upon grinding, the polymeric filler or binder will smear as opposed to fracturing or powdering. The filler or binder can be included in a dosage form in any manner and location that

allows the filler or binder to function as an abuse deterrent feature while not interfering with an immediate release profile of the API. For example, a filler or binder can be included in a core of a coated particle. A core may contain any amount of polymeric filler or binder such as from 0 to 100 percent filler or binder on a total weight of the core, or up to 50, 75, or 80 weight percent filler or binder based on a total weight of the core.

Yet another type of abuse deterrent feature can be a film layer that surrounds or covers API in a dosage form and that is optionally resistant to being dissolved by one or more of the solvents commonly used by abusers to dissolve an API for injection, including water and C_1-C_4 alcohols such as ethanol, methanol, and mixtures thereof. The film layer may be prepared from any film material that is disposed as a continuous layer on a coated particle at a location to enclose and surround the API. Examples of film layers can optionally and preferably provide properties of a solvent-resistant film, which is a film that is slow or difficult to dissolve in a limited or small volume of one the solvents commonly used by abusers to dissolve API of a dosage form. To access an API of a dosage form an abuser may grind the dosage form and combine the ground dosage form with a solvent (as described) in an attempt to produce a solution that contains the concentrated API and the solvent, and that may be efficiently injected or snorted. By being slow to dissolve or insoluble in one or more of water, or a C_1-C_4 alcohol such as ethanol, methanol, etc., a solvent-resistant film layer that surrounds API of a dosage form can prevent an abuser from easily accessing and so manipulating the API.

In exemplary embodiments, an immediate release dosage form can include these features in a coated particle, such as a core-shell particle. An exemplary core-shell particle can include a core and one or more layers surrounding the core. For such a core-shell particle, the API may be included in the core, or in one or more layers surrounding the core, or in both the core and one or more layers surrounding the core. The dosage form may additionally contain core-shell particles that do not include the API in either the core, or in any layer surrounding the core. The core can include any one or more of: a gelling polymer, wax, binder, or filler, alone or in combination. Alternately, the core may comprise a microcrystalline cellulose or sugar sphere.

A film layer may surround and enclose the core, or an API-containing layer that is disposed around the core. The film layer may preferably be a solvent-resistant film in the form of a continuous coating that covers the core, which contains API, or that covers an

API-containing layer or coating disposed around the core, or that covers a core that has no API-containing layer or coating disposed around the core and contains no API.

According to other various embodiments, a coated particle as described herein can be useful in a dosage form that includes one or more optional abuse deterrent features, and a matrix such as a compressed matrix that is formed to allow for immediate release of the API present in the coated particles. An exemplary matrix composition may comprise additional gelling polymer, disintegrant, or both additional gelling polymer and disintegrant. The expression "additional gelling polymer" as used above means an amount of gelling polymer that is in addition to an amount of gelling polymer present in the coated particles. The additional gelling polymer may be the same or different in nature, chemistry, molecular weight, etc., as compared to the gelling polymer that is included in the coated particles. A disintegrant as a component of the matrix may be useful to facilitate release of the API of the dosage form, e.g., API present in the coated particles.

The active pharmaceutical ingredient included in the dosage form, especially in the coated particle surrounded by a film layer (e.g., a solvent resistant film), can be any active pharmaceutical ingredient desired to be administered orally, and may in particular be a type of active pharmaceutical ingredient that is commonly susceptible to abuse. Examples of active pharmaceutical ingredients that are considered to be commonly susceptible to abuse include psychoactive drugs, tranquilizers, sedative hypnotics, anxiolytics, stimulants, depressants, and narcotic analgesics, among others. Certain more specific classes of drugs commonly abused includes opioids, barbiturates, benzodiazepines, amphetamines, as well as many other drugs that are known to cause psychological or physical dependence.

Dosage forms of the present description can be useful as immediate release dosage forms, and may also include abuse deterrent features as described. The abuse deterrent features can discourage or prevent abuse by nasal insufflation, by injection, and can also be effective to prevent or significantly limit the success of abuse by the common methods (especially with immediate release oral dosage forms) of orally taking multiple dosage form units together. The final mode of abuse (sometimes referred to herein as "multi-tablet dosing") is often particularly difficult to deter, especially in immediate release oral dosage forms, making these described dosage forms particularly useful as abuse-deterrant oral immediate release dosage forms.

Embodiments of the described dosage forms can be effective in the absence of other types of abuse deterrent features such as nasal irritants, emetic agents, bittering agents, and effervescent agents, to inhibit nasal insufflation or other forms of abuse, or the inclusion of drug antagonists of the subject drug.

In one aspect, the invention relates to an immediate release dosage form that includes core-shell particles. The core-shell particles include: an inner core containing a gelling polymer; at least one layer surrounding the core, the at least one layer including a film layer surrounding the core; and an active pharmaceutical ingredient. The active pharmaceutical ingredient is also surrounded by the film layer that surrounds the core.

In another aspect, the invention relates to an immediate release dosage form that includes core-shell particles. The core-shell particles include a core and an active pharmaceutical layer surrounding the core. The active pharmaceutical layer contains an active pharmaceutical ingredient. The core contains less than 5 weight percent of a total amount of the active pharmaceutical ingredient in the core-shell particles.

In yet another aspect the invention relates to an immediate release dosage form that contains core-shell particles. The core-shell particles include: a core and an active pharmaceutical ingredient. The dosage form further includes a matrix. The matrix includes disintegrant and an additional amount of gelling polymer.

In still another aspect, the invention relates to an immediate release dosage form that includes two types of core-shell particles. One type of core-shell particles includes a core and an active pharmaceutical layer surrounding the core as discussed above. The core of these particles optionally contains less than 5 weight percent of the total amount of the API in that core-shell particle, and in some instances contains less than 1 weight percent of the total amount of the API in that core-shell particle, or even contains no significant amount of the API. The other type of core shell particles comprise the core, but do not contain an active pharmaceutical layer surrounding the core.

Brief Description of the Drawings

Figures 1A, 1B, and 1C illustrate embodiments of core-shell particles as described, in cross section.

Figures 2A and 2B illustrate embodiments of core-shell particles as described, in cross section.

Figure 3 is a perspective view of an embodiment of a dosage form as described.

Figure 4 shows a plot of Multiple Tablet oral Abuse Resistance (Supratherapeutic Dosing) – Dissolution of Hydrocodone Bitartrate in 0.1N HCl media as a function of time.

Figure 5 shows a plot of multiple tablet oral abuse resistance (supratherapeutic dosing) – dissolution of acetaminophen in 0.1N HCl media as a function of time.

Figure 6 shows a plot of multiple tablet oral abuse resistance (supratherapeutic dosing) – dissolution of hydrocodone bitartrate in 0.1N HCl media as a function of time.

Figure 7 shows a plot of multiple tablet oral abuse resistance (supratherapeutic dosing) – dissolution of acetaminophen in 0.1N HCl media as a function of time

Figure 8 shows a plot of multiple tablet oral abuse resistance (supratherapeutic dosing) – dissolution of hydrocodone bitartrate in 0.1N HCl media as a function of time.

Figure 9 shows a plot of multiple tablet oral abuse resistance (supratherapeutic dosing) – dissolution of acetaminophen in 0.1N HCl media as a function of time.

Figure 10 shows a plot of multiple tablet oral abuse resistance (supratherapeutic dosing) – dissolution of oxycodone hydrochloride from oxycodone hydrochloride /acetaminophen tablets (5/325 mg/tablet and 7.5/325 mg/ tablet of oxycodone hydrochloride/ acetaminophen) in 0.1N HCl media as a function of time.

Figure 11 shows a plot of multiple tablet oral abuse resistance (supratherapeutic dosing) – dissolution of acetaminophen from oxycodone hydrochloride/acetaminophen tablets (5/325 mg/tablet and 7.5/325 mg/ tablet of oxycodone hydrochloride/ acetaminophen) in 0.1N HCl media as a function of time.

Figure 12 shows a plot of multiple tablet oral abuse resistance (supratherapeutic dosing) – dissolution of hydrocodone bitartrate from hydrocodone bitartrate /acetaminophen tablets (5/325 mg/tablet and 7.5/325 mg/ tablet of hydrocodone bitartrate/acetaminophen) in 0.1N HCl media as a function of time.

Figure 13 shows a plot of multiple tablet oral abuse resistance (supratherapeutic dosing) – dissolution of acetaminophen from hydrocodone bitartrate /acetaminophen tablets (5/325 mg/tablet and 7.5/325 mg/ tablet of hydrocodone bitartrate/acetaminophen) in 0.1N HCl media as a function of time.

Figure 14 shows a plot of multiple tablet oral abuse resistance (supratherapeutic dosing) – dissolution of hydrocodone bitartrate from hydrocodone bitartrate /acetaminophen tablets (10/325 mg/ tablet of hydrocodone bitartrate/acetaminophen, tested both as intact tablets and crushed tablets) in 0.1N HCl media as a function of time.

Figure 15 shows a plot of multiple tablet oral abuse resistance (supratherapeutic dosing) – dissolution of acetaminophen from hydrocodone bitartrate /acetaminophen tablets (10/325 mg/ tablet of hydrocodone bitartrate/acetaminophen, tested both as intact tablets and crushed tablets) in 0.1N HCl media as a function of time.

Detailed Description

The present description relates to immediate release dosage forms that include one or more abuse deterrent features for reducing the potential for a) parenteral abuse, b) abuse by nasal insufflation ("snorting"), and c) abuse by simultaneous oral ingestion of multiple oral dosage form units (tablets or capsules) of a drug. These abuse deterrent features are achieved by preparing the dosage form to include certain structural features and certain ingredients that have now been determined to effectively prevent an abuser from realizing the intended biological effect of the drug abuse by using certain presently-common methods used to abuse the API. Advantageously, a dosage form prepared to contain one or more of the described abuse deterrent features, as a deterrent to abuse of one or more API that is commonly susceptible to abuse, can still be constructed to provide immediate release of the one or more API upon normal therapeutic use by oral ingestion.

As used herein, expressions such as "abuse deterrent" and "preventing" or "deterring" or "inhibiting" practices and processes associated with the abuse and overdose of drugs, relate to features of the claimed formulations that provide significant physical and chemical impediments to these practices and processes. The objective in such deterrence includes both making abuse practices significantly more difficult to carry out, and making any product resulting from an attempt to carry out such abuse practices on the claimed formulations significantly less desirable, less profitable, and less abusable to the potential abuser.

The term "immediate release" refers to a dosage form that upon oral ingestion by a human releases substantially all of a contained active pharmaceutical ingredient into a gastrointestinal tract for biological uptake in a short time. *In vitro* methods of measuring a release profile of a dosage form, for the purpose of determining whether a dosage form exhibits an immediate release or extended release dissolution profile, are known in the pharmaceutical arts. By such methods, examples of immediate release dosage forms as described herein can be measured to be capable of releasing substantially all of a total amount of at least one type of active pharmaceutical ingredient (e.g., an API commonly

susceptible to abuse) contained in the dosage form (e.g., at least 75, 80, or 90 weight percent of the total amount of the API in a dosage form) into a solution (e.g., acidic aqueous solution) of a suitable pH within 240 minutes, e.g., in less than 180 minutes, less than 90 minutes, or less than 60, 30, 15, or 5 minutes. For example, a release profile of a dosage form of the present description may be measured by a method that exposes the dosage form to a volume of up to 900 milliliters (e.g., 300 milliliters, or 900 milliliters, based on various test methods) of hydrochloric acid (0.01 to 0.1N) (e.g., aqueous hydrochloric acid) at a pH of from 1 to 2, and at a temperature of 37 degrees Celsius. According to some embodiments, the dosage forms described herein, demonstrate not less than 90% of API released in 60 minutes when administered at therapeutic doses, wherein the release profiles may be evaluated by dissolution in 300 mL of 0.1N HCl media using USP II apparatus at 50 RPM paddle speed and 37°C. A release profile of a dosage form of the present description may alternatively be measured by a method that exposes the dosage form to a volume of up to 900 milliliters (e.g., 300 milliliters, or 900 milliliters, based on various test methods) of hydrochloric acid (0.01 to 0.1N) (e.g., aqueous hydrochloric acid) at a pH of about 4.5 (representative of the pH conditions of a fed stomach), and at a temperature of 37 degrees Celsius.

The term "extended release" can be defined as not more than 95% release of the API at 60 minutes, wherein the release profiles may be evaluated, for example, by dissolution in 300 mL of 0.1N HCl media using USP II apparatus at 50 RPM paddle speed and 37°C. According to some embodiments, the dosage forms described herein, demonstrate:

- not less than 90% of API released in 60 minutes when administered at therapeutic doses; and
- not more than 95% release of the API at 60 minutes when administered at supratherapeutic doses;

wherein the release profiles may be evaluated by dissolution in 300 mL of 0.1N HCl media using USP II apparatus at 50 RPM paddle speed and 37°C. In this context, a "supratherapeutic dose" will be understood to correspond to administration of five or more, six or more, seven or more, eight or more, nine or more, ten or more, eleven or more, or twelve or more individual dose units, e.g., tablets, simultaneously. It will also be understood that administering multiple individual dose units simultaneously would reasonably include administering those multiple doses sequentially over a short time

interval, e.g., over an interval of less than 60 minutes, less than 30 minutes, less than 15 minutes, less than 5 minutes or less than one minute.

Dosage forms as described can be formulated to provide an immediate release profile of an API, and can also be prepared to include effective or advantageous abuse deterrent features that are effective to deter abuse of the same API (e.g., one that is commonly susceptible to abuse) that exhibits the immediate release profile. The combination of immediate release of an API with broad abuse resistance of the same API for multiple abuse modalities including multi-tablet dosing, as described herein, is not believed to be previously known. More particularly, dosage forms as described herein can provide an immediate release profile of an API, and can at the same time include abuse deterrent features that provide general abuse deterrence or abuse resistance of the same API. The dosage forms can also be more specifically characterized as resistant to certain common methods of abuse, such as 1) abuse by injection (e.g., by steps that include grinding a dosage form and dissolving API of the dosage form), 2) abuse by nasal insufflation (e.g., also by grinding and optionally dissolving API of a dosage form), and 3) abuse by multi-tablet dosing by oral consumption, meaning simultaneous oral ingestion of multiple or excessive quantities of orally administered dosage forms such as tablets or capsules. The third mode of abuse, multi-tablet dosing, is particularly common with immediate release dosage forms and is particularly difficult to defend against by design of a dosage form structure or by formulation. Accordingly, that the presently-described dosage forms can be effective to prevent or deter abuse (or even accidental overdose) by the mode of multi-tablet dosing can be a particularly useful feature of the dosage forms described herein.

In vitro testing of exemplary dosage forms as described herein indicates that exemplary dosage forms provide deterrence against abuse by multi-tablet dosing. More specifically, *in vitro* testing of exemplary dosage forms was performed by conducting dissolution testing of one or more dosage forms (tablets) in 300 milliliters of 0.1N HCL maintained at 37 degrees Celsius using a 50 RPM paddle speed. See, Example 26 (a) and Figures 4 and 5 herein. As shown at Figures 4, 5, 6, 7, 8 and 9, the amount (percentage per tablet) of API (opioid) or APAP (acetaminophen) released in the media is reduced with an increase in the number of tablets. The data also suggest that the tested dosage forms are effective to prevent increased levels of API uptake in an individual who would accidentally ingest multiple tablets, preventing or reducing the risk of an unintentional

overdose of the API. (In Figures 4 and 5, the 1 tablet and 2 tablet dosage forms are as prepared in Example 3, *infra*, and the 5 tablet, 8 tablet, and 12 tablet dosage forms are as prepared in Example 5, *infra*. The tablets used in Figures 6, 7, 8 and 9 are as prepared as per Example 17.)

In addition, *in vitro* testing as described herein indicates that exemplary dosage forms provide deterrence against abuse by multi-tablet dosing, even if the dosage form is crushed prior to administration/testing. Specifically, *in vitro* testing was performed by conducting dissolution testing of multiple (twelve) crushed tablets according to the same protocol as described above for testing intact tablets (i.e., in 300 or 900 milliliters of 0.1N HCl maintained at 37 degrees Celsius using a 50 RPM paddle speed). See, Example 93 and Figures 14-15 herein. As shown in Figures 14-15, the percentage of the API (the opioid and APAP) that was released in the media was reduced with an increase in the number of crushed tablets. This data suggests that the dosage forms are effective to prevent increased levels of API uptake in an individual who would ingest multiple crushed tablets, and thereby prevent or reduce the risk of an overdose of the API. The tablets used in Example 94, which provided the data shown in Figures 14-15 were prepared as per Example 93.)

Accordingly dosage forms as described herein provide a method of preventing a short-term concentration spike of the drug in the bloodstream of a patient who is prescribed the drug, or in the bloodstream of an abuser who consumes the drug for recreational purposes, in the event that a patient or the abuser intentionally or unintentionally consumes a supratherapeutic dose of the drug. In addition, dosage forms as described herein provide a method whereby a drug overdose may be prevented in the event that a patient intentionally or unintentionally consumes a supratherapeutic dose of the drug. By "supratherapeutic is meant a dose that exceeds what would normally be prescribed for therapy, for example a dose in excess of four, five, six, seven, eight, nine, ten, eleven or twelve individual dose units (*e.g.*, tablets, capsules, etc.).

As one type of abuse deterrent feature, a dosage form as described can include one or more gelling polymers. A gelling polymer can act as an abuse deterrent feature by compromising abuse practices wherein an active pharmaceutical ingredient of a dosage form is being dissolved in a small volume of solvent or being accessible or easily isolatable if combined with solvent with the gelling polymer also present. A gelling polymer can also deter or prevent abuse of an API in a dosage form by increasing the

viscosity of a combination of the ground dosage form with solvent (especially a "small volume" of solvent) to a viscosity that is sufficiently high to prevent the combination or the API from being taken up by and injected using a syringe. A preferred gelling polymer contained in a ground dosage form, when exposed to a limited volume (or "small volume") of solvent such as a C_{1-4} alcohol (e.g., ethanol or methanol) or water, can form a non-injectable mass ranging from an insoluble mass, to a gel, to a viscous slurry, each of which exhibits a viscosity that substantially prevents either uptake by or injection from a needle of a hypodermic syringe.

Suitable gelling polymers include one or a combination of polymers that, as part of a dosage form, upon contact of the dosage form with a small volume of solvent, will absorb the solvent and swell to form a viscous or semi-viscous substance that significantly reduces or minimizes the amount of free solvent that can contain an amount of a solubilized API and that can be drawn into a syringe. The gelled polymer can also reduce the overall amount of drug extractable with the solvent by entrapping the drug in a gel matrix.

The gelling polymer can be present in the dosage form at a location and in an amount that together allow the gelling polymer to produce a viscous gel in the event of an abuser grinding the dosage form and combining the crushed dosage form with a solvent. On the other hand, the gelling polymer, as present in the dosage form, will preferably not interfere with desired dissolution of the dosage form, the desired release (immediate release) of API from the dosage form, or the uptake of the API by a patient ingesting the intact immediate release dosage form for an intended therapeutic purpose. An exemplary location for the gelling polymer is in a coated particle that also includes active pharmaceutical ingredient, such as in a core or in a layer coated to surround the core; wherein an amount of active pharmaceutical ingredient is contained in either the core, or a layer coated to surround the core, or is contained in both. Another exemplary location is within a matrix used to form a compressed tablet, a capsule (e.g., a compressed capsule), a caplet, or another type of dosage form that contains a coated particle that contains active pharmaceutical ingredient. Gelling polymer may also be present, in the core, or in a layer surrounding the core, of a coated particle that does not include an active pharmaceutical ingredient.

The gelling polymer can be present in a dosage form at any desired amount and at any portion of, or location in a dosage form structure. The amount of gelling polymer can

be any useful amount, meaning an amount that can produce an abuse-deterrent viscous mixture or gel if the dosage form is crushed, ground, powdered, etc., and mixed with solvent. A useful amount of total gelling polymer in a dosage form may be in a range from 0.5 to 90 weight percent gelling polymer based on a total weight of the dosage form, e.g., from 0.7 to 20, or 2 to 15 weight percent gelling polymer based on total weight of the dosage form.

These amounts of total gelling polymer can be present in one or more locations of the dosage form, to achieve the specified total amount, such as in a portion at a coated particle (e.g., core), a matrix (e.g., compressed matrix) structure that supports and contains the coated particles, or in both the coated particles and the matrix.

A core (uncoated) of a core-shell particle can contain any useful amount of gelling polymer, such as from 0 up to and including 100 percent gelling polymer in a core of a core-shell particle, e.g., from 10 to 95 weight percent gelling polymer based on a total weight of the core, such as from 40 to 85 or 50 to 75 weight percent gelling polymer based on total weight core.

Described in terms of total weight of a dosage form, an amount of gelling polymer present in a core of a core shell polymer may be, e.g., in a range from 0.5 to 15 weight percent gelling polymer (present in the core) per total weight of the dosage form, such as from 1 to 10 weight percent gelling polymer (present in the core) per total weight dosage form. An amount of gelling polymer present in a matrix of a dosage form may be any desired amount, such as an amount in a range from 0.5 to 15 weight percent gelling polymer (as excipient in a matrix) based on a total weight of the dosage form, such as from 1 to 10 weight percent gelling polymer (present as excipient in a matrix) based on total weight dosage form.

A useful gelling polymer can be any polymeric material that exhibits the ability to retain a significant fraction of adsorbed solvent in its molecular structure, e.g., the solvent being a solvent otherwise useful by an abuser to extract API from a dosage form or a crushed or powdered dosage form, the solvent for example being water or a C_1 to C_4 alcohol such as ethanol or methanol, etc. Examples of gelling polymers include materials that can swell or expand to a very high degree when placed in contact with such a solvent. The swelling or expansion may cause the gelling polymer to experience from a two- to one-thousand-fold volume increase from a dry state. More specific examples of gelling polymers include swellable polymers sometimes referred to as osmopolymers or

hydrogels. The gelling polymer may be non-cross-linked, lightly crosslinked, or highly crosslinked. The crosslinking may involve covalent or ionic bonds with the polymer possessing the ability to swell in the presence of a solvent, and when cross-linked will not dissolve in the solvent.

A gelling polymer, upon dissolution or dispersion in an aqueous solution or dispersion (e.g., water) at a concentration of 2% w/w (based on the dry material), creates a solution/dispersion with a viscosity of from about 100 to about 200,000 mPa·s (e.g., 4,000 to 175,000 mPa·s, and 4,000 to 50,000 mPa·s) as measured at 20 degrees Celsius (+/- 0.2 degree Celsius) using the analysis method described in the USP 33 monograph for hypromellose (incorporated herein by reference).

Generally suitable gelling polymers include pharmaceutically acceptable polymers that undergo an increase in viscosity upon contact with a solvent, as described. Various examples of polymers are known to be useful in this manner, generally including natural and synthetic starches (i.e., modified or pregelatinized modified starch), natural and synthetic celluloses, acrylates, and polyalkylene oxides. Examples of natural starches include natural starches include corn starch, potato starch, rice starch, tapioca starch and wheat starch, hydroxypropyl starch such as hydroxypropyl corn starch, hydroxypropyl pea starch and hydropropyl potato starch (derivative of natural starch) . Examples of synthetic starches, i.e., modified or pregelatinized modified starch, include acetylated distarch adipate, waxy maize basis, acid-treated maize starch, acid-treated waxy maize starch, distarch phosphate, waxy maize basis, oxidized waxy maize starch, and sodium octenyl succinate starch. Examples of celluloses include carboxymethylcellulose calcium, carboxymethylcellulose sodium, ethycellulose, methylcellulose, cellulose ethers such as hydroxypropyl cellulose, hydroxyethylcellulose, hydroxyethylmethyl cellulose, hydroxypropyl methyl cellulose, carboxymethylcellulose sodium, and low substituted hydroxypropyl cellulose. Examples of acrylates include Eudragit RS, RL, NE, NM. Examples of polyalkylene oxides include polyethylene oxide such as POLYOX N10, N80, N60K, WSR-1105 LEO, or WSR-301 LEO, or WSR-303 LEO.

Accordingly, examples of suitable gelling polymers include polyethylene oxide, polyvinyl alcohol, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, methyl cellulose, hydroxyethylmethylcellulose, sodium carboxymethylcellulose, hydroxyethylcellulose, polyacrylic acid and polyvinyl carboxy polymers such as those commercially available under the trade name Carbopol®, and other high molecular weight

polymers capable of attaining a viscosity level effective to prevent uptake in a syringe, if combined with a small volume of solvent as described.

Other examples of suitable gelling polymers can include, if of sufficiently high molecular weight: ethylcellulose, cellulose acetate, cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate and cellulose triacetate, cellulose ether, cellulose ester, cellulose ester ether, cellulose; acrylic resins comprising copolymers synthesized from acrylic and methacrylic acid esters, for example acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamide copolymer, poly(methyl methacrylate), polymethacrylate, poly(methyl methacrylate) copolymer, polyacrylamide, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers.

Exemplary gelling polymers can include natural polymers such as those derived from a plant or animal, as well as polymers prepared synthetically. Examples include polyhydroalkylcellulose having a molecular weight greater than 50,000; poly(hydroxy-alkylmethacrylate) having a molecular weight of from 5,000 to 5,000,000; poly(vinyl-pyrrolidone) having a molecular weight of from 100,000 to 3,000,000; anionic and cationic hydrogels; poly(electrolyte) complexes; poly(vinyl alcohol) having a low acetate residual; a swellable mixture of agar and carboxymethyl cellulose; a swellable composition comprising methyl cellulose mixed with a sparingly cross-linked agar; a polyether having a molecular weight of from 10,000 to 6,000,000; water-swellable copolymer produced by a dispersion of finely divided copolymer of maleic anhydride with styrene, ethylene, propylene, or isobutylene; water swellable polymer of N-vinyl lactams; and the like.

Other polymers useful as a gelling polymer include pectin having a molecular weight ranging from 30,000 to 300,000; polysaccharides such as agar, acacia, karaya, tragacanth, algins and guar; polyacrylamides; water-swellable indene maleic anhydride polymers; Good-rite® polyacrylic acid having a molecular weight of 80,000 to 200,000; Polyox® polyethylene oxide polymers having a molecular weight of 100,000 to 7,000,000; starch graft copolymers; Aqua-Keep® acrylate polymers with water absorbability of 400 times its original weight; diesters of polyglucan; a mixture of cross-linked polyvinyl alcohol and poly(-vinyl-2-pyrrolidone); poly(ethylene glycol) having a molecular weight of 4,000 to 100,000.

In various specific embodiments, a gelling polymer may be, or may include, hydroxypropyl methyl cellulose (e.g., Hypromellose or HPMC), and hydroxy methyl cellulose, methyl cellulose, hydroxyethylmethyl cellulose, and sodium carboxymethyl cellulose. The hydroxypropyl methyl cellulose can have a molecular weight ranging from 10,000 to 1,500,000. Examples of suitable, commercially available hydroxypropyl methylcellulose polymers include HPMC K100M, Methocel K100LV and Methocel K4M.

A specific class of gelling polymer is the class of carbomer polymers, which are polymers derived from acrylic acid (e.g., acrylic acid homopolymers) and crosslinked with polyalcohol allyl ethers, e.g., crosslinked with polyalkenyl ethers of pentaerythritol or sucrose. Carbomer polymers are hydrophilic and are not substantially soluble in water. Rather, these polymers swell when dispersed in water forming a colloidal, mucilage-like dispersion. Carboxyl groups provided by acrylic acid residues of the polymer backbone are responsible for certain behavior of the polymers. Particles of this polymer can be viewed as a network structure of polymer chains interconnected by crosslinks. The structure can swell in water by up to one thousand times of an original (dry) volume (and ten times an original diameter of polymer particles) to form a gel when exposed to a pH environment above 4-6. The pKa of these polymers can be 6 ± 0.5. Accordingly, carboxylate groups pendant from the polymer backbone can ionize at a pH above 6, producing a repulsion between the negatively-charged particles, which adds to the swelling of the polymer if exposed to solvent at this pH range. For this reason, a dosage form as described herein can preferably include a pH adjuster in an amount and location within the dosage form to raise the pH of a carbomer polymer to at least 6, to substantially neutralize the carboxylate groups. A suitable amount of a pH adjuster may be from about 1 to about 10 millimoles, or from about 5 to about 9 millimoles, or from about 6 to about 8 millimoles, or from about 7 to about 7.5 millimoles of the pH adjuster per gram of the carbomer polymer that is present in the dosage form. Typically, the pH adjuster is present in a dosage form according to the invention in an amount that is from about 1 to about 5 percent by weight, or from about 2 to about 4 percent by weight, or about 3 to 4 percent by weight based on the total weight of the dosage form.

Carbomer polymers are often referred to in the art using alternative terminology such as, for example, carbomer homopolymer, acrylic acid polymers, carbomera, Carbopol, carboxy polymethylene, carboxyvinyl polymer, Pemulen, polyacrylic acid, and

poly(acrylic acid), The USP–NF lists three umbrella monographs i.e. for "carbomer copolymer," for "carbomer homopolymer," and for "carbomer interpolymer."

Certain carbopol (carbomer) polymers that may be useful as a gelling polymer can have an average equivalent weight of 76 per carboxyl group. Examples of suitable commercially available carbomers include Carbopol® 934, 934P NF, Carbopol® 974P NF and Carbopol® 971P NF, Carbopol® 940, and Carbopol® 941, Carbopol® 71G, commercially available from Lubrizol. Examples of such polymers are described in U.S. Pat. Nos. 2,798,053 and 2,909,462, the entireties of which are incorporated herein by reference. Theoretical molecular weight ranges of Carbopol® products are in a range from 700,000 to 3 billion, theoretical estimation. For dosage forms as described herein, a gelling polymer (e.g., Carbopol®) can have a molecular weight and viscosity-increasing performance that will reduce or substantially inhibit an ability of an abuser to extract API from a combination of dosage form and a small volume of solvent, as described, while also being capable of being processed into a compressed dosage form.

A gelling polymer can also be characterized by viscosity of a solution prepared from the gelling polymer. Product information for commercially available Carbopol® polymers reports that viscosities of different Carbopol® polymers are as follows:

Type of Carbomer	Viscosity specified (cP)
Carbomer Homopolymer Type A (compendial name for Carbopol 71G, Carbopol 971P and Carbopol 981)	4,000 – 11,000
Carbomer Homopolymer Type B (compendial name for Carbopol 934P, and Carbopol 934)	25,000 – 45,000
Carbomer Homopolymer Type C (compendial name for Carbopol 980)	40,000 – 60,000

(Type A and Type B viscosities measured using a Brookfield RVT, 20rpm, neutralized to pH 7.3-7.8, 0.5 weight percent mucilage, spindle #5.)

Another example of a type of preferred gelling polymer is the class of xanthan gum polymers, which includes natural polymers useful as hydrocolloids, and derived from fermentation of a carbohydrate. A molecular weight of a Xanthan gum may be approximately 1,000,000. Xanthan gum has been shown to provide particularly useful extraction resistance in a dosage form as described, and therefore may be preferred in

dosage forms as described, especially if present in an amount of at least 2 or 3 weight percent based on a total weight of a dosage form.

Without limiting the scope of useful gelling polymers to any specific type or molecular weight, examples of useful gelling polymers, and useful respective molecular weights, are shown at Table below.

Gelling Polymer	Weight Average Molecular Weight
Carbomer	700,000 to 3 billion (estimated)
HPMC 2910 K types	164,000 - 1,200,000
HPMC 2910 E types	20,000 - 746,000
hydroxyethylcellulose	90,000 - 1,300,000
ethylcellulose	75,000 - 215,000
carboxymethylcellulose	49,000 - 725,000
sodium carboxymethylcellulose	49,000 - 725,000
povidone	4,000 - 1,300,000
copovidone	47,000
hydroxypropyl cellulose	40,000 - 1,150,000
xanthan gum	1,000,000
polyethylene oxide	Average molecular wt: 100,000 – 7,000,000

The dosage form may optionally include another abuse deterrent in the form of a wax, such as a wax/fat material as described in Applicant's co-pending United States patent application 2008/0311205, the entirety of which is incorporated herein by reference. The wax can be a solid wax material that is present in the dosage form at a location that inhibits an abuser from crushing, grinding, or otherwise forming the dosage form into a ground powder that might be abused by a nasal insufflation mode, or from which active pharmaceutical agent can be easily accessed and removed such as by dissolution or extraction using a solvent.

The wax may be present in the dosage form at a location and in an amount to also not interfere with desired uptake of the active pharmaceutical ingredient by a patient upon oral ingestion, in an immediate release dosage form. An exemplary location is at a core of a core-shell particle, especially a core that also contains gelling polymer and that either may or may not contain active pharmaceutical ingredient. Wax located at a core of a

particle (e.g., a core-shell particle) that also includes active pharmaceutical ingredient (e.g., at a layer covering the core, or within the core) will become mixed with the active pharmaceutical ingredient upon crushing or grinding, etc., of the particle. As discussed previously, the dosage form may also include core shell particles that do not contain an API. Wax that is located at a core of such a particle (*e.g.*, a core-shell particle) that does not contain API will also become mixed with the API (e.g., API present in API-containing core shell particles that are also present in the dosage form) upon crushing, grinding, etc., of the dosage form. When the wax is mixed with the active pharmaceutical ingredient, the active ingredient is inhibited or prevented from becoming thereafter dissolved in a solvent such as water, or otherwise efficiently accessed by an abuser.

A core (uncoated) of a core-shell particle can contain any useful amount of wax, up to and including 100 percent wax, e.g., from 0.1 to 85 weight percent wax based on a total weight of the core, such as from 15 to 60 or 25 to 50 weight percent wax based on total weight core. More generally, a useful amount of wax in a dosage form (e.g., with the wax located in the coated particle, e.g., in the core) may be in a range from 0.05 to 15 weight percent wax based on total weight of a dosage form, e.g., from 0.1 to 10 or from 2 to 5 weight percent wax based on total weight of the dosage form.

The wax may be a wax (e.g., fat) material that is generally hydrophobic and that may be either solid or liquid at room temperature, preferably solid at room temperature (25 degrees Celsius). Generally useful fats include those hydrophobic materials that are fatty acid-based compounds generally having a hydrophilic/lipophilic balance (HLB) of 6 or less, more preferably 4 or less, and most preferably 2 or less. A fat can have any melting temperature, with preferred fats being solid at room temperature and having a melting point that is at least 30 degrees Celsius, e.g., at least 40 degrees Celsius, e.g., at least 50 degrees Celsius. Useful fats include fatty acids and fatty esters that may be substituted or unsubstituted, saturated or unsaturated, and that have a chain length of at least 10, 12, or 14 carbons. The esters may include a fatty acid group bound to any of an alcohol, glycol, or glycerol. With regard to glycercols, for example, mono-, di-, and tri-fatty substituted glycerols can be useful as well as mixtures thereof.

Suitable wax ingredients include fatty acid esters, glycerol fatty acid esters, fatty glyceride derivatives, waxes, and fatty alcohols such as, for example, glycerol behenate (a.k.a. glyceryl behenate, glycerin behenate, glycerol docosanoate) (e.g., COMPRITOL®), glycerol palmitostearate (PRECIROL®), glycerol monostearate, stearoyl macroglycerides

(GELUCIRE® 50/13). Other waxes more generally include insect and animal waxes, vegetable waxes, mineral waxes, petroleum waxes, and synthetic waxes; particularly examples include beeswax, carnauba wax, condelilla wax, montan wax, ouricury wax, rice-bran wax, jojoba wax, microcrystalline wax, cetyl ester wax, cetyl alcohol, anionic emulsifying wax, nonionic emulsifying wax and paraffin wax.

The dosage form may optionally include another abuse deterrent in the form of a filler or binder material provided in a manner to compromising abuse practices wherein an abuser crushes, grinds, or otherwise forms the dosage form into a ground powder that might be abused by a nasal insufflation mode, or from which active pharmaceutical agent can be easily accessed and removed such as by dissolution or extraction using a solvent.

The binder or filler may be present in the dosage form at a location and in an amount to also not interfere with desired uptake of the active pharmaceutical ingredient by a patient upon oral ingestion, in an immediate release dosage form. An exemplary location is at a core of a core-shell particle. Suitable filler or binder located at a core of a particle (e.g., a core-shell particle) that also includes active pharmaceutical ingredient (e.g., at a layer covering the core, or within the core) will become mixed with the active pharmaceutical ingredient upon crushing or grinding, etc., of the particle. As discussed previously, the dosage form may also include core shell particles that do not contain an API. Filler or Binder that is located at a core of such a particle (*e.g.*, a core-shell particle) that does not contain API will also become mixed with the API (e.g., API present in API-containing core shell particles that are also present in the dosage form) upon crushing, grinding, etc., of the dosage form. When a filler or binder is mixed with the active pharmaceutical ingredient, the active pharmaceutical ingredient is inhibited or prevented from becoming thereafter dissolved in a solvent such as water or otherwise efficiently accessed by an abuser.

When present within a core or particle of a dosage form, e.g., at a core of a core-shell particle, filler or binder may be present in any useful amount, such as from 0 up to and including 100 percent filler or binder (singly or in combination) in a core of a core-shell particle, e.g., from 10 to 95 weight percent filler or binder (singly or in combination) based on total weight of the core, such as from 40 to 85 or 50 to 75 weight percent based on total weight core. Examples of cores that contain high levels of filler include spherical particles that contain 100 percent sugar, and spherical particles that contain 100 percent microcrystalline cellulose. Inert spherical filler products such as these, having useful

particle sizes, are commercially available under the trade name Celphere®, and under the trade name Suglets® (sugar spheres, also containing starch), including as follows: CELPHERE SCP-100 (Particle size (μm) 75-212); CELPHERE SCP-102 (Particle size (μm) 106-212); CELPHERE SCP-203 (Particle size (μm) 150-300); CELPHERE SCP-305 (Particle size (μm) 300-500); CELPHERE SCP-507 (Particle size (μm) 500-710); CELPHERE SCP-708 (Particle size (μm) 710-850). The particle sizes of these can be considered to be useful for any core as described herein, prepared of any single filler, gelling polymer, binder, any combination thereof, or any single or combination of materials combined with API.

Another optional abuse deterrent feature that can be included in a dosage form as described is a film layer or coating as part of a core-shell particle that is located over and surrounds an API. The film layer may also be present as a layer or coating on core shell particles which do not contain an API or an API layer. The film layer can be any film layer capable of being applied as a film layer to core-shell particles, to surround API, or to core-shell particles that do not contain an API or an API layer.

The film layer may be prepared from, and will include any pharmaceutically acceptable film forming polymer material, such as one or more of a binder (e.g. as described herein, such as hydroxypropyl cellulose, poly(methyl methacrylates), ethyl cellulose, hydroxypropyl methyl cellulose, hydroxyl methyl cellulose, polyvinyl alcohol, and the like), a solvent-resistant layer, and a pH-sensitive layer (also sometimes referred to as a reverse enteric material or layer), e.g., Eudragit® E 100. The film layer may include any one of these materials alone (e.g., a film layer may include 100 percent of a single one of these types of materials), or a film layer may include a combination of two or more of these types of materials.

A solvent-resistant layer is a film layer that retards or prevent release of a drug in a solvent (e.g., one or more of water, ethanol, and methanol) while still allowing the drug to release normally in a gastrointestinal tract when ingested as an immediate release oral dosage form. This type of abuse deterrent feature, e.g., solvent-resistant film, can inhibit access to an API of a dosage form by preventing or impeding an abuser from dissolving an intact or powdered dosage form in a solvent type that is often used by an abuser (e.g., water, ethanol, methanol). At the same time, the solvent-resistant film can dissolve in a human gastrointestinal tract with sufficient rapidity to allow for an immediate release profile. As an abuse deterrent feature this type of solvent-resistant film covers and

encloses API of a core-shell particle and acts as a film barrier or retardant to prevent or retard access to the API by use of solvent.

A solvent-resistant film is one that does not readily or immediately dissolve in a small volume of a solvent of the type often used by an abuser to dissolve an API, such as any one of water or a C_1-C_4 alcohol such as ethanol or methanol. A "small volume" refers to an amount of such a solvent that can contain an amount of dissolved API that is sufficiently concentrated to be useful to an abuser to realize the intended biological effect of the drug abuse, and that is also capable of being administered for abuse of the API, e.g., a volume that can contain an amount (concentration) of API that is effective to achieve a desired "high" if administered by injection or nasal insufflation, the volume also being sufficiently small to allow the volume to be administered by injection or nasal insufflation. For a dosage form to be useful for abuse as such, an API in the dosage form must be capable of being accessed and dissolved at sufficient concentration by an abuser without undue complication, into a "small volume" of solvent, which is a volume that can be administered by injection or by nasal insufflation. Generally, a "small volume" of solvent means 50 milliliters or less, or 20 milliliters or less, or 10 milliliters or less, or 5 milliliters or less (volumes which could be injected or used for nasal insufflation).

A solvent-resistant film layer can be a film placed on a core-shell particle that is difficult to dissolve in a "small volume" of water or a C_1-C_4 alcohol such as ethanol or methanol, e.g., that does not immediately dissolve in one or more of water or any one of a C_1-C_4 alcohol such as methanol or ethanol. The solvent-resistant film thereby retards or prevents an abuser from accessing an API portion of a core-shell particle if the core-shell particle is placed in one of these solvents. The solvent-resistant film need not be completely or substantially insoluble in any one of these solvents, or in all of the solvents, and it must be capable of allowing the API to be accessed with sufficient rapidity, in a gastrointestinal tract, for the dosage form to be useful as an immediate release dosage form.

A particular example of a solvent-resistant film is a film that exhibits solubility properties that depend on the pH of a solvent. An example of a solvent-resistant film may be a film that is substantially or completely insoluble at a pH that is greater than a pH condition of a human stomach, and that is sufficiently soluble at a pH condition of a stomach (and gastrointestinal tract) to allow the film to dissolve and release API with sufficient rapidity that the dosage form can be useful as an immediate release oral dosage

form. A pH-sensitive layer is a type of solvent-resistant film, and can be disposed in a dosage form to surround an active pharmaceutical ingredient and inhibit or prevent access to and dissolution of the active pharmaceutical ingredient in a solvent outside of a stomach (e.g., at a neutral pH environment), while still allowing the active pharmaceutical ingredient to be efficiently released from an immediate release dosage form at a lower pH environment of a user's stomach. This type of abuse deterrent feature can prevent or significantly impede an abuser's access to an active pharmaceutical agent of a dosage form (e.g., at the core of a core-shell particle or in a layer disposed on the core, or in both the core and the layer disposed on the core) by use of a solvent that is outside of a stomach and that does not have a relatively acidic pH, such as water or a C_1-C_4 alcohol such as ethanol, methanol, etc., or a mixture thereof, having a pH that is higher than a pH found in a human stomach, for example a pH greater than 4; greater than 5; or greater than 5.5; or greater than 6.

A pH-sensitive layer may be useful as a solvent-resistant film, placed in a dosage form as a layer of a core-shell particle to surround, cover, or enclose a portion of the core-shell particle that contains active pharmaceutical ingredient. For example in a core-shell particle, an active pharmaceutical ingredient may be located as desired at a core or at a layer outside of an uncoated or coated core; a solvent-resistant film in the form of a pH-sensitive layer may be disposed as a separate layer surrounding or covering the portion of the core-shell particle that contains the active pharmaceutical ingredient. The pH-sensitive layer may be in direct contact with (adjacent to) a core or a layer that includes active pharmaceutical ingredient; alternately a core-shell particle may include one or more intermediate layers between a pH-sensitive layer and a core or layer that includes active pharmaceutical ingredient. In addition, a pH-sensitive layer may be included in the dosage form as a layer of a core-shell particle that does not contain either an API layer or any API.

A useful pH-sensitive layer may include a polymer or other material that can be placed as a layer of a particle as described herein, such as to cover a more inner layer or core that contains active pharmaceutical ingredient, to form a pH-sensitive film surrounding or covering active pharmaceutical ingredient. The pH-sensitive film can be solubilized by exposure to a liquid that exhibits a pH that may be present in a stomach of a user of the dosage form, such as a pH below 6 or below 5.5. To function as an abuse deterrent feature, i.e., to inhibit or prevent efficient access to the active pharmaceutical

ingredient by exposing the dosage form (optionally ground or powdered) to an easily-available solvent, the pH-sensitive layer can contain polymer that is not easily or substantially soluble at a pH that is higher than a pH found in a human stomach, e.g., a pH greater than 6; by being insoluble at a pH greater than 6, the pH-sensitive polymer will not dissolve in many solvents easily available and commonly used by an abuser to extract a water-soluble drug from a dosage form such as water, ethanol, methanol, etc.

Examples of pH-sensitive polymer useful in a pH-sensitive layer include the class of reverse enteric polymers that contain cationic-functional groups and that exhibit pH-dependent solubility as described herein. Examples include polymers that contain basic functional groups such as amino groups, and that exhibit solubility at pH conditions found in a (human) stomach but not at relatively higher pH conditions, e.g., not above a pH of 4, 5, or 5.5, or not above a pH of 6. More specific examples of such pH-sensitive polymers include copolymers of dimethyl aminoethyl methacrylates, and neutral methacrylic acid esters; e.g., dimethyl aminoethyl methacrylate, butyl methacrylates, and methyl methacrylates, such as at a ratio of 2:1:1. Examples of such polymers are commercially available under the trade name Eudragit® E-100, Eudragit® E PO, Eudragit® E 12,5, and similar amino-functional pH-sensitive polymers. A preferred pH-sensitive polymer is the polymer Eudragit E100, but any polymer that is sufficiently hydrophilic at a low pH and hydrophobic at a higher pH to exhibit pH-dependent solubility as described, may also be effective if otherwise acceptable for use in a pharmaceutical dosage form, for example as a non-toxic ingredient of an oral dosage form. Reverse enteric compositions are also described in EP 1694724 B1, titled "pH Sensitive Polymer and Process for Preparation Thereof."

When present as a coating of a particle that contains active pharmaceutical ingredient, a solvent-resistant film layer may be present at any amount useful as an abuse deterrent feature, such as in a range from 0.1 to 90 weight percent of a total weight of a core-shell particle, e.g., from 3 to 50 or 4 to 40 weight percent solvent-resistant polymer per total weight core-shell particle. More generally, a useful amount solvent-resistant film layer or polymer in a dosage form may be in a range from 1 to 50 weight percent solvent-resistant film layer or polymer based on a total weight of a dosage form, e.g., from 2 to 30 or from 3 to 15 weight percent solvent-resistant polymer based on total weight dosage form. Similarly, when present as a coating of a particle that does not contain an API, a solvent-resistant film layer may be present at any amount useful as an abuse deterrent

feature, for example in the same numerical ranges as are disclosed above for coating particles that contain API.

A dosage form as presently described can also preferably include a disintegrant, which functions to cause the dosage form to expand and break up during use, e.g., at conditions of a human stomach, to allow active pharmaceutical ingredient of the dosage form to be released in a manner to achieve an immediate release profile. Disintegrants are known ingredients of pharmaceutical dosage forms, with various examples being known and commercially available. Examples of disintegrants include compositions of or containing sodium starch glycolate, starch (e.g., maize starch, potato starch, rice starch, tapioca starch, wheat starch, corn starch and pregelatinized starch), croscarmellose sodium, crospovidone (crosslinked polyvinyl N-pyrrolidone or PVP) (polyplasdone XL-10), sodium starch glycolate (EXPLOTAB® or PRIMOJEL®), any combination of two or more of the foregoing, and other pharmaceutically acceptable materials formed into particles having a particle size, density, etc., to allow processing of the disintegrant into a useful immediate release dosage form.

The disintegrant can be present in an immediate release dosage form at any location that allows the disintegrant to function as desired, to expand within the intact dosage form, upon ingestion, to cause the ingested dosage form to break apart and allow for desired immediate release of active pharmaceutical ingredient from the dosage form, in a stomach. One useful location for a disintegrant can be as a component of an excipient used to contain core-shell particles that contain active pharmaceutical ingredient, as described herein, in a dosage form such as a compressed tablet or capsule.

When included as an excipient of a dosage form, disintegrant may be present in an amount useful to achieve immediate release of an API of a dosage form. Examples of useful amounts of disintegrant in an immediate release dosage form as described herein may be in a range from 0.5 to 50 weight percent disintegrant based on a total weight of the dosage form, e.g., from 1 to 30 weight percent disintegrant based on total weight of the dosage form. The amount of disintegrant in a matrix of a dosage form can be consistent with these amounts, e.g., disintegrant can be included in a matrix (e.g., total of a dosage form that is other than the coated particles or API) of a dosage form in an amount in a range from 0.5 to 50 weight percent disintegrant based on a total weight of the matrix, e.g., from 1 to 30 weight percent disintegrant based on total weight matrix.

A dosage form as described can also include any of various known and conventional pharmaceutical excipients that may be useful to achieve desired processing and performance properties of an immediate release dosage form. These excipients include fillers, binders, lubricants, glidants, coloring agents, pH-adjusters, etc., and can be included in core-shell particles or in a matrix (e.g., compressed matrix) of a tablet or capsule. A more detailed description of pharmaceutical excipients that may also be included in the tablets of the present invention can be found in The Handbook of Pharmaceutical Excipients, 5th ed. (2006).

A pH-adjuster can be included in an immediate release dosage form as described, for example at a location to affect pH at a specific location of the dosage form that is only a portion of a total dosage form. As an example, a pH-adjuster in the form of a base may be included at a location of a gelling polymer that contains acid functionalities, to neutralize the acid functionalities. The amount of pH-adjuster included at the location of the gelling polymer can be an amount effective to neutralize the acid functionalities of the gelling polymer at that location. More specifically, a component of a dosage form as described that includes an acid-functional gelling polymer such as a carbopol may include a base in an amount and location to neutralize the acid functionalities of that polymer. The pH-adjuster can be located at a location effective to cause such neutralization, e.g., at the location of the dosage form that contains the acid-functional gelling polymer, for example at a core of a core-shell particle or as part of an excipient that includes acid-functional gelling polymer and that functions to bind particles together as a dosage form.

Examples of fillers that may be useful in an immediate release dosage form as described include lactose, starch, dextrose, sucrose, fructose, maltose, mannitol, sorbitol, kaolin, microcrystalline cellulose, powdered cellulose, calcium sulfate, calcium phosphate, dicalcium phosphate, lactitol or any combination of the foregoing. As compared to non-filler ingredients such as gelling polymers, a filler will have a molecular weight that does not result in a substantial viscosity increase or formation of a gel as described herein for a gelling polymer, if combined with a solvent such as water.

A filler may be present in any portion of a dosage form as described, including a core-shell particle; the filler may be present in a core, in a layer containing an active pharmaceutical ingredient that is disposed on the core, in a solvent resistant film, in the matrix, or in two or more of these portions of the dosage form. The filler may be present at any one or more of these portions of a dosage form in an amount to provide desired

processing or functional properties of a portion of the dosage form and of the entire dosage form. The amount of total filler in a dosage form can also be as desired to provide desired functionality, including an immediate release profile, for example in an amount in a range from 0 to 80 weight percent filler based upon the total weight of the dosage form, e.g. from 5 to 50 percent filler based on total weight dosage form.

Examples of binders that may be included in a dosage form as described include polymeric material such as alginic acid, sodium carboxymethylcellulose, microcrystalline cellulose, dextrin, ethylcellulose, gelatin, starch, pregelatinized starch, polyvinyl alcohol, polyethylene oxide, polyvinylpyrrolidone, polyacrylamides, polyvinyloxoazolidone, polyvinylalcohols, methylcellulose, hydroxypropyl cellulose, hydroxymethyl cellulose and any combination of two or more of these. A binder may be a water soluble material; as compared to non-binder ingredients such as a gelling polymer, a binder is of a molecular weight that does not result in formation of a gel or a highly viscous composition upon combining with a small volume of water. A binder can exhibit a relatively low molecular weight as compared to a gelling polymer, and a relatively lower viscosity (e.g., when measured in a 2% aqueous solution). Polymer useful as a binder may typically have a molecular weight of less than 50,000, e.g., less than 30,000, or less than 10,000.

A binder may be present in any portion of a dosage form as described, including a core or a film or coating of a core-shell particle, or as part of an excipient to contain or bind core-shells particles in a dosage form. Filler may be included in a core of a core-shell particle in combination with active pharmaceutical ingredient, gelling polymer or both; as part of an active pharmaceutical layer located over a core or another layer of a core-shell particle; as part of a solvent-resistant film; or within an excipient useful to bind particles into a dosage form. A binder may be present at any one or more of these portions of an immediate release dosage form as described, in an amount to provide desired processing or functional properties in each portion of the dosage form and of the overall dosage form. The amount of total binder in a dosage form can also be as desired to provide desired functionality, including immediate release functionality, for example in an amount in a range from 0.1 to 10 weight percent binder based on a total weight of a dosage form, e.g., from 0.5 to 7 weight percent binder based on total weight dosage form.

Examples of lubricants include inorganic materials such as talc (a hydrated magnesium silicate; polymers, such as, PEG 4000; fatty acids, such as stearic acid; fatty acid esters, such as glyceride esters (*e.g.*, glyceryl monostearate, glyceryl tribehenate, and

glyceryl dibehenate); sugar esters (e.g., sorbitan monostearate and sucrose monopalmitate); glyceryl dibehenate (Compritol® 888 ATO); and metal salts of fatty acids (e.g., magnesium stearate, calcium stearate, and zinc stearate). Accordingly, commonly used lubricants include talc, glyceryl monostearates, calcium stearate, magnesium stearate, stearic acid, glyceryl behenate, polyethylene glycol, poloxamer and combinations of the foregoing. Lubricant may be included in an immediate release dosage form as described, in any useful amount, such as an amount in a range from 0.1 to 10 weight percent lubricant based on a total weight of a dosage form, e.g., from 0.5 to 7 weight percent lubricant based on total weight dosage form.

Examples of glidants include colloidal silicon dioxide, untreated fumed silica (e.g., as available under the trade name Cab-O-Sil®), and crystalline or fused quartz. Glidant may be included in an immediate release dosage form as described, in any useful amount.

Examples of coloring agents include FD&C-type dyes and lakes, fruit and vegetable extracts, titanium dioxide, iron oxides and mixtures thereof. A coloring agent may be incorporated into a dosage form by blending the coloring agent any other ingredient. Alternately, coloring agent may be applied to an outer surface of a dosage form.

Any active pharmaceutical ingredient alone or in combination can be included in an immediate release dosage form as described herein. With abuse deterrent features as described herein, some being operative based on specific structural or compositional features of a core-shell particle, APIs that can be particularly useful can be those types of active pharmaceutical ingredients that can be subject to abuse, addiction, overdosing, or two or more of these; such APIs can be located in the dosage form at a location to cause the API to be subject to abuse deterrent features of the core-shell particle, e.g., at a core or inner layer of a core-shell particle.

Drugs commonly susceptible to abuse include sedative-hypnotics, stimulants (e.g., central nervous system ((CNS) stimulants), anxiolytics, antipsychotics, dissociative anesthetics, and narcotic analgesics including but not limited to drugs that can cause psychological or physical dependence on the drug. An API can include any therapeutically acceptable drug salt, drug derivative, drug analog, drug homologue, or polymorph of an active pharmaceutical ingredient.

Sedative hypnotics include, for example, barbiturates, for example phenobarbital, methobarbital, amobarbital, pentobarbital, and secobarbital and pharmaceutically

acceptable salts thereof; benzodiazepines, for example diazepam, chlorodiazepoxide, lorazepam, triazolam, temazepam, alprazolam and flurazepam and pharmaceutically acceptable salts thereof; phenothiazines, such as for example, alimemazine, chlorpromazine, thioridazine, and pharmaceutically acceptable salts thereof, and sleep medications, such as for example, zolpidem, zaleplon, and eszopiclone and pharmaceutically acceptable salts thereof. Anxiolytics include, for example, benzodiazepines, for example diazepam, chlordiazepoxide, estazolam, lorazepam, triazolam, alprazolam, clonazepam and flurazepam and pharmaceutically acceptable salts thereof. CNS Stimulants include, for example, amphetamines, such as for example, dextroamphetamine, levoamphetamine (benzadrine), methamphetamine (methadrine), pseudoephedrine, and Adderall (amphetamine mixed salts) and pharmaceutically acceptable salts thereof, and non-amphetamine psychostimulants such as methylphenidate, modafinil and armodafinil and pharmaceutically acceptable salts thereof. Narcotic analgesics include opioids such as, for example, buprenorphine, butorphanol, codeine, dihydrocodeine, dihydromorphine, hydrocodone, hydromorphone, morphine, oxycodone, oxymorphone, methadone, fentanyl, meperidine, tramadol, propoxyphene, and pharmaceutically acceptable salts thereof. Antipsychotic agents can include, for example, phenothiazines as listed above, butyrophenones, such as, for example, droperidol and haloperidol, dibenzoxazepines such as loxapine, and atypical antipsychotic agents such as aripiprazole, clozapine, olanzapine, quetiapine, risperidone ziprasidone, paliperidone and remoxipride.

Other specific drugs which may be susceptible to abuse include for example, muscle relaxants such as for example cyclobenzaprine and pharmaceutically acceptable salts thereof, cannabinols (*e.g.*, Δ^1-cannabidiol. Δ^2-cannabidiol, Δ^3-cannabidiol, $\Delta^{3,7}$-cannabidiol, Δ^4-cannabidiol, Δ^5-cannabidiol, and Δ^6-cannabidiol); cannabinoids, such as dronabinol, delta-9-tetrahydrocannabinol (THC), cannabidiol (CBD), nabilone, dexanabinol, ajulemic acid, cannabinor, rimonabant and taranabant, and pharmaceutically acceptable salts thereof; and dissociative anesthetic agents such as ketamine and Esketamine, and pharmaceutically acceptable salts thereof.

The amount of active pharmaceutical ingredient included in an immediate release dosage form can be any useful amount, as is known and as may be found in relevant literature such as Goodman & Gillman's, The Pharmacological Basis of Therapeutics, 9th ed. pages 219-222, 361-396, 521-535 1996. For example, typical therapeutic amounts of

oxycodone range 5 mg, 10 mg, or up to 400 mg, for the hydrochloride salt. Often, when processed into a suitable immediate release dosage form, the active pharmaceutical ingredient can be present in such dosage form in an amount normally prescribed, typically 0.5 to 25 percent on a dry weight basis, based on the total weight of the dosage form. With respect to narcotic analgesics such as opioids in a single unit dosage form, such as at a level from about 1 to about 500 mg, or from about 1 to about 250 mg, or from about 1 to about 100 mg; for example, 2.5, 5, 7.5, 10, 15, 20, or 30, milligram (mg) per dosage form unit. In other embodiments, a dosage form contains any appropriate amount of an API to provide a therapeutic effect.

The present invention is also directed to methods of treatment, comprising orally administering an effective amount of the herein described immediate release abuse deterrent dosage form. For example, provided herein is a method of treating or preventing pain or discomfort in a subject in need thereof by administering an effective amount of the herein described immediate release abuse deterrent dosage form containing an API that is a narcotic analgesic drug such as an opioid drug.

Also provided herein is a method for treating sleep disorders in a subject in need thereof by administering an effective amount of the herein described immediate release abuse deterrent dosage form containing an API that is a sedative hypnotic drug such as a barbiturate.

Also provided herein is a method for treating anxiety in a subject in need thereof by administering a an effective amount of the herein described immediate release abuse deterrent dosage form containing an API that is an anxiolytic drug such as a benzodiazepine.

Also provided herein is a method for treating psychoses in a subject in need thereof by administering an effective amount of the herein described immediate release abuse deterrent dosage form containing an API that is an antipsychotic drug such as quetiapine.

An "effective amount" of when used in connection with composition described herein is an amount sufficient to produce a therapeutic result in a subject in need thereof. For example a therapeutic result can include, but is not limited to treating or preventing pain, sleep disorders, anxiety or psychotic symptomology by a subject.

A dosage form as described can optionally include one or more additional APIs of a type that is not commonly susceptible to abuse. These additional APIs may be any suitable or desired API, such as those in the class of non-steroidal analgesic drugs. The

expression "non-steroidal analgesic drugs" as used herein refers to drugs that include those commonly referred to as non-steroidal anti-inflammatory drugs, or "NSAIDS," and acetaminophen, which is non-steroidal, but does not act via an inflammation mechanism. Accordingly, the term "non-steroidal analgesic drugs" would include acetaminophen, and also include NSAIDS such as aspirin, ibuprofen, and naproxen. The dosage form also exhibits immediate release properties with respect to these not-commonly-subject-to-abuse APIs. And these APIs can be present in the dosage form at any useful level, typically 0.5 to 25, e.g., 1 to 10 weight percent of the API on a dry weight basis, based on a total weight of the dosage form, e.g., at a level of or between 5, 25, 50, 75, 100, 125, 150, 175, 200, 300, 325, 500, 750 or up to or exceeding 1000 milligram (mg) per dosage form unit. In other embodiments, a dosage form contains an appropriate amount of an API to provide a therapeutic effect.

An immediate release dosage form as described can include one or more of the described abuse deterrent features, alone or in combination; e.g., one or more of: gelling polymer as part of a core-shell particle (e.g., at a core of the core-shell particle); wax as part of a core-shell particle (e.g., at a core of the core-shell particle); binder or filler as part of a core-shell particle (e.g., at a core of the core-shell particle); a film layer that may optionally be a solvent-resistant film (e.g., pH-sensitive film) as part of a core-shell layer; or gelling polymer as a component of an excipient or binder used to hold core-shell particles together as part of in an immediate release dosage form. With these abuse deterrent features, other types of known abuse deterrent features may not be necessary and may be specifically excluded from an immediate release dosage form as described. Certain embodiments of the described dosage forms can specifically exclude other types of abuse deterrents.

In specific, some dosage forms include nasal irritant to discourage or prevent abuse by nasal insufflation. The nasal irritant can be a mucous membrane irritant or nasal passageway irritant that, if inhaled through a nasal passageway when contained in a ground or powdered dosage form, can induce pain or irritation of the abuser's nasal passageway tissue. Examples include surfactants such as sodium lauryl sulfate, poloxamer, sorbitan monoesters, and glyceryl monooleates. Certain particular embodiments of dosage forms of the present description do not require, and can specifically exclude, nasal irritant agents such as those described above.

Alternately, dosage forms can include an emetic agent, to cause vomiting. Certain particular embodiments of dosage forms of the present description do not require and can specifically exclude an emetic agent.

Alternately, some dosage forms include an effervescent agent that acts as a deterrent to abuse by nasal insufflation. The effervescent includes an acidic component and a basic component that release a gas such as oxygen or carbon dioxide when combined in the presence of an aqueous media, such as upon nasal insufflation. See, e.g., patent publication WO 2013/077851, the entirety of which is incorporated herein by reference. The acid source may be, for example, citric acid, tartaric acid, malic acid, maleic acid, lactic acid, glycolic acid, ascorbic acid, fumaric acid, adipic acid, succinic acid, salts thereof, and combinations thereof. The base may be, for example, a carbonate or bicarbonate. Dosage forms of the present description do not require, and can specifically exclude, an effervescent agent in the form of an acid and a base that can combine to a gas such as oxygen or carbon dioxide.

Still other dosage forms include a biologically active chemical compound that functions as an antagonist to an active pharmaceutical ingredient. An antagonist may prevent the potential abuse of a dosage form in a manner, including the method of consuming multiple or several or more dosage form units at once. Antagonist agents are compounds that block or negate the effect of an active pharmaceutical ingredient, and are available and known for various classes of drugs including opioids and other pharmaceutical agents. Examples of antagonist agents for opioids include compounds such as naltrexone, naloxone, nalmefene, cyclazacine, levallorphan. Specific examples of antagonist agents and methods for preparing antagonist agents for incorporation into a dosage form are provided in U.S. Patent Nos. 7,682,633 and 7,658,939, which are incorporated herein by reference. According to the present description, an immediate release dosage form that includes an opioid and that includes one or more abuse deterrent feature as described herein (e.g., a gelling polymer, wax, solvent-resistant film, or a combination thereof), can be formulated to not contain and to specifically exclude an antagonist of an API that is also included in the dosage form, e.g., an opioid antagonist in a dosage form containing an opioid.

Referring to Figures 1A and 1B, a dosage form can include particles 10A that contain API. The particle (e.g., coated particle or "core-shell" particle) can include a core 12a (or "uncoated core"), which may be coated with one or more layers, films or coatings,

e.g., 14a, 16a, or any additional layer or coating that is coated over, underneath, or intermediate to these. In Figures 1B and 1C, the layer designated 16a may be an API containing layer, and the layer designated as 14a may be a solvent resistant, e.g., a pH sensitive film layer. Particle 10A can contain one or more of the ingredients described herein, such as any one or more of API (especially an API that is susceptible to abuse), a gelling polymer, optional wax, optional solvent-resistant layer, as well as one or more additional layer or layers under, over, or intermediate to these layers or between either layer and the core. Each layer can be present in size or amount (e.g., thickness) that will result in a useful immediate release dosage form having one or more of the presently described abuse deterrent features. Other optional components of a core or layer of particle 10a can be filler, binder, other excipient, or solvent (not more than a residual amount, if any) such as water or ethanol for use in preparing the coated particle, and that is substantially removed after formation of the core, coating, or coated particle. Examples of the core 10A can include any amount of the different ingredients of: a gelling polymer (e.g. from 0 to 100 percent of a core), filler as described herein such as sugar (mannitol) or microcrystalline cellulose (e.g., from 0 to 100 percent of a core), binder (e.g., from 0 to 100 percent of a core), and wax (e.g., from 0 to 100 percent of a core).

While core-shell particles 10a are believed to be new and inventive, certain method steps useful to prepare these novel coated particles may be known. Available methods include certain methods and processing steps known to be useful for preparing particles and coated particles in the pharmaceutical arts. A core-shell particle 10a can be prepared by an initial step of mixing ingredients of core 12a with a solvent such as water or ethanol and forming the mixture into a spherical core particle by known methods. The particle may be dried and separated by size, and then one or more coating in the form of a continuous film or layer can be applied to the core, optionally successively to produce multiple layers surrounding the core. General processing to produce a multi-layer coated particle can include a series of steps such as compounding, mixing, granulation, wet milling, coating (by any method such as fluidized bed coating, spray coating, etc.), and one or more drying steps such as by use of a fluidized bed or other drying method. Intermittently between core-forming and coating steps, e.g., after a drying step, coated or uncoated particles can be sorted or separated based on size to produce a composition or a collection of particles having a desired size range and distribution. Accordingly, the

coated granulate compositions according to the invention may be prepared by a process comprising:

(i) granulating a wax or a gelling polymer, or a mixture thereof, in the presence of a hydroalcoholic solution or suspension comprising a suitable binder, to form granules;

(ii) layering the granules formed in step (i) with a solution or suspension comprising an API; and

(iii) coating the layered granules formed in step (ii) with a solution or suspension comprising a film forming polymer material to form a coated layered granulate.

The process above may further comprise steps of milling and drying the granulate formed in step (i).

In instances wherein the core comprises a sugar sphere or a microcrystalline cellulose sphere, the steps of the process above would be modified as follows:

(i) providing a sugar sphere (or microcrystalline cellulose sphere);

(ii) layering the sugar sphere (or microcrystalline cellulose sphere) with a solution or suspension comprising an API; and

(iii) coating the layered sphere formed in step (ii) with a solution or suspension comprising a film forming polymer material to form a coated layered sphere.

Compressed tablets according to the invention may be prepared by a process comprising:

(i) combining the coated layered granulate (or the coated layered sphere) prepared according to either of the above processes with a second API (e.g., acetaminophen), a gelling polymer, and a disintegrant, and optionally, with at least one additional excipient selected from a filler, a colorant, and a pH adjusting agent, to form a first mixture and then blending the first mixture for a suitable time;

(ii) adding a lubricant to the blended mixture formed in step (i) to form a second mixture, and then blending the second mixture for a suitable time;

(iii) compressing the blended mixture formed in step (ii) to form compressed tablets.

A suitable time for the blending in step (i) may be, for example, from about 5 to about 90 minutes, or from about 10 to about 60 minutes, or from about 20 to about 40 minutes, or about 30 minutes. A suitable time for the blending in step (ii) may be, for

example, from about 1 to about 30 minutes, or from about 5 to about 20 minutes, or about 10 minutes.

In certain embodiments as shown at Figures 1A, 1B, and 1C, an immediate release dosage form as described can include a core-shell particle 10A that includes a core 12A that contains only a minor amount of API or that contains an insubstantial amount of API. Core 12A may contain less than 5 weight percent, e.g., less than 1 or less than 0.5 weight percent active pharmaceutical ingredient based on a total weight of the core of the core-shell particle. Alternatively, core 12A may contain less than 5 weight percent of a total amount of pharmaceutical ingredient in a core-shell polymer, e.g., less than 5, less than 1, or less than 0.5 weight percent active pharmaceutical ingredient based on total weight of API in the core-shell particle. In these embodiments a major portion of API can be contained outside of core 12A, e.g., in an API layer 16a, which can contain at least 50, at least 75, or at least 90, or at least 95 weight percent of a total amount of the API in a core-shell polymer.

Core 12A can include binder, gelling polymer (e.g., HPMC), wax, or filler, optionally alone or in combination, each in an amount to allow the materials of the core to function as one or more abuse deterrent features as described herein. See the examples included herewith for examples of useful amounts and ranges of amounts of these ingredients.

Referring to figure 1A, core 12A contains gelling polymer, wax, binder, or filler, or any combination of these, and no API (meaning not more than an insignificant amount, such as less than 0.5 or less than 0.1 weight percent based on the weight of core 12A). As shown at Figures 1B and 1C, core 12A, not containing API, can be coated with a coating layer that contains API, e.g., an active pharmaceutical layer or API layer 16A. As shown at Figure 1B, core-shell particle 10A includes core 12A, which does not contain any API, and API layer 16A, which contains an amount of API, such as a total amount of API (e.g., API commonly susceptible to abuse) to be contained in a dosage form prepared from particles 10A. API layer 16A can contain one or more ingredients as described herein useful to form API layer 16A as a layer over an outer surface of core 12A. (API in API layer 16A can be a type of API that is commonly susceptible to abuse, such as an opioid, and can account for all of or most of (e.g., at least 70, at least 80, at least 90, or at least 95 percent) the total amount of that type of API in the core-shell particles and in the dosage form; in this embodiment the core can contain less than 10, less than 5, or less than 1

percent of the total amount of API in the core-shell particles, and less than 10, 5, or 1 percent of the total amount of API in the dosage form.) Useful non-API ingredients in an API layer can include a binder along with the API. The API and binder can be carried in a solvent (e.g., water, ethanol, or both) and coated and dried to form a preferably continuous film layer on an outer surface of core 12A, i.e., API layer 16A. See the examples included herewith for examples of useful amounts and ranges of amounts of these ingredients.

A core-shell particle 10A can also optionally include a film layer, e.g., a solvent-resistant layer (e.g., a pH-sensitive layer) 14A as described herein.

In certain alternate embodiments a dosage form as described can include a core-shell particle 10B that includes a core 12B that does contain a useful amount of API, such as an amount of API useful in an immediate release dosage form having one or more abuse deterrent features as described herein, prepared to include particles 10B. See figures 2A and 2B. According to such embodiments, core 12B of particle 10B can contain a gelling polymer, optional wax, optional binder or filler, and an amount of API.

Referring to figure 2A, core 12B contains gelling polymer, optional wax, optional binder, and API. Referring to figure 2B, core 12B, containing API, can optionally be coated with solvent-resistant layer (e.g., a pH-sensitive layer) 14B as described herein for use in an immediate release dosage form. Core 12B may also optionally be coated with a coating layer that contains API, e.g., an active pharmaceutical layer or API layer prior to application of the solvent-resistant layer. Accordingly, API containing core-shell particles as described herein may contain API of a type that is susceptible to abuse:

- in an API layer surrounding the core and in a substantial amount in the core;
- in an API layer surrounding the core and in an insubstantial amount in the core;
- only in an API layer surrounding the core; or
- only in the core.

In certain alternate embodiments, a dosage form as described can include a core-shell particle 10B, as depicted in Figure 2B, that that does not contain an API layer, and does not contain any API. Referring to Figure 2C, such a particle 10B, containing no API, may include core 12B containing gelling polymer, optional wax, and optional binder, which core 12B may optionally be coated with solvent-resistant layer (e.g., a pH-sensitive layer) 14B as described herein for use in an immediate release dosage form.

A coated particle 10a or 10b that includes API, and optionally, a coated particle 10B that does not include API, can be included in any of a variety of dosage forms,

examples including a compressed tablet or compressed capsule, a suppository, capsule, caplet, pill, gel, soft gelatin capsule, etc. As one example, a dosage form 12 can be prepared as a compressed tablet or compressed capsule. Tablet or capsule 12 can contain core-shell particles 10 (e.g., 10A or 10B) distributed within a matrix 20, compressed to form the compressed tablet or capsule 12. Core-shell particles 10A or 10B can be as described herein, generally or specifically, and can contain an amount of API suited to provide a desired dosage upon ingestion of tablet or capsule 12; e.g., matrix 20 does not include any substantial amount of API.

Matrix 20 can include ingredients useful in combination with the core-shell particles 10A, 10B, to produce an immediate release dosage form. Examples of useful excipients of an immediate release dosage form can include ingredients that allow the dosage form to break up or disintegrate upon ingestion and facilitate exposure to fluid in a stomach, such as a useful amount of disintegrant. Examples of such excipients for such a dosage form can also include one or more ingredients that act as an abuse deterrent feature, such as a gelling polymer as described herein. Other excipients can be useful for processing to form a compressed dosage form, and also may allow the compressed dosage form to function as an immediate release dosage form, with one or more abuse deterrent features.

The following non-limiting examples show various dosage forms as described herein. The described and exemplified dosage forms can be made from methods that include granulating, coating, and compressing steps as follows.

General Procedure

Granulation

1. Glyceryl behenate and hypromellose K100M are dry mixed in a high shear granulator. Hydroalcoholic solution of ethylcellulose is added. Alternatively the granulation can be produced through top spraying the hydroalcoholic solution in a fluid bed granulator. Optionally, a portion of the ethyl cellulose, for example from about 10 to about 50% by weight, or from about 10 to about 40% by weight, or from about 15 to about 30 % by weight, is dry mixed with the Glyceryl behenate and hypromellose K100M prior to adding the hydroalcoholic solution containing the balance of the ethyl cellulose.

1. (alternative when API is included in the core) Glyceryl behenate and hypromellose K100M and API are dry mixed in a high shear granulator. Hydroalcoholic solution of ethylcellulose is added. Alternatively the granulation can be produced through top spraying the hydroalcoholic solution in a fluid bed granulator. Optionally, a portion of the ethyl cellulose, for example from about 10 to about 50% by weight, or from about 10 to about 40% by weight, or from about 15 to about 30 % by weight, is dry mixed with the Glyceryl behenate and hypromellose K100M prior to adding the hydroalcoholic solution containing the balance of the ethyl cellulose.
2. The granules are then wet milled using a size reduction mill (Granumill) and then dried using a fluid bed, and optionally screened.

Layering

3. The polymer granules are then layered using Wurster fluid bed layering process with API (or alternatively, granulated using high shear granulation or top spray fluid bed granulation process).
3. (alternative when the coated granule will not contain API) The layering step is omitted and the coating of Step 4 below is applied to the granulate prepared in Step 1.

Coating

4. The layered granules of Step 3(or alternatively, when the coated granule will not contain API, the granules prepared in Step 1)are then coated using a fluid bed coater equipped with a Wurster insert (bottom spray assembly) with ethanolic suspension of Eudragit E100 copolymer and magnesium stearate. Coated particles are then screened and blended.

Blending and tablet compression

The blending, compression and bottling process for hydrocodone and acetaminophen tablets manufactured using the coated intermediate is as follows:

1. The API-containing coated granules, APAP, crospovidone, Carbopol 71G, sodium bicarbonate, mannitol, optionally coated granules containing no API, and optionally a desired colorant, are then added to the blender and mixed.

2. Magnesium stearate (and optionally colorant) is then added to the blender and mixed. The blend is compressed into tablets using a rotary tablet press.

Example 1: Preparation of coated granules

Table 1: Components for granule formulation

Component	% w/w
hypromellose	60
glyceryl behenate	26
ethyl cellulose	14
TOTAL	100

Granules were manufactured in a high shear granulator, where hypromellose and glyceryl behenate were dry mixed for 3 minutes. Then, a 10% hydroalcoholic solution of ethylcellulose N10 was slowly added while maintaining the granulator impeller and chopper speed at pre-selected values that provide enough shear for granule formation and growth. Solution addition was continued until the entire amount of ethylcellulose was added. The granules were then wet milled using a size reduction mill (Granumill) and were subsequently loaded into fluid bed for drying.

Table 2: Components for layered granule formulation

Component	% w/w
hydrocodone bitartrate	10
polymer granules (EC, HPMC and Compritol)	85
Hypromellose 2910	5
TOTAL	100

The prepared granules were then layered in a bottom spray fluid bed coater with a 12% aqueous solution of hydrocodone bitartrate and HPMC 2910.

Table 3: Components for coated granules formulation

Component	% w/w
Hydrocodone bitartrate layered granules, 10%	50
Eudragit E-100	33
magnesium stearate	17
TOTAL	100

The hydrocodone bitartrate layered granules were then coated in a bottom spray fluid bed coater with 25 % alcoholic suspension of Eudragit E-100 copolymer and magnesium stearate. The resulting coated granules were subsequently used for further blending and compression process.

Example 2: Hydrocodone/acetaminophen tablets

Table 4: Hydrocodone/acetaminophen Tablet Formulation

Component	%	mg/tablet
Hydrocodone bitartrate coated granules, 5%	20.0	200
Paracetamol[1]	33.7	337
mannitol	10.3	103
carbopol	5.0	50
microcrystalline cellulose	12.0	120
crospovidone	15.0	150
sodium bicarbonate	3.0	30
magnesium stearate	1.0	10
Total	**100**	**1000**
[1] Contains 95% acetaminophen (APAP) and 5% gelatin		

The coated granules were prepared according to Example 1 above and mixed with paracetamol and other excipients (carbomer, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose) and blended in a V-blender for 30 minutes. Magnesium stearate was then added to lubricate the blend and the mixture was blended for an additional 5 minutes prior to compressing into hydrocodone/acetaminophen tablets.

Example 3: Hydrocodone Bitartrate/ Acetaminophen

Table 5: Hydrocodone/acetaminophen Granule Formulation

Core Shell composition		
Component	**Location**	**mg/tablet**
HPMC K100M	Core	51.1
compritol	Core	21.9
Ethocel	Core	12
hydrocodone bitartrate	API layer	10
HPMC 2910	API layer	5
Eudragit E-100	Film	66.7
magnesium stearate	Film	33.3
Total		200

Table 6: Hydrocodone/acetaminophen Tablet Formulation

Components	**mg/tablet**
Core Shell composition (above)	200
APAP	325
gelatin	12.1
mannitol	42.9
carbopol	50
microcrystalline cellulose	130
crospovidone	200
sodium bicarbonate	30
magnesium stearate	10
Total	1000

5

Table 7: Hydrocodone/acetaminophen Overall Tablet composition

Overall Tablet composition	
Components	**mg/tablet**
HPMC K100M	51.1
compritol	21.9
Ethocel	12
hydrocodone bitartrate	10
HPMC 2910	5
Eudragit E-100	66.7
APAP*	325
gelatin	12.1
mannitol	42.9
carbopol	50
microcrystalline cellulose	130
crospovidone	200
sodium bicarbonate	30
magnesium stearate	43.3
Total	**1000**
* acetaminophen (acetyl-para-aminophenol).	

Coated granules were prepared according to the procedure described in Example 1. The prepared coated granules were then mixed with acetaminophen and other excipients (carbopol, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose) and blended in a V-blender for 30 minutes. Magnesium stearate was then added to lubricate the blend and the mixture was blended for an additional 5 minutes prior to compressing into hydrocodone/acetaminophen tablets.

Example 4: Hydrocodone Bitartrate/ Acetaminophen

Table 8: Hydrocodone/acetaminophen granule composition

Core Shell composition		
Component	**Location**	**mg/tablet**
HPMC K100M	core	25.5
compritol	core	10.9
Ethocel	core	6
hydrocodone bitartrate	API layer	5
HPMC 2910	API layer	2.5
Eudragit E-100	film	33.4
magnesium stearate	film	16.7
Total		100

Table 9: Hydrocodone/acetaminophen tablets

Component	**mg/Tab**
Core Shell composition (above)	100
APAP	325
gelatin	12.14
mannitol	34.88
carbopol	50
microcrystalline cellulose	96
crospovidone	144
sodium bicarbonate	30
magnesium stearate	8
Total	800.02

Coated granules were prepared according to the procedure described in Example 1. The prepared coated granules were then mixed with acetaminophen and other excipients (carbopol, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose) and blended in a V-blender for 30 minutes. Magnesium stearate was then added to lubricate the blend and the mixture was blended for an additional 5 minutes prior to compressing into hydrocodone/acetaminophen tablets.

Table 10: Hydrocodone/acetaminophen tablet composition

Overall Tablet composition	
Components	**mg/tablet**
HPMC K100M	25.5
compritol	10.9
ethocel	6
hydrocodone bitartrate	5
HPMC 2910	2.5
Eudragit E-100	33.4
APAP	325
gelatin	12.14
mannitol	34.88
carbopol	50
microcrystalline cellulose	96
crospovidone	144
sodium bicarbonate	30
magnesium stearate	24.7
Total	800.02

Example 5: Hydrocodone Bitartrate/ Acetaminophen

Table 11: Hydrocodone/acetaminophen granule composition

Core Shell composition		
Component	**Location**	**mg/tablet**
HPMC K100M	core	50.1
compritol	core	21.5
ethocel	core	11.8
hydrocodone bitartrate	API layer	9.8
HPMC 2910	API layer	4.9
Eudragit E-100	film	65.4
magnesium stearate	film	32.7
Total		196.2

Table 12: Hydrocodone/acetaminophen tablet composition

Component	**mg/TAB**
Core Shell composition (above)	196.1
APAP	325
gelatin	12.14
mannitol	46.2
carbopol	50
microcrystalline cellulose	130
crospovidone	200
red iron oxide	0.6
sodium bicarbonate	30
magnesium stearate	10
Total	1000

Coated granules were prepared according to the procedure described in Example 1. The prepared coated granules were then mixed with acetaminophen and other excipients (carbopol, crospovidone, sodium bicarbonate, mannitol, red iron oxide, microcrystalline cellulose) and blended in a V-blender for 30 minutes. Magnesium stearate was then added

to lubricate the blend and the mixture was blended for an additional 5 minutes prior to compressing into hydrocodone/acetaminophen tablets.

Table 13: Hydrocodone/acetaminophen tablet composition

Overall Tablet composition	
Components	mg/tablet
HPMC K100M	50.1
compritol	21.5
ethocel	11.8
hydrocodone bitartrate	9.8
HPMC 2910	4.9
Eudragit E-100	65.4
APAP	325
gelatin	12.14
mannitol	46.2
carbopol	50
microcrystalline cellulose	130
crospovidone	200
red iron oxide	0.6
sodium bicarbonate	30
magnesium stearate	42.7
Total	1000.14

Example 6: Oxycodone hydrochloride (single API) (Celphere core)

Table 14: Oxycodone granule composition

Core Shell composition		
Components	**Location**	**mg/tablets**
Celphere (MCC)	core	42
oxycodone hydrochloride	API layer	5.2
HPMC 2910	API layer	1.7
Eudragit E-100	film	1.9
magnesium stearate	film	0.6
Total		51.4

Microcrystalline cellulose particles were layered in a bottom spray fluid bed coater with a 12% aqueous solution of oxycodone hydrochloride and HPMC 2910.
The oxycodone hydrochloride layered particles were then coated in a bottom spray fluid bed coater with 25 % alcoholic suspension of Eudragit E-100 copolymer and magnesium stearate. The resulting coated particles were subsequently used for further blending and compression process.

Table 15: Oxycodone tablet composition

Component	**mg/TAB**
Core Shell composition (above)	51.54
lactose	96.46
microcrystalline cellulose	40
crospovidone	10
magnesium stearate	2
Total	200

The coated particles were mixed with other excipients (crospovidone and lactose) and blended in a V-blender for 30 minutes. Magnesium stearate was then added to lubricate the blend and the mixture was blended for an additional 5 minutes prior to compressing into oxycodone tablets.

Table 16: Oxycodone hydrochloride tablet composition

Overall Tablet composition	
Components	mg/tablet
microcrystalline cellulose	82
oxycodone hydrochloride	5.2
HPMC 2910	1.7
Eudragit E-100	1.9
lactose	96.46
crospovidone	10
magnesium stearate	2.6
Total	199.86

Example 7: Hydrocodone Bitartrate/ Acetaminophen (sugar sphere core)

Table 17: Hydrocodone bitartrate granule composition

Core Shell composition		
Component	Location	mg/tablet
sugar sphere	core	47.3
PEO	core	24.7
EPO	core	20.5
hydrocodone bitartrate	API layer	5
HPMC 2910	API layer	2.5
Eudragit E-100	film	75
magnesium stearate	film	25
Total		200

Sugar sphere particles were layered in a bottom spray fluid bed coater with an aqueous solution of hydrocodone bitartrate and HPMC 2910.

The hydrocodone bitartrate layered particles were then coated in a bottom spray fluid bed coater with 25 % alcoholic suspension of Eudragit E-100 copolymer and magnesium stearate. The resulting coated particles were subsequently used for further blending and compression process.

Table 18: Hydrocodone bitartrate tablet composition

Core Shell composition (above)	**mg/tablet**
	200
APAP	325
binder	17.8
mannitol	192.2
microcrystalline cellulose	200
crospovidone	50
magnesium stearate	15
Total	1000

The coated spheres were mixed with acetaminophen and other excipients (mannitol, microcrystalline cellulose, binder and crospovidone) and blended in a V-blender for 30 minutes. Magnesium stearate was then added to lubricate the blend and the mixture was blended for an additional 5 minutes prior to compressing into oxycodone tablets.

Table 19: Hydrocodone bitartrate tablet composition

Overall Tablet composition	
Components	**mg/tablet**
sugar	47.3
PEO(polyethylene oxide)	24.7
EPO(Eudragit E-PO)	20.5
hydrocodone bitartrate	5
HPMC 2910	2.5
Eudragit E-100	75
APAP	325
binder	17.8
mannitol	192.2
microcrystalline cellulose	200
crospovidone	50
magnesium stearate	40
Total	1000

Example 8: Hydrocodone Bitartrate/ Acetaminophen (Celphere core)

Table 20: Hydrocodone bitartrate granule composition

Core Shell composition		
Component	**Location**	**mg/tablet**
Celphere (MCC)	core	117.5
hydrocodone bitartrate	API layer	5
HPMC 2910	API layer	2.5
Eudragit E-100	film	83.4
magnesium stearate	film	41.6
Total		250

Table 21: Hydrocodone bitartrate tablet composition

Component	**mg/tablet**
Core Shell composition (above)	250
APAP	325
gelatin	12.14
mannitol	102.9
microcrystalline cellulose	120
xanthan gum	30
crospovidone	150
magnesium stearate	10
Total	1000.04

Coated spheres were prepared as in Example 7, and mixed with acetaminophen and other excipients (mannitol, microcrystalline cellulose, xanthan gum and crospovidone) and blended in a V-blender for 30 minutes. Magnesium stearate was then added to lubricate the blend and the mixture was blended for an additional 5 minutes prior to compressing into hydrocodone tablets.

Table 22: Hydrocodone bitartrate granule composition

Overall Tablet composition	
Component	**mg/tablet**
microcrystalline cellulose	237.5
hydrocodone bitartrate	5
HPMC 2910	2.5
Eudragit E-100	83.4
APAP	325
gelatin	12.14
mannitol	102.9
xanthan gum	30
crospovidone	150
magnesium stearate	51.6
Total	1000.04

Example 9: Hydrocodone Bitartrate/ Acetaminophen (Celphere core)

Table 23: Hydrocodone bitartrate granule composition

Core Shell composition		
Component	**Location**	**mg/tablet**
Celphere (MCC)	core	117.5
hydrocodone bitartrate	API layer	5
HPMC 2910	API layer	2.5
Eudragit E-100	film	83.4
magnesium stearate	film	41.6
Total		250

Table 24: Hydrocodone bitartrate tablet composition

Component	**mg/tablet**
Core Shell composition (above)	250
APAP	325
gelatin	12.14
mannitol	84.9
microcrystalline cellulose	120
Carbopol	30
sodium bicarbonate	18
crospovidone	150
magnesium stearate	10
Total	1000.04

Coated spheres were prepared as in Example 7, and mixed with acetaminophen and other excipients (mannitol, microcrystalline cellulose, carbopol, sodium bicarbonate and crospovidone) and blended in a V-blender for 30 minutes. Magnesium stearate was then added to lubricate the blend and the mixture was blended for an additional 5 minutes prior to compressing into tablets.

Table 25: Hydrocodone bitartrate tablet composition

Overall Tablet composition	
Components	**mg/tablet**
hydrocodone bitartrate	5
HPMC 2910	2.5
Eudragit E-100	83.4
APAP	325
gelatin	12.14
mannitol	84.9
microcrystalline cellulose	237.5
carbopol	30

Overall Tablet composition	
Components	**mg/tablet**
sodium bicarbonate	18
crospovidone	150
magnesium stearate	51.6
Total	1000.04

Example 10: Oxycodone Hydrochloride / Acetaminophen

Table 26: Oxycodone bitartrate granule composition

Core Shell composition		
Component	**Location**	**mg/tablet**
HPMC K100M	core	71
Compritol	core	30.5
Ethocel	core	16.8
oxycodone hydrochloride	API layer	4.5
HPMC 2910	API layer	2.2
Eudragit E-100	film	83.4
magnesium stearate	film	41.6
Total		250

5

Table 27: Oxycodone tablet composition

Component	**mg/tablet**
Core Shell composition (above)	250
APAP	325
gelatin	12.14
lactose	84.9
carbopol	30
microcrystalline cellulose	120
crospovidone	150
sodium bicarbonate	18
magnesium stearate	10
Total	1000.04

Granules were prepared and coated as described in Example 1. The coated granules were then mixed with acetaminophen and other excipients (carbopol, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose) and blended in a V-blender for 30 minutes. Magnesium stearate was then added to lubricate the blend and the mixture was blended for an additional 5 minutes prior to compressing into oxycodone/acetaminophen tablets.

Table 28: Oxycodone / acetaminophen tablet composition

Overall Tablet composition	
Components	mg/tablet
HPMC K100M	71
compritol	30.5
ethocel	16.8
oxycodone hydrochloride	4.5
HPMC 2910	2.2
Eudragit E-100	83.4
APAP	325
gelatin	12.14
lactose	84.9

Overall Tablet composition	
Components	mg/tablet
carbopol	30
microcrystalline cellulose	120
crospovidone	150
sodium bicarbonate	18
magnesium stearate	51.6
Total	1000

Example 11: Oxycodone Hydrochloride / Acetaminophen

Table 29: Oxycodone hydrochloride granule composition

Core Shell composition		
Component	**Location**	**mg/tablet**
HPMC K100M	core	71
compritol	core	30.3
ethocel	core	16.7
oxycodone hydrochloride	API layer	5
HPMC 2910	API layer	2.5
Eudragit E-100	film	83.4
magnesium stearate	film	41.6
Total		250.5

Table 30: Oxycodone / acetaminophen tablet composition

Component	**mg/tablet**
Core Shell composition (above)	250
APAP	325
gelatin	12.14
mannitol	82.9
xanthan gum	50
microcrystalline cellulose	120
crospovidone	150
magnesium stearate	10
Total	1000.04

Granules were prepared and coated as described in Example 1. The coated granules were then mixed with acetaminophen and other excipients (xanthan gum, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose) and blended in a V-blender for 30 minutes. Magnesium stearate was then added to lubricate the blend and the mixture was blended for an additional 5 minutes prior to compressing into oxycodone/ acetaminophen tablets.

Table 31: Oxycodone / acetaminophen tablet composition

Overall Tablet composition	
Components	mg/tablet
HPMC K100M	71
Compritol	30.3
Ethocel	16.7
oxycodone hydrochloride	5
HPMC 2910	2.5
Eudragit E-100	83.4
APAP	325
gelatin	12.14
mannitol	82.9
xanthan gum	50
microcrystalline cellulose	120
crospovidone	150
magnesium stearate	51.6
Total	1000.54

Example 12: Oxycodone Hydrochloride / Acetaminophen

Table 32: Oxycodone hydrochloride granule composition

Core Shell composition		
Component	**Location**	**mg/tablet**
HPMC K100M	core	71
Compritol	core	30.5
Ethocel	core	16.8
oxycodone hydrochloride	API layer	4.5
HPMC 2910	API layer	2.2
Eudragit E-100	film	83.4
magnesium stearate	film	41.6
Total		250

Table 33: Oxycodone / acetaminophen tablet composition

Component	**mg/tablet**
Core Shell composition (above)	250
APAP	325
gelatin	12.14
mannitol	52.9
Carbopol	50
microcrystalline cellulose	120
Crospovidone	150
sodium bicarbonate	30
magnesium stearate	10
Total	1000.04

Granules were prepared and coated as described in Example 1. The coated granules were then mixed with acetaminophen and other excipients (carbopol, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose) and blended in a V-blender for 30 minutes. Magnesium stearate was then added to lubricate the blend and the mixture was blended for an additional 5 minutes prior to compressing into oxycodone/acetaminophen tablets.

Table 34: Oxycodone / acetaminophen tablet composition

Overall Tablet composition	
Components	**mg/tablet**
HPMC K100M	71
compritol	30.5
ethocel	16.8
oxycodone hydrochloride	4.5
HPMC 2910	2.2
Eudragit E-100	83.4
APAP	325
gelatin	12.14
mannitol	52.9
carbopol	50
microcrystalline cellulose	120
crospovidone	150
sodium bicarbonate	30
magnesium stearate	51.6
Total	1000

Example 13: Hydrocodone Bitartrate/ Acetaminophen

Table 35: Hydrocodone bitartrate granule composition

Core Shell composition		
Component	Location	mg/tablet
HPMC K100M	core	51
compritol	core	21.9
ethocel	core	12
hydrocodone bitartrate	API layer	10
HPMC 2910	API layer	5
Eudragit E-100	film	66.7
magnesium stearate	film	33.3
Total		199.9

Table 36: Hydrocodone Bitartrate / APAP tablet composition

Component	**mg/TAB**
Core Shell composition (above)	200
APAP	325
gelatin	12.14
mannitol	74.86
carbopol	80
microcrystalline cellulose	100
crospovidone	150
sodium bicarbonate	48
magnesium stearate	10
Total	1000

Granules were prepared and coated as described in Example 1. The coated granules were then mixed with acetaminophen and other excipients (carbopol, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose) and blended in a V-blender for 30 minutes. Magnesium stearate was then added to lubricate the blend and the mixture was blended for an additional 5 minutes prior to compressing into hydrocodone /acetaminophen tablets.

Table 37: Hydrocodone Bitartrate / APAP tablet composition

Overall Tablet composition	
Components	mg/tablet
HPMC K100M	51
Compritol	21.9
Ethocel	12
hydrocodone bitartrate	10
HPMC 2910	5
Eudragit E-100	66.7
APAP	325
gelatin	12.14
mannitol	74.86
carbopol	80
microcrystalline cellulose	100
crospovidone	150
sodium bicarbonate	48
magnesium stearate	43.3
Total	999.9

Example 14: Hydrocodone Bitartrate / Acetaminophen

Table 38: Hydrocodone Bitartrate granule composition

Core Shell composition		
Component	Location	mg/tablet
HPMC K100M	core	42
compritol	core	18.1
ethocel	core	9.9
hydrocodone bitartrate	API layer	10
HPMC 2910	API layer	5
Eudragit E-100	film	56.8
magnesium stearate	film	28.4
Total		170.2

Table 39: Hydrocodone / APAP tablet composition

Component	**mg/tablet**
Core Shell composition (above)	170
APAP	325
gelatin	12.14
mannitol	24.905
carbopol	49.98
microcrystalline cellulose	102
crospovidone	127.5
sodium bicarbonate	30.005
magnesium stearate	8.5
Total	850.03

Granules were prepared and coated as described in Example 1. The coated granules were then mixed with acetaminophen and other excipients (carbopol, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose) and blended in a V-blender for 30 minutes. Magnesium stearate was then added to lubricate the blend and the mixture was blended for an additional 5 minutes prior to compressing into hydrocodone /acetaminophen tablets.

Table 40: Hydrocodone / APAP tablet composition

Overall Tablet composition	
Components	**mg/tablet**
HPMC K100M	42
compritol	18.1
ethocel	9.9
hydrocodone bitartrate	10
HPMC 2910	5
Eudragit E-100	56.8
APAP	325
gelatin	12.14
mannitol	24.905
carbopol	49.98
microcrystalline cellulose	102
crospovidone	127.5
sodium bicarbonate	30.005
magnesium stearate	36.9
Total	850.23

Example 15: Hydrocodone Bitartrate/ Acetaminophen

Table 41: Hydrocodone bitartrate granule composition

Core Shell composition		
Component	Location	mg/tablet
HPMC K100M	core	51
compritol	core	21.9
ethocel	core	12
hydrocodone bitartrate	API layer	10
HPMC 2910	API layer	5
Eudragit E-100	film	66.7
magnesium stearate	film	33.3
Total		199.9

Table 42: Hydrocodone / APAP tablet composition

Component	**mg/tablet**
Core Shell composition (above)	200
APAP	325
gelatin	12.14
mannitol	134.9
carbopol	30
microcrystalline cellulose	120
crospovidone	150
sodium bicarbonate	18
magnesium stearate	10
Total	1000.04

Granules were prepared and coated as described in Example 1. The coated granules were then mixed with acetaminophen and other excipients (carbopol, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose) and blended in a V-blender for 30 minutes. Magnesium stearate was then added to lubricate the blend and the mixture was blended for an additional 5 minutes prior to compressing into hydrocodone /acetaminophen tablets.

Table 43: Hydrocodone / APAP tablet composition

Overall Tablet composition	
Component	mg/tablet
HPMC K100M	51
compritol	21.9
ethocel	12
hydrocodone bitartrate	10
HPMC 2910	5
Eudragit E-100	66.7
APAP	325
gelatin	12.14
mannitol	134.9
carbopol	30
microcrystalline cellulose	120
crospovidone	150
sodium bicarbonate	18
magnesium stearate	43.3
Total	999.94

Example 16: Hydrocodone Bitartrate/ Acetaminophen

Table 44: Hydrocodone bitartrate granule composition

Core Shell composition		
Component	Location	mg/tablet
HPMC K100M	core	51
compritol	core	21.9
ethocel	core	12
hydrocodone bitartrate	API layer	10
HPMC 2910	API layer	5
Eudragit E-100	film	66.7
magnesium stearate	film	33.3
Total		199.9

Table 45: Hydrocodone / APAP tablet composition

Component	**mg/tablet**
Core Shell composition (above)	200
APAP	325
gelatin	12.14
mannitol	102.9
carbopol	50
microcrystalline cellulose	120
Crospovidone	150
sodium bicarbonate	30
magnesium stearate	10
Total	1000.04

Granules were prepared and coated as described in Example 1. The coated granules were then mixed with acetaminophen and other excipients (carbopol, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose) and blended in a V-blender for 30 minutes. Magnesium stearate was then added to lubricate the blend and the mixture was blended for an additional 5 minutes prior to compressing into hydrocodone /acetaminophen tablets.

Table 46: Hydrocodone / APAP tablet composition

Overall Tablet composition	
Components	**mg/tablet**
HPMC K100M	51
Compritol	21.9
Ethocel	12
hydrocodone bitartrate	10
HPMC 2910	5
Eudragit E-100	66.7
APAP	325
gelatin	12.14
mannitol	102.9
carbopol	50
microcrystalline cellulose	120
crospovidone	150
sodium bicarbonate	30
magnesium stearate	43.3
Total	999.94

Example 17: Hydrocodone Bitartrate / Acetaminophen

Table 47: Hydrocodone / APAP tablet composition

Components (mg/tab)	5/325 mg	7.5/325 mg	10/325 mg
Hypromellose K100M PH	25.5	38.3	51.1
Compritol 888 ATO	11	16.4	21.9
ethyl cellulose	6	9	12
hydrocodone bitartrate	5	7.5	10
Hypromellose 2910	2.5	3.8	5
Eudragit E-100	33.4	50	66.7
paracetamol Dc272n**	342.11	342.11	342.11
mannitol Ez	29.89	38.81	37.29
carbopol 71g	50	50	50
microcrystalline cellulose	96	108	130
crospovidone	144	171	200
sodium bicarbonate #1	30	30	30
FD&C Blue #2 Ht Aluminum Lake	NA	0.54	NA
Iron Oxide Yellow 510p	NA	0.54	NA
Iron Oxide Red 212p	NA	NA	0.6
magnesium stearate non-bovine	24.6	34	43.3
alcohol SDA-3A, anhydrous*	*	*	*
purified water*	*	*	*
Total Tablet Weight	800	900	1000

* Removed during Processing

Granules were prepared and coated as described in Example 1. The coated granules were then mixed with Paracetamol and other excipients (carbopol, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose and coloring agents) and blended in a V-blender for 30 minutes. Magnesium stearate was then added to lubricate the blend and the mixture was blended for an additional 5 minutes prior to compressing into hydrocodone /acetaminophen tablets.

Table 48: Hydrocodone bitartrate granule composition

	5/325 mg Dose	7.5/325 mg Dose	10/325 mg Dose
Granulation	%	%	%
Hypromellose	3.19	4.26	5.11
Compritol 888 ATO	1.37	1.83	2.19
ethylcellulose	0.75	1	1.2
alcohol SDA-3A, anhydrous	*	*	*
purified water	*	*	*
TOTAL	5.31	7.09	8.5
Layering	%	%	%
hydrocodone bitartrate	0.63	0.83	1
polymer granules (EC, HPMC and Compritol)	5.31	7.09	8.5
Hypromellose 2910	0.31	0.42	0.5
purified water	*	*	*
TOTAL	6.25	8.34	10
Coating	%	%	%
hydrocodone layered granules, 10%	6.25	8.34	10
Eudragit E-100	4.17	5.56	6.67
magnesium stearate	2.08	2.77	3.33
alcohol, SDA-3A, anhydrous	*	*	*
TOTAL	12.5	16.67	20

* Removed during Processing

Example 18: Armodafinil

Table 49: Armodafinil tablet composition

Armodafinil:			
Components (mg/tab)	**50 mg**	**150 mg**	**200 mg**
hypromellose	64.26	36	48
Compritol 888 ATO	17.85	10	14
ethylcellulose	10.71	10	14
armodafinil	50	150	200
Eudragit E-100	21	30	40
Mannitol Ez	17	25	25
Carbopol 71g	50	50	50
microcrystalline cellulose	100	125	125
crospovidone	150	200	200
sodium bicarbonate #1	30	30	30
magnesium stearate non-bovine	71	25	32
Lutrol F68 (1:5)	150	200	200
sodium lauryl sulphate (3%)	23	30	40
Alcohol SDA-3A, anhydrous*	*	*	*
purified water*	*	*	*
Total Tablet Weight	754.82	921	1018

* Removed during Processing

Granules are prepared and coated as described in Example 1. The coated granules are then mixed with the other excipients (carbopol, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose) and blended in a V-blender for 30 minutes. Magnesium stearate (non-bovine) is then added to lubricate the blend and the mixture is blended for an additional 5 minutes prior to compressing into armodafinil tablets.

Table 50: Armodafinil granule compositions

	50mg Dose		150mg Dose		200mg Dose	
Granulation	mg/g	mg/tab	mg/g	mg/tab	mg/g	mg/tab
hypromellose	450	64.26	175	36	175	48
armodafinil	350	49.98	725	150	725	200
Compritol 888 ATO	125	17.85	50	10	50	14
ethylcellulose	75	10.71	50	10	50	14
Alcohol SDA-3A, anhydrous	*	*	*	*	*	*
purified water	*	*	*	*	*	*
TOTAL	1000	142.8	1000	206	1000	276
Coating	mg/g	mg/tab	mg/g	mg/tab	mg/g	mg/tab
armodafinil granules, 35%	820	142.84	820	207	820	276
Eudragit E-100	120	20.90	120	30	120	40
magnesium stearate	60	10.45	60	15	60	20
Alcohol, SDA-3A, anhydrous	*	*	*	*	*	*
TOTAL	1000	174.2	1000	252	1000	336

* Removed during Processing

Example 19: Phenobarbital

Table 51: Phenobarbital Tablet compositions

Components (mg/tab)	**15 mg**	**30 mg**	**60 mg**	**100 mg**
hypromellose	19.3	38.6	77.2	128.52
Compritol 888 ATO	5.4	10.7	21.4	35.7
ethylcellulose	3.2	6.4	12.9	21.43
phenobarbital	15	30	60	100
Eudragit E-100	6.3	15.5	25.1	42
Mannitol Ez	20	20	20	20.1
Carbopol 71g	50	50	50	50
microcrystalline cellulose	100	100	100	100
crospovidone	130	130	130	200
sodium bicarbonate #1	30	30	30	30
magnesium stearate non-bovine	9.1	12.3	19.1	31
Lutrol F68 (1:5)	100	100	120	200
sodium lauryl sulphate (3%)	22.8	28	35	50
Alcohol SDA-3A, anhydrous*	*	*	*	*
purified water*	*	*	*	*
Total Tablet Weight	511.1	571.5	700.7	1008.7

* Removed during Processing

Table 52: Phenobarbital granule compositions

	15 mg Dose		30 mg Dose		60 mg Dose		100 mg Dose	
Granulation	mg/g	mg/tab	mg/g	mg/tab	mg/g	mg/tab	mg/g	mg/tab
Hypromellose	450	19.31	450	38.57	450	77.18	450	128.57
phenobarbital	350	15.02	350	30	350	60.03	350	100
Compritol 888 ATO	125	5.36	125	10.71	125	21.44	125	35.71
ethyl cellulose	75	3.22	75	6.43	75	12.86	75	21.43
Alcohol SDA-3A,	*	*	*	*	*	*	*	*
Purified Water	*	*	*	*	*	*	*	*
TOTAL	1000	42.91	1000	85.71	1000	171.51	1000	285.71
Coating	mg/g	mg/tab	mg/g	mg/tab	mg/g	mg/tab	mg/g	mg/tab
phenobarbital, 35%	820	42.89	820	85.69	820	171.46	820	285.69
Eudragit E-100	120	6.28	120	12.54	120	25.09	120	41.81
magnesium stearate	60	3.14	60	6.27	60	12.55	60	20.90
Alcohol, SDA-3A,	*	*	*	*	*	*	*	*
TOTAL	1000	52.3	1000	104.5	1000	209.1	1000	348.4

* Removed during Processing

Granules are prepared and coated as described in Example 1. The coated granules are then mixed with the other excipients (carbopol, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose) and blended in a V-blender for 30 minutes. Magnesium stearate (non-bovine) is then added to lubricate the blend and the mixture is blended for an additional 5 minutes prior to compressing into phenobarbital tablets.

Example 20: Diazepam

Table 53: Diazepam Tablet compositions

Components	2 mg (mg/tab)	5 mg (mg/tab)	10 mg (mg/tab)
Hypromellose K100M PH	22.2	55.6	111.2
Compritol 888 ATO	9.5	23.8	47.64
Ethyl cellulose N10	5.2	13.1	26.2
diazepam	2	5	10
Hypromellose 2910	1	2.5	5
Eudragit E-100	26.7	66.7	133.4
mannitol Ez	70	70	70
carbopol 71g	50	50	50
microcrystalline cellulose	95	95	94
crospovidone	90	95	150
sodium bicarbonate #1	30	30	30
magnesium stearate non-	18.1	38.6	74.6
Alcohol SDA-3A,	*	*	*
purified water*	*	*	*
Total Tablet Weight	419.7	545.3	802.04

*Removed during processing

Granules are prepared and coated as described in Example 1. The coated granules are then mixed with the other excipients (carbopol, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose) and blended in a V-blender for 30 minutes. Magnesium stearate (non-bovine) is then added to lubricate the blend and the mixture is blended for an additional 5 minutes prior to compressing into Diazepam tablets.

Table 54: Diazepam Coated Granule compositions

	2 mg Dose		5 mg Dose		2 mg Dose	
Granulation	mg/g	mg/tab	mg/g	mg/tab	mg/g	mg/tab
hypromellose	600.86	22.23	600.86	55.58	600.86	111.16
Compritol 888 ATO	257.51	9.53	257.51	23.82	257.51	47.64
ethyl cellulose	141.63	5.24	141.63	13.10	141.63	26.20
Alcohol SDA-3A,	*	*	*	*	*	*
purified water	*	*	*	*	*	*
TOTAL	1000	37	1000	92.5	1000	185
Layering	mg/g	mg/tab	mg/g	mg/tab	mg/g	mg/tab
diazepam	50	2	50	5	50	10
polymer granules (EC,	925	37	925	92.5	925	185
Hypromellose 2910	25	1	25	2.5	25	5
purified water	*	*	*	*	*	*
TOTAL	1000	40	1000	100	1000	200
Coated, 2.5%	mg/g	mg/tab	mg/g	mg/tab	mg/g	mg/tab
diazepam layered	500	40	500	100	500	200
Eudragit E-100	333.6	26.69	333.6	66.71	333.6	133.43
magnesium stearate	166.4	13.31	166.4	33.29	166.4	66.57
Alcohol, SDA-3A,	*	*	*	*	*	*
TOTAL	1000	80	1000	200	1000	400

Example 21: Hydrocodone (single API)

Granules are prepared and coated as described in Example 1. The coated granules are then mixed with the other excipients (carbopol, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose) and blended in a V-blender for 30 minutes. Magnesium stearate (non-bovine) is then added to lubricate the blend and the mixture is blended for an additional 5 minutes prior to compressing into hydrocodone tablets.

Example 22: Hydrocodone (single API) – (continued from Example 21 above)

Table 55: Hydrocodone Tablet compositions

Components	**5 mg (mg/tab)**	**10 mg (mg/tab)**
Hypromellose K100M PH	25.5	51.1
Compritol 888 ATO	11	21.9
Ethyl cellulose N10	6	12.04
hydrocodone bitartrate	5	10
Hypromellose 2910	2.5	5
Eudragit E-100	33.4	66.7
Mannitol Ez	70	70
Carbopol 71g	50	50
microcrystalline cellulose	95	95
Crospovidone	100	120
Sodium Bicarbonate #1	30	30
Magnesium Stearate Non-Bovine	21.6	39.3
Alcohol SDA-3A, Anhydrous*	*	*
purified water*	*	*
Total Tablet Weight	450	571.04

*Removed during processing

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Table 56: Hydrocodone bitartrate Coated Granule compositions

	5 mg Dose		10 mg Dose	
Granulation	mg/g	mg/tab	mg/g	mg/tab
hypromellose	600.86	25.54	600.86	51.07
Compritol 888 ATO	257.51	10.94	257.51	21.89
ethyl cellulose	141.63	6.02	141.63	12.04
Alcohol SDA-3A, anhydrous	*	*	*	*
purified water	*	*	*	*
TOTAL	1000	42.5	1000	85
Layering	mg/g	mg/tab	mg/g	mg/tab
hydrocodone bitartrate	100	5	100	10
polymer granules (EC, HPMC and Compritol)	850	42.5	850	85
Hypromellose 2910	50	2.5	50	5
purified water	*	*	*	*
TOTAL	1000	50	1000	100
Coating	mg/g	mg/tab	mg/g	mg/tab
hydrocodone bitartrate layered granules, 10%	500	50	500	100
Eudragit E-100	333.6	33.36	333.6	66.71
magnesium stearate	166.4	16.64	166.4	33.29
Alcohol, SDA-3A, anhydrous	*	*	*	*
TOTAL* (removed during processing)	1000	100	1000	200

Example 23: Hydrocodone Bitartrate / Acetaminophen

Coated granules were prepared according to the Example 1 above. The prepared coated granules were then mixed with Paracetamol and other excipients (carbomer, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose, colorants such as FD and C blue, red iron oxide or yellow iron oxide are premixed and blended in a bin blender for 30 minutes. Magnesium stearate was then added to lubricate the blend and the resulting mixture was blended for an additional 5 minutes prior to compressing into hydrocodone/acetaminophen tablets.

Table 57: Hydrocodone / APAP Tablet compositions

Component (% w/w)	**5/325 mg**	**7.5/325 mg**	**10/325 mg**
Hydrocodone bitartrate coated	12.5	16.7	20.0
Paracetamol	42.76	38.0	34.21
mannitol	3.74	4.3	3.73
carbopol	6.25	5.6	5.0
microcrystalline cellulose	12.0	12.0	13.0
crospovidone	18.0	19.0	20.0
sodium bicarbonate	3.75	3.3	3.0
FD&C Blue #2 HT Aluminum Lake	NA	0.06	NA
Iron Oxide Red 212P	NA	NA	0.06
Iron Oxide Yellow 510P	NA	0.06	NA
magnesium stearate	1.0	1.0	1.0
Total	**100**	**100**	**100**

Example 24: Extraction study of Formulations according to Examples 3

The dosage form (intact and crushed) prepared according to Example 3 above (10/325mg hydrocodone bitartrate/Acetaminophen tablet) was taken up in a small volume of water and extracted to simulate the amount of hydrocodone that was available to abusers via intravenous (IV) route. The resultant mixture was assessed for ability to draw the mixture through a filter material into a syringe for IV injection. Various needle sizes and extraction volumes were evaluated. Filtrates were assayed by HPLC for content of hydrocodone bitartrate.

Table 58: Amount of hydrocodone extracted from two lots of 10/325mg hydrocodone bitartrate/Acetaminophen tablets at 100° C and Room Temperature (RT)

Lot #	Intact tablet (mg)		Crushed tablet (mg)	
	100°C	RT	100°C	RT
1	0 mg	0.09 mg	0 mg	0 mg
2	0 mg	0.07 mg	0 mg	0 mg

Example 25: Simulated nasal fluid extraction study of Formulations according to Example 3

The dosage form prepared according to Example 3 above (10/325mg hydrocodone bitartrate/Acetaminophen tablets) was crushed using a pestle and mortar and placed in 10 mL of simulated nasal fluid at 37 °C, with gentle agitation to simulate the amount of hydrocodone bitartrate available for abuse by nasal insufflation. Aliquots were removed at 10 and 30 minutes for analysis of hydrocodone bitartrate by HPLC. The amount of hydrocodone bitartrate extracted from crushed tablets for simulated nasal insufflation is provided in the table below.

This method is for the determination of hydrocodone bitartrate released from simulated nasal fluid extractions of hydrocodone bitartrate extended-release tablets.

A. HPLC ANALYSIS PARAMETERS

Column	GL Sciences Inertsil Phenyl-3, 4.6 mm x 50 mm, 5-μm
Column Temperature	45°C
Detection	UV at 280 nm
Solvent A	0.1% HFBA in water
Solvent B	MeOH
Mobile Phase	70:30 Solvent A:Solvent B
Injector Flush	50:50 MeOH:water
Flow Rate	2.0 mL/min
Injection Volume	50 μL
Run Time	4 min
Peak Response	Area
Diluent	0.1 N HCl

B. HPLC SOLUTION PREPARATION

Solvent A (0.1% HFBA in H_2O): Combine 1 mL of HFBA and 1 L of HPLC grade water, and mix well. Solvent A is stable for 14 days. Proportionate volumes may be prepared.

Mobile Phase (70:30 Solvent A:MeOH): Combine 700 mL of Solvent A and 300 mL of MeOH, and mix well. Prepared solutions are stable for 1 month. Proportionate volumes may be prepared. Alternatively, the HPLC pump may be used to mix the mobile phase.
Diluent/Medium (0.1 N HCl): Combine 25 mL of 12 N HCl and 3 L of DI water, and mix well. 0.1N HCl is stable for 4 weeks. Proportionate volumes may be prepared.
Injector Flush (50:50 MeOH:H_2O): Combine 500 mL of MeOH and 500 mL of HPLC grade water, and mix well. 50:50 MeOH:H_2O is stable for 1 month. Proportionate volumes may be prepared.

C. Simulated Nasal Fluid (SNF) preparation

Add 8.7 g sodium chloride (NaCl) 3.0 g potassium chloride (KC1), 0.6 g calcium chloride ($CaC1_2$), 4.4 g sodium phosphate dibasic (Na_2HPO_4), and 1.1 g sodium phosphate monobasic (NaH2PO4) in one liter of water. Mix well. Measure and record pH (must be between 6.0 and 7.0). Store at room temperature. SNF is stable for 2 weeks. Proportionate volumes may be prepared.

D. Hydrocodone Bitartrate Standard Solution

Stock Standard Solution: Dry a portion of hydrocodone bitartrate standard at 2 hours under vacuum at 105°C per the USP. In duplicate, accurately weigh 30 mg ± 5 mg of hydrocodone bitartrate into separate 100-mL volumetric flasks. Add approximately 50 mL of 0.1 N HCl diluent. Dissolve by sonication for approximately 10 minutes. Dilute to volume with diluent, and mix well. These are the stock standard solutions of approximately 300 micrograms/mL (as anhydrous hydrocodone bitartrate) and are stable for 29 days under ambient laboratory conditions (unprotected from light). Proportionate volumes may be prepared.

Working Standard Solution: Pipette 15 mL of each stock standard solution into separate 50-mL volumetric flasks. Dilute to volume with 0.1 N HCl diluent, and mix well. These working standard solutions are approximately 90 micrograms/mL (as anhydrous hydrocodone bitartrate) and are stable for 43 days under ambient laboratory conditions (unprotected from light). Proportionate volumes may be prepared.

E. Simulated Nasal Insufflation Extraction Sample Preparation

1. Crush one tablet and transfer approximately 575 mg, accurately weighed, of the crushed material to pre-labeled 20 mL glass vial. For drug substance controls, weigh an appropriate mass of material and transfer into a pre-labeled 20 mL glass vial.

2. Heat the water bath and simulated nasal fluid to 37 °C.

3. Pipette 10 mL the pre-heated 37 °C simulated nasal fluid into each vial containing crushed tablet material.

4. Cap and invert two times to wet powder. Put vial on the metal shelf inside of the water bath and shake at 100 rpm.

5. At 10 min, take the vial out of shelf.

6. Uncap and withdraw a 3-mL solution from each of the vials using a micropipette.

7. Transfer solution into a 5-mL polypropylene syringe and filter the solution through a 25-mm diameter, 1-µm porosity glass filter into a glass test tube (16x100mm).

8. Place vial back into water bath and continue shaking.

9. At 30 min, stop the shaking, uncap and withdraw a 3-mL solution from each of the vials using a micropipette.

10. Transfer solution into a 5-mL polypropylene syringe and filter the solution through a 25-mm diameter, 1-µm porosity glass filter into a glass test tube (16x100mm).

11. Pipette 1 mL of solution from each test tube into separate 50-mL volumetric flasks and dilute to volume with 0.1 N HCl. Mix by inverting 10 times.

12. Pass and discard a 1-mL aliquot of the sample solution through a 25-mm diameter, 1-µm porosity, glass syringe filter prior to collection of a second aliquot into a glass HPLC vial and cap.

13. Inject each sample once.

Table 59: Simulated nasal fluid extraction of 10/325mg hydrocodone bitartrate/Acetaminophen tablets

Lot	Amount extracted at 10 minutes from crushed tablets containing 10/325mg hydrocodone bitartrate/acetaminophen	Amount extracted at 30 minutes from crushed tablets containing 10/325mg hydrocodone bitartrate/acetaminophen
1	14%	45%
2	60%	66%

Example 26(a): Assessment of Abuse by Multitablet Ingestion

The dosage form prepared according to Example 3 and 5 above was evaluated for multiple tablet oral abuse resistance by stirring the selected number of tablets in 300 mL of 0.1N HCl. Dissolution was performed using USP Apparatus II at 50 rpm and 37 °C. One to twelve tablets were added to the vessel simultaneously and aliquots were removed after 5, 10, 15, 30, 60, 120, 240 and 360 minutes of agitation and analyzed for hydrocodone bitartrate (Figure 4) and APAP (Figure 5) by HPLC. The results were plotted against time and appear in Figures 4 and 5.

Example 26(b): Assessment of Abuse by Multitablet Ingestion

The dosage form prepared according to Example 17 above was evaluated for multiple tablet oral abuse resistance by stirring the selected number of tablets in 300 mL of 0.1N HCl. Dissolution was performed using USP Apparatus II at 50 rpm and 37 °C. One to twelve tablets were added to the vessel simultaneously and aliquots were removed after 5, 10, 15, 30, 60, 120, 240 and 360 minutes of agitation and analyzed for hydrocodone bitartrate (Figure 6) and APAP (Figure 7) by HPLC. The results were plotted against time and appear in Figures 6 and 7.

Example 26(c): Assessment of Abuse by Multitablet Ingestion

The dosage form prepared according to Example 17 above was evaluated for multiple tablet oral abuse resistance by stirring the selected number of tablets in 300 mL of 0.1N HCl. Dissolution was performed using USP Apparatus II at 50 rpm and 37 °C. One to twelve tablets were added to the vessel simultaneously and aliquots were removed after 5, 10, 15, 30, 60, 120, 240 and 360 minutes of agitation and analyzed for hydrocodone bitartrate and APAP by HPLC. The results were plotted against time and appear in Figure 8 (hydrocodone bitartrate) and Figure 9 (APAP).

Example 27: Coated esketamine granules

Coated esketamine granules are prepared as per the process described in Example 1 with slight variation from Example 1 in components as illustrated below.

Table 60: Esketamine hydrochloride granule compositions

Granulation	**% w/w**
hypromellose	60
glyceryl behenate	26
ethylcellulose	14
TOTAL	100
Layering	**% w/w**
esketamine hydrochloride	5
polymer granules (EC, HPMC and Compritol)	92.5
Hypromellose 2910	2.5
TOTAL	100
Coating	**% w/w**
esketamine layered granules	50
Eudragit E-100	33
magnesium stearate	17
TOTAL	100

Example 28: Esketamine HCl Tablets

The coated granules prepared per Example 27 above are subsequently mixed with other components (carbomer, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose) and blended in a V-blender for 30 minutes. Magnesium stearate is added to lubricate the blend and the resulting mixture was blended for additional 5 minutes prior to compressing into tablets.

Table 61: Esketamine hydrochloride tablet compositions

Components mg/tab	**1 mg**	**2 mg**	**5 mg**	**10 mg**
hypromellose	11.1	22.2	55.6	111.2
glyceryl behenate	4.8	9.5	23.8	47.64
ethylcellulose	2.6	5.2	13.1	26.2
esketamine hydrochloride	1	2	5	10
Hypromellose 2910	0.5	1	2.5	5
Eudragit E-100	13.3	26.7	66.7	133.4
mannitol	70	70	70	70
carbopol	50	50	50	50
microcrystalline cellulose	94	95	95	94
crospovidone	90	90	95	150
sodium bicarbonate	30	30	30	30
magnesium stearate	11	18	38.6	74.6
Total Tablet Weight	378.3	419.6	545.3	802.04

Example 29: Coated esketamine granules

Coated esketamine granules are prepared as per the process described in Example 1 with slight variation from Example 1 in components as illustrated in the Table below.

Table 62: Esketamine hydrochloride coated granule compositions

Granulation	**% w/w**
hypromellose	60
glyceryl behenate	26
ethyl cellulose	14
TOTAL	100
Layering	**% w/w**
esketamine hydrochloride	10
polymer granules (EC, HPMC and Compritol)	85
hypromellose 2910	5
TOTAL	100
Coating	**% w/w**
esketamine layered granules	50
Eudragit E-100	33
magnesium stearate	17
TOTAL	100

Example 30: Esketamine HCl Tablets

Coated granules prepared per Example 29 above are subsequently mixed with other components (carbomer, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose) and blended in a V-blender for 30 minutes. Magnesium stearate is added to lubricate the blend and the resulting mixture was blended for additional 5 minutes prior to compressing into tablets.

Table 63: Esketamine hydrochloride tablet composition

Components (mg/tab)	14 mg
Hypromellose	71.5
glyceryl behenate	30.6
ethyl cellulose	16.9
esketamine hydrochloride	14
Hypromellose 2910	7
Eudragit E-100	93.4
mannitol	70
Carbopol	50
microcrystalline cellulose	130
Crospovidone	150
sodium bicarbonate	30
magnesium stearate	55
Total Tablet Weight	718.4

Example 31: Coated esketamine granules

Esketamine granules are manufactured using a process similar to that described in Example 1 above with some modification to the process. The active ingredient instead of being layered on the granules resides in the core where it is granulated with other excipients as per the Table below, and is subsequently coated with Eudragit E-100. Granules are manufactured in a high shear granulator where hypromellose, Esketamine hydrochloride and glyceryl behenate are dry mixed for 3 minutes. Then a 10% hydroalcoholic solution of ethylcellulose is slowly added while maintaining the granulator impeller and chopper speed at pre-selected values that provide enough shear for granule formation and growth. Solution addition is continued until the entire amount of ethylcellulose is added. The granules are then wet milled using a size reduction mill (Granumill) and subsequently loaded into fluid bed for drying.

Esketamine hydrochloride granules are then coated in a bottom spray fluid bed coater with 25 % alcoholic suspension of Eudragit E-100 copolymer and magnesium stearate (2:1). The coated granules are subsequently used in blending and compression process.

Table 64: Esketamine hydrochloride granule composition

Granulation	**% w/w**
esketamine hydrochloride	35
hypromellose	45
glyceryl behenate	12.5
ethylcellulose	7.5
Total	100
Coating	**% w/w**
esketamine granules	82
Eudragit E-100	12
magnesium stearate	6
TOTAL	100

Example 32: Esketamine HCl Tablets

Coated granules prepared per Example 31 above are subsequently mixed with other components (carbomer, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose) and blended in a V-blender for 30 minutes. Magnesium stearate is added to lubricate the blend and the resulting mixture was blended for additional 5 minutes prior to compressing into tablets.

Table 65: Esketamine hydrochloride tablet composition

Components (mg/tablet)	**28 mg**	**56 mg**	**84 mg**
hypromellose	36	72	108
glyceryl behenate	10	20	30
ethylcellulose	6	12	18
esketamine hydrochloride	28	56	84
Eudragit E-100	11.7	23.4	35.1
mannitol	17	17	20.1
carbopol	50	50	50
microcrystalline cellulose	100	100	100
crospovidone	150	150	150
sodium bicarbonate	30	30	30
magnesium stearate	12	20	30
Total Tablet Weight	450.7	550.4	655.2

Example 33: Coated esketamine granules

Esketamine granules are manufactured using a process similar to that described in Example 1 and Example 32 above with some modification to the process. The active ingredient, is granulated with other excipients per the table below, and is subsequently coated with Eudragit E-100.

Granules containing Esketamine hydrochloride are manufactured in a high shear granulator where hypromellose, esketamine hydrochloride and glyceryl behenate are dry mixed for 3 minutes. Then a 10% hydroalcoholic solution of ethylcellulose is slowly added while maintaining the granulator impeller and chopper speed at pre-selected values that provide enough shear for granule formation and growth. Solution addition is continued until the entire amount of ethylcellulose is added. The granules are then wet milled using a size reduction mill (Granumill) and then loaded into fluid bed for drying.

The granules are then coated in a bottom spray fluid bed coater with 25 % alcoholic suspension of Eudragit E-100 copolymer and magnesium stearate (2:1). The resulting coated granules are subsequently used for blending and compression process.

Table 66: Esketamine hydrochloride granule composition

Granulation	**% w/w**
esketamine hydrochloride	72.5
hypromellose	17.5
glyceryl behenate	5
ethylcellulose	5
TOTAL	100
Coating	**% w/w**
esketamine granules	82
Eudragit E-100	12
magnesium stearate	6
Total	100

Example 34: Esketamine HCl Tablets

The coated granules prepared per Example 33 above are subsequently mixed with other components (carbomer, crospovidone, sodium bicarbonate, mannitol,

microcrystalline cellulose), and blended in a V-blender for 30 minutes. Magnesium stearate is added to lubricate the blend and blended for additional 5 minutes prior to compressing into tablets.

Table 67: Esketamine hydrochloride tablet compositions

Components (mg/tab)	**200 mg**	**300 mg**	**400 mg**
Hypromellose	48	72	96.4
glyceryl behenate	14	21	27.6
ethyl cellulose	14	21	27.6
esketamine hydrochloride	200	300	400
Eudragit E-100	40	61	81
mannitol	25	25	25
Carbopol	75	75	75
microcrystalline cellulose	125	125	125
Crospovidone	300	300	300
sodium bicarbonate	45	45	45
magnesium stearate	140	150	160
Total Tablet Weight	1026	1195	1362.6

Example 35: Coated Zolpidem granules

Coated Zolpidem tartrate granules are prepared as per the process described in Example 1 as per the composition illustrated in the Table below.

Table 68: Zolpidem tartrate granule compositions

Granulation	**% w/w**
hypromellose	60
glyceryl behenate	26
ethylcellulose	14
TOTAL	100
Layering	**% w/w**
zolpidem tartrate	10
polymer granules (EC, HPMC and Compritol)	85
Hypromellose 2910	5
TOTAL	100
Coating	**% w/w**
zolpidem layered granules	50
Eudragit E-100	33
magnesium stearate	17
TOTAL	100

Example 36: Zolpidem tartrate tablets

Coated zolpidem granules are prepared as per the process described in Example 35 above. The coated granules are mixed with other components (carbomer, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose and blended in a V-blender for 30 minutes. Magnesium stearate is added to lubricate the blend and blended for additional 5 minutes prior to compressing into tablets.

Table 69: Zolpidem tartrate tablet compositions

Components (mg/tab)	5 mg	10 mg
hypromellose	25.5	51.1
glyceryl behenate	11	21.9
ethylcellulose	6	12
zolpidem tartrate	5	10
Hypromellose 2910	2.5	5
Eudragit E-100	33.4	66.7
mannitol	70	70
carbopol	50	50
microcrystalline cellulose	95	94
crospovidone	100	100
sodium bicarbonate	30	30
magnesium stearate	21.6	39.3
Total Tablet Weight	450	550

Example 37: Coated Quetiapine fumarate granules

Quetiapine granules are manufactured using a process similar to that described in Example 1 above with some modification to the process. The Quetiapine fumarate, instead of being layered on the granules, resides in the core where it granulated along with other excipients per Table 70 (Granulation) and is subsequently coated with Eudragit E-100 and magnesium stearate.

Granules are manufactured in a high shear granulator where hypromellose, Quetiapine fumarate, a portion of the Lutrol, sodium lauryl sulphate and glyceryl behenate are dry mixed for 3 minutes. Then a 10% hydroalcoholic solution of ethylcellulose is slowly added while maintaining the granulator impeller and chopper speed at pre-selected values that provide enough shear for granule formation and growth. Solution addition is continued until the entire amount of ethylcellulose is added. The granules are then wet milled using a size reduction mill (Granumill) and then loaded into fluid bed for drying.

The quetiapine fumarate granules are then coated in a bottom spray fluid bed coater with alcoholic suspension of Eudragit E-100 copolymer and magnesium stearate. The resulting coated granules are then used in blending and compression process.

Table 70: Quetiapine fumarate coated granule composition

Granulation	**% w/w**
quetiapine fumarate	23.7
Hypromellose	37.6
glyceryl behenate	13.4
ethyl cellulose	8.1
sodium lauryl sulphate	9.1
Lutrol	8.1
TOTAL	100
Coating	**% w/w**
quetiapine granules	62.5
Eudragit E-100	25
magnesium stearate	12.5
TOTAL	100

Example 38: Quetiapine fumarate tablets

The coated granules prepared per Example 37 above are subsequently mixed with other components (carbomer, crospovidone, remaining portion of Lutrol, sodium bicarbonate, mannitol, microcrystalline cellulose), and blended in a V-blender for 30 minutes. Magnesium stearate is added to lubricate the blend and blended for additional 5 minutes prior to compressing into tablets.

Table 71: Quetiapine fumarate tablet compositions

Components (mg/ tablet)	25 mg (mg/ tablet)	50 mg (mg/ tablet)	100 mg (mg/ tablet)
hypromellose	16	32	63
glyceryl behenate	9	18	36
ethylcellulose	5	11	22
quetiapine fumarate	25	50	100
Eudragit E-100	27	53	107
mannitol	17	17	20.1
carbopol	50	50	50
microcrystalline cellulose	100	100	100
crospovidone	150	150	200
sodium bicarbonate	30	30	30
magnesium stearate	18	31	63
Lutrol	45	51	62
sodium lauryl sulphate	6	12	24
Total Tablet Weight	498	605	877.1

Example 39: Coated Quetiapine granules

Quetiapine granules are manufactured using a process similar to that described in Example 1 and with some modification to the process. The Quetiapine fumarate, instead of being layered on the granules, resides in the core where it is granulated along with other excipients per Table 72 and is subsequently coated with Eudragit E-100.

Granules are manufactured in a high shear granulator where hypromellose, Quetiapine fumarate, sodium lauryl sulphate, portion of Lutrol and glyceryl behenate are dry mixed for 3 minutes. Then a 10% hydroalcoholic solution of ethylcellulose is slowly added while maintaining the granulator impeller and chopper speed at pre-selected values that provide enough shear for granule formation and growth. Solution addition is continued until the entire amount of ethylcellulose is added. The granules are then wet milled using a size reduction mill (Granumill) and then loaded into fluid bed for drying.

Quetiapine Fumarate granules are then coated in a bottom spray fluid bed coater with alcoholic suspension of Eudragit E-100 copolymer and magnesium stearate. The resultant coated granules are subsequently used for blending and compression process.

Table 72: Quetiapine fumarate granule compositions

Granulation	**% w/w**
quetiapine fumarate	14.3
hypromellose	59.2
glyceryl behenate	4.1
ethylcellulose	4.1
sodium lauryl sulphate	10.1
Lutrol	8.2
TOTAL	100
Coating	**% w/w**
quetiapine granules	82
Eudragit E-100	12
magnesium stearate	6
TOTAL	100

Example 40: Quetiapine fumarate tablets

The coated granules prepared as per Example 39 above are subsequently mixed with other components (carbomer, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose, and remaining portion of Lutrol) and blended in a V-blender for 30 minutes. Magnesium stearate is added to lubricate the blend and blended for additional 5 minutes prior to compressing into tablets.

Table 73: Quetiapine fumarate tablet compositions

Components (mg/tab)	**200 mg**	**300 mg**	**400 mg**
hypromellose	48	72.5	97
glyceryl behenate	14	20.8	28
ethyl cellulose	14	20.8	28
quetiapine fumarate	200	300	400
Eudragit E-100	40	74	99
mannitol	25	25	25
carbopol	50	65	65
microcrystalline cellulose	125	125	125
crospovidone	200	275	275
sodium bicarbonate	45	45	45
magnesium stearate	36	48	64
Lutrol	78	91.6	105
sodium lauryl sulphate	34	51.2	69
Total Tablet Weight	909	1213.9	1425

Example 41: Coated Hydromorphone granules

Coated hydromorphone granules are prepared as per the process described in Example 1 with slight variation from Example 1 in components as illustrated below.

Table 74: Hydromorphone hydrochloride granule composition

Granulation	**% w/w**
hypromellose	60
glyceryl behenate	26
ethyl cellulose	14
TOTAL	100
Layering	**% w/w**
hydromorphone hydrochloride	5
polymer granules (EC, HPMC and Compritol)	92.5
Hypromellose 2910	2.5
TOTAL	100
Coating	**% w/w**
hydromorphone layered granules	50
Eudragit E-100	33
magnesium stearate	17
TOTAL	100

Example 42: Hydromorphone hydrochloride tablets

Coated hydromorphone granules are prepared as per the process described in Example 1 and Example 41 above. The coated granules are subsequently mixed with other components (carbomer, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose), and blended in a V-blender for 30 minutes. Magnesium stearate is added to lubricate the blend and blended for additional 5 minutes prior to compressing into tablets.

Table 75: Hydromorphone hydrochloride tablet compositions

Components (mg/tablet)	**2 mg**	**4 mg**	**8 mg**
hypromellose	22.2	44.4	88.9
glyceryl behenate	9.5	19.1	38.1
ethyl cellulose	5.2	10.5	21
hydromorphone hydrochloride	2	4	8
Hypromellose 2910	1	2	4
Eudragit E-100	26.7	53.4	106.7
mannitol	70	70	70
carbopol	50	50	50
microcrystalline cellulose	95	95	94
crospovidone	90	95	150
sodium bicarbonate	30	30	30
magnesium stearate	18.1	58.3	60.4
Total Tablet Weight	419.7	531.7	721.1

Example 43: Coated Methamphetamine granules

Coated methamphetamine granules are prepared according to the process described in Example 1.

Table 76: Methamphetamine hydrochloride granule composition

Granulation	**% w/w**
hypromellose	60
glyceryl behenate	26
ethyl cellulose	14
TOTAL	100
Layering	**% w/w**
methamphetamine hydrochloride	5
polymer granules (EC, HPMC and Compritol)	92.5
Hypromellose 2910	2.5
TOTAL	100
Coating	**% w/w**
methamphetamine layered granules	50
Eudragit E-100	33
magnesium stearate	17
TOTAL	100

Example 44: Methamphetamine hydrochloride tablets

Coated methamphetamine granules are prepared as per the process described in Example 1 and Example 43 above. The coated granules are subsequently mixed with other components (carbomer, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose), and blended in a V-blender for 30 minutes. Magnesium stearate is added to lubricate the blend and blended for additional 5 minutes prior to compressing into tablets.

Table 77: Methamphetamine hydrochloride tablet composition

Components (mg/tablet)	5 mg
hypromellose	55.6
glyceryl behenate	23.8
ethyl cellulose	13.1
methamphetamine hydrochloride	5
Hypromellose 2910	2.5
Eudragit E-100	66.7
mannitol	70
carbopol	50
microcrystalline cellulose	95
crospovidone	100
sodium bicarbonate	30
magnesium stearate	39
Total Tablet Weight	550.7

Example 45: Coated oxymorphone granules

Coated oxymorphone granules are prepared as per the process described in Example 1.

Table 78: Oxymorphone hydrochloride granule composition

Granulation	**% w/w**
hypromellose	60
glyceryl behenate	26
ethyl cellulose	14
TOTAL	100
Layering	**% w/w**
oxymorphone hydrochloride	10
polymer granules (EC, HPMC and Compritol)	85
Hypromellose 2910	5
TOTAL	100
Coating	**% w/w**
oxymorphone layered granules	50
Eudragit E-100	33
magnesium stearate	17
TOTAL	100

Example 46: Oxymorphone hydrochloride tablets

Coated oxymorphone granules are prepared as per the process described in Example 1 and Example 45 above. The coated granules are subsequently mixed with other components (carbomer, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose), and blended in a V-blender for 30 minutes. Magnesium stearate is added to lubricate the blend and blended for additional 5 minutes prior to compressing into tablets.

Table 79: Oxymorphone hydrochloride tablet compositions

Components (mg/tablet)	5 mg	10 mg
hypromellose	25.5	51.1
glyceryl behenate	11	21.9
ethyl cellulose	6	12
oxymorphone hydrochloride	5	10
Hypromellose 2910	2.5	5
Eudragit E-100	33.4	66.7
mannitol	70	70
carbopol	45	45
microcrystalline cellulose	95	94
crospovidone	100	100
sodium bicarbonate	27	27
magnesium stearate	21.6	39.3
Total Tablet Weight	442	542

Example 47: Coated oxycodone granules

Coated oxycodone granules are prepared as per the process described in Example 1.

Table 80: Oxycodone hydrochloride granule composition

Granulation	**% w/w**
hypromellose	60
glyceryl behenate	26
ethylcellulose	14
TOTAL	100
Layering	**% w/w**
oxycodone hydrochloride	10
polymer granules (EC, HPMC and Compritol)	85
Hypromellose 2910	5
TOTAL	100
Coating	**% w/w**
oxycodone layered granules	50
Eudragit E-100	33
magnesium stearate	17
TOTAL	100

Example 48: Oxycodone hydrochloride tablets

Coated oxycodone granules are prepared as per the process described in Example 1 and Example 47 above. The coated granules are subsequently mixed with other components (carbomer, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose), and blended in a V-blender for 30 minutes. Magnesium stearate is added to lubricate the blend and blended for additional 5 minutes prior to compressing into tablets.

Table 81: Oxycodone hydrochloride tablet compositions

Components (mg/tablet)	5 mg	15 mg	30 mg
hypromellose	25.5	76.6	153.3
glyceryl behenate	11	32.8	65.7
ethyl cellulose	6	18.1	36.1
oxycodone hydrochloride	5	15	30
Hypromellose 2910	2.5	7.5	15
Eudragit E-100	33.4	100.1	200.1
mannitol	70	37.29	70
carbopol	45	50	50
microcrystalline cellulose	95	130	94
crospovidone	100	150	200
sodium bicarbonate	27	30	30
magnesium stearate	21.6	57	110
Total Tablet Weight	442	704.39	1054.2

Example 49: Coated Morphine sulphate granules

Coated morphine granules are prepared as per the process described in Example 1.

Table 82: Morphine Sulfate tablet compositions

Granulation	**% w/w**
hypromellose	60
glyceryl behenate	26
ethyl cellulose	14
TOTAL	100
Layering	**% w/w**
morphine sulphate	10
polymer granules (EC, HPMC and Compritol)	85
Hypromellose 2910	5
TOTAL	100
Coating	**% w/w**
morphine layered granules	50
Eudragit E-100	33
magnesium stearate	17
TOTAL	100

Example 50: Morphine sulphate tablets

Coated morphine granules are prepared as per the process described in Example 1 and Example 49 above. The coated granules are subsequently mixed with other components (carbomer, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose), and blended in a V-blender for 30 minutes. Magnesium stearate is added to lubricate the blend and blended for additional 5 minutes prior to compressing into tablets.

Table 83: Morphine sulphate tablet compositions

Components (mg/tablet)	6 mg	15 mg	30 mg
hypromellose	30.6	76.6	153.3
glyceryl behenate	13.1	32.8	65.7
ethyl cellulose	7.2	18.1	36.1
morphine sulphate	6	15	30
Hypromellose 2910	3	7.5	15
Eudragit E-100	40.02	100.1	200.1
mannitol	70	70	70
carbopol	45	50	50
microcrystalline cellulose	95	130	94
crospovidone	100	150	200
sodium bicarbonate	27	30	30
magnesium stearate	24.5	57	110
Total Tablet Weight	461.42	737.1	1054.2

Example 51: Coated mixed amphetamine salts granules

Coated granules containing mixed amphetamine salts (dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate, amphetamine sulfate) are prepared as per the process described in Example 1.

Table 84: Mixed amphetamine salt granule formulation

Granulation	**% w/w**
hypromellose	60
glyceryl behenate	26
ethyl cellulose	14
TOTAL	100
Layering	**% w/w**
Mixed amphetamine salts (*Dextroamphetamine saccharate, amphetamine aspartate)	10
polymer granules (EC, HPMC and Compritol)	85
Hypromellose 2910	5
TOTAL	100
Coating	**% w/w**
mixed amphetamine salt layered granules	50
Eudragit E-100	33
magnesium stearate	17
TOTAL	100

Example 52: Mixed amphetamine salt tablets

Coated granules containing mixed amphetamine salts are prepared as per the process described in Example 1 and Example 51 above. The coated granules are subsequently mixed with other components such as carbomer, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose and blended in a V-blender for 30 minutes. Magnesium stearate is added to lubricate the blend and blended for additional 5 minutes prior to compressing into tablets.

Table 85: Mixed amphetamine salt tablet formulation

Total Amphetamine/ Base Equivalence	3.13 mg 5 mg	4.7 mg 7.5 mg	6.3 mg 10 mg	7.8 mg 12.5 mg	9.4 mg 15 mg	12.6 mg 20 mg	18.8 mg 30 mg
Components (mg/tablet)							
hypromellose	25.5	38.3	51.1	63.8	76.6	102.15	153.3
glyceryl behenate	10.9	16.4	21.9	27.4	32.8	43.8	65.7
ethyl cellulose	6.02	9.03	12.04	15.05	18.1	24.1	36.1
Mixed amphetamine salts*	5	7.5	10	12.5	15	20	30
Hypromellose 2910	2.5	3.75	5	6.25	7.5	10	15
Eudragit E-100	33.4	50.04	66.7	83.4	100.1	133.4	200.1
mannitol	70	70	70	70	70	70	70
carbopol	45	45	45	50	50	50	50
microcrystalline cellulose	95	95	95	130	130	130	150
crospovidone	100	100	100	150	150	160	200
sodium bicarbonate	27	27	27	30	30	30	30
magnesium stearate	21.5	30	38.6	48	57	75	110
Total Tablet Weight	441.82	492.02	542.34	686.4	737.1	848.45	1110.2
*dextroamphetamine saccharate, amphetamine aspartate monohydrate equivalent, dextroamphetamine sulfate, amphetamine sulfate.							

Example 53: Codeine phosphate granules

Coated granules containing Codeine phosphate are prepared as per the process described in Example 1 with some modifications to the composition as described below.

Table 86: Codeine phosphate granule formulation

Granulation	**% w/w**
Hypromellose	60
glyceryl behenate	26
ethyl cellulose	14
TOTAL	100
Layering	**% w/w**
codeine phosphate.	20
polymer Granules (EC, HPMC and Compritol)	70
Hypromellose 2910	10
TOTAL	100
Coating	**% w/w**
codeine phosphate layered granules	70
Eudragit E-100	20
magnesium stearate	10
TOTAL	100

Example 54: Codeine phosphate tablets

Coated granules containing codeine phosphate are prepared as per the process described in Example 1 and Example 53 above. The coated granules are subsequently mixed with other active ingredient (paracetamol), and other components (carbomer, crospovidone, sodium bicarbonate, mannitol, colorant, microcrystalline cellulose), and blended in a V-blender for 30 minutes. Magnesium stearate is added to lubricate the blend and blended for additional 5 minutes prior to compressing into tablets.

Table 87: Codeine phosphate/APAP tablet formulation

Components (mg/tablet)	30/300 mg	60/300 mg
hypromellose	63.1	126.2
glyceryl behenate	27	54.1
ethyl cellulose	14.9	29.7
codeine phosphate	30	60
Hypromellose 2910	15	30
Eudragit E-100	42.9	85.7
paracetamol*	315.8	315.8
mannitol	29.4	29.4
carbopol	50	50
microcrystalline cellulose	180	180
crospovidone	200	200
sodium bicarbonate	30	30
FD&C blue # 2	NA	0.6
Iron Oxide Yellow 510P	0.5	NA
magnesium stearate	31.5	57
Total Tablet Weight	1030.1	1248.5
*The paracetamol grade Contains 300 mg of APAP and 15.8		

Example 55: Methylphenidate hydrochloride granules

Coated granules containing methylphenidate hydrochloride are prepared as per the process described in Example 1.

Table 88: Methylphenidate hydrochloride granule formulation

Granulation	% w/w
hypromellose	60
glyceryl behenate	26
ethyl cellulose	14
TOTAL	100

Layering	**% w/w**
methylphenidate hydrochloride	10
polymer granules (EC, HPMC and Compritol)	85
Hypromellose 2910	5
TOTAL	100
Coating	**% w/w**
methylphenidate hydrochloride layered granules	50
Eudragit E-100	33
magnesium stearate	17
TOTAL	100

Example 56: Methylphenidate hydrochloride tablets

Coated granules containing methylphenidate hydrochloride are prepared as per the process described in Example 1 and Example 55 above. The coated granules are subsequently mixed with other components (carbomer, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose), and blended in a V-blender for 30 minutes. Magnesium stearate is added to lubricate the blend and blended for additional 5 minutes prior to compressing into tablets.

Table 89: Methylphenidate hydrochloride tablet formulation

Components (mg/tablet)	**5 mg**	**20 mg**
hypromellose	25.5	102.15
glyceryl behenate	10.9	43.8
ethyl cellulose	6.02	24.1
methylphenidate hydrochloride	5	20
Hypromellose 2910	2.5	10
Eudragit E-100	33.4	133.4
mannitol	70	70
carbopol	45	50
microcrystalline cellulose	95	150
crospovidone	100	160
sodium bicarbonate	27	30
magnesium stearate	21.5	75
Total Tablet Weight	441.82	868.45

Example 57: Oxycodone hydrochloride granules

Coated granules containing oxycodone hydrochloride were prepared and coated as per the process described in Example 1.

Table 90: Oxycodone hydrochloride granule formulation

Granulation	**% w/w**
Hypromellose	60
glyceryl behenate	26
ethyl cellulose	14
TOTAL	100
Layering	**% w/w**
oxycodone hydrochloride	10
polymer granules (EC, HPMC and Compritol)	85
Hypromellose 2910	5
TOTAL	100
Coating	**% w/w**
oxycodone layered granules, 10%	50
Eudragit E-100	33
magnesium stearate	17
TOTAL	100

Granules were manufactured in a high shear granulator where Hypromellose and glyceryl behenate were dry mixed for 3 minutes. Then a 10% hydroalcoholic solution of ethylcellulose N10 was slowly added while maintaining the granulator impeller and chopper speed at pre-selected values that provide enough shear for granule formation and growth. Solution addition was continued until the entire amount of ethylcellulose was added. The granules were then wet milled using a size reduction mill (Granumill) and were subsequently loaded into fluid bed for drying. The prepared granules were then layered in a bottom spray fluid bed coater with a 12% aqueous solution of oxycodone hydrochloride and HPMC 2910 (2:1).

The oxycodone hydrochloride layered granules were then coated in a bottom spray fluid bed coater with 25 % alcoholic suspension of Eudragit E-100 copolymer and

magnesium stearate (2:1). The resulting coated granules were subsequently used for further blending and compression process.

Example 58: Oxycodone / acetaminophen tablets

The coated granules prepared according to the example 57 above were mixed with another active agent, Paracetamol, and other excipients (carbomer, crospovidone, sodium bicarbonate, mannitol, FD&C blue, microcrystalline cellulose), and blended in a V-blender for 30 minutes. Magnesium stearate was then added to lubricate the blend and blended for additional 5 minutes prior to compressing into oxycodone/APAP tablets.

Table 91: Oxycodone hydrochloride tablet formulation

Component	**% w/w**
oxycodone coated granules	20.0
paracetamol*	33.7
mannitol	4.2
carbopol	5.0
microcrystalline cellulose	13.0
crospovidone	20.0
sodium bicarbonate	3.0
FD&C blue	0.06
magnesium stearate	1.0
Total	**100**
*Contains 95% acetaminophen and 5% gelatin	

Example 59: Oxycodone / acetaminophen tablets

The coated granules prepared according to the example 57 above were mixed with another active agent, Paracetamol, and other excipients (carbomer, crospovidone, sodium bicarbonate, mannitol, FD&C blue, microcrystalline cellulose), and blended in a V-blender for 30 minutes. Magnesium stearate was then added to lubricate the blend and blended for additional 5 minutes prior to compressing into oxycodone/APAP tablets.

Table 92: Oxycodone / acetaminophen tablet formulations

Component (% w/w)	**5/325 mg**	**7.5/325 mg**	**10/325 mg**
oxycodone coated granules	12.5	16.7	20.0
paracetamol*	42.8	38.0	34.2
mannitol	3.7	4.37	3.79
carbopol	6.25	5.6	5
microcrystalline cellulose	12	12	13
crospovidone	18	19	20
sodium bicarbonate	3.75	3.3	3
Iron Oxide yellow	0.06	NA	NA
FD&C Blue # 2	NA	0.06	NA
magnesium stearate	1.0	1.0	1.0
Total	**100**	**100**	**100**
*Contains 95% acetaminophen and 5% gelatin			

Example 60: Armodafinil granules

Armodafinil granules are manufactured using a process similar to that described in Example 1 and with some modification to the process. The active ingredient, Armodafinil, instead of being layered on the granules, resides in the core where it is granulated along with other excipients as per Table 93, and is subsequently coated with Eudragit E-100.

Granules are manufactured in a high shear granulator where hypromellose, Armodafinil, povidone and glyceryl behenate are dry mixed for 3 minutes. Then a 10% hydroalcoholic solution of ethylcellulose is slowly added while maintaining the granulator impeller and chopper speed at pre-selected values that provide enough shear for granule formation and growth. Solution addition is continued until the entire amount of ethylcellulose is added. The granules are then wet milled using a size reduction mill (Granumill) and subsequently loaded into fluid bed for drying.

Armodafinil granules are then coated in a bottom spray fluid bed coater with alcoholic suspension of Eudragit E-100 copolymer and magnesium stearate. The resultant coated granules are subsequently used for blending and compression process.

Table 93: Armodafinil granule formulations

Granulation	**% w/w**
armodafinil	66.99
hypromellose	16.75
glyceryl behenate	3.83
ethyl cellulose	3.83
povidone	8.61
TOTAL	100
Coating	**% w/w**
armodafinil granules	70
Eudragit E-100	20
magnesium stearate	10
TOTAL	100

Example 61: Armodafinil tablets

The coated granules prepared as per Example 60 above are subsequently mixed with other components (carbomer, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose), and blended in a V-blender for 30 minutes. Magnesium stearate is added to lubricate the blend and blended for additional 5 minutes prior to compressing into tablets.

Table 94: Armodafinil tablet formulations

Components (mg/tablet)	50 mg (mg/tablet)	150 mg (mg/tablet)	200 mg (mg/tablet)
hypromellose	12.5	37.5	50
glyceryl behenate	2.9	8.6	11
ethyl cellulose	2.9	8.6	11
armodafinil	50	150	200
Eudragit E-100	21.3	64	85
mannitol	17	25	25
carbopol	50	50	50
microcrystalline cellulose	100	125	125
crospovidone	150	200	200
sodium bicarbonate	30	30	30
magnesium stearate	16	40	52
povidone	6.4	19.3	26
Total Tablet Weight	459	758	865

Example 62: Phenobarbital granules

Phenobarbital granules are manufactured using a process similar to that described in Example 1 and with some modification to the process. The active ingredient, Phenobarbital, instead of being layered on the granules, resides in the core where it is granulated along with other excipients per the Table below, and is subsequently coated with Eudragit E-100.

Granules are manufactured in a high shear granulator where hypromellose, phenobarbital, povidone and glyceryl behenate are dry mixed for 3 minutes. Then a 10% hydroalcoholic solution of ethylcellulose is slowly added while maintaining the granulator impeller and chopper speed at pre-selected values that provide enough shear for granule formation and growth. Solution addition is continued until the entire amount of ethylcellulose is added. The granules are then wet milled using a size reduction mill (Granumill) and subsequently loaded into fluid bed for drying.

The phenobarbital granules are then coated in a bottom spray fluid bed coater with alcoholic suspension of Eudragit E-100 copolymer and magnesium stearate. The resultant coated granules are subsequently used for blending and compression process.

Table 95: Phenobarbital granule formulations

Granulation	**% w/w**
phenobarbital	66.99
hypromellose	16.75
glyceryl behenate	3.83
ethyl cellulose	3.83
povidone	8.61
TOTAL	100
Layering	**% w/w**
phenobarbital granules	50
Eudragit E-100	33
magnesium stearate	17
TOTAL	100

Example 63: Phenobarbital tablets

The coated granules prepared as per Example 62 above are subsequently mixed with other components (carbomer, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose), and blended in a V-blender for 30 minutes. Magnesium stearate is added to lubricate the blend and blended for additional 5 minutes prior to compressing into tablets.

Table 96: Phenobarbital tablet formulations

Components	15 mg (mg/tablet)	30 mg (mg/tablet)	60 mg (mg/tablet)	100 mg (mg/tablet)
hypromellose	3.8	7.5	15	25.01
glyceryl behenate	1	2	3.4	5.72
ethyl cellulose	1	2	3.4	5.72
phenobarbital	15	30	60	100
Eudragit E-100	15	30	59	98.5
mannitol	20	20	20	20
carbopol	50	50	50	50
microcrystalline cellulose	75	100	100	100
crospovidone	130	130	200	200
sodium bicarbonate	30	30	30	30
magnesium stearate	12	20	36	59
povidone	2	4	7.7	12.9
Total Tablet Weight	354.8	425.5	584.5	706.85

Example 64: Diazepam granules

Coated diazepam granules are prepared as per the process described in Example 1 with slight variation from Example 1 in components as illustrated in the Table below.

Table 97: Diazepam granule formulations

Granulation	**% w/w**
hypromellose	60
glyceryl behenate	26
ethyl cellulose	14
TOTAL	100
Layering	**% w/w**
diazepam	5
polymer granules (EC, HPMC and Compritol)	92.5
Hypromellose 2910	2.5
TOTAL	100
Coating	**% w/w**
diazepam layered granules	50
Eudragit E-100	33
magnesium stearate	17
TOTAL	100

Example 65: Diazepam tablets

Coated diazepam granules are prepared as per the process described in Example 1 and Example 64 above. The coated granules are subsequently mixed with other components (carbomer, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose), and blended in a V-blender for 30 minutes. Magnesium stearate is added to lubricate the blend and blended for additional 5 minutes prior to compressing into tablets.

Table 98: Diazepam tablet formulations

Components (mg/tablet)	**2 mg**	**5 mg**	**10 mg**
hypromellose	22.2	55.6	111.2
glyceryl behenate	9.5	23.8	47.64
ethyl cellulose	5.2	13.1	26.2
diazepam	2	5	10
Hypromellose 2910	1	2.5	5
Eudragit E-100	26.7	66.7	133.4
mannitol	70	70	70
carbopol	50	50	50
microcrystalline cellulose	95	95	94
crospovidone	120	120	150
sodium bicarbonate	30	30	30
magnesium stearate	18.1	38.6	74.6
Total Tablet Weight	449.7	570.3	802.04

Example 66: Hydrocodone bitartrate granules

Coated granules containing hydrocodone bitartrate are prepared as per the process described in Example 1.

Table 99: Hydrocodone bitartrate granule formulations

Granulation	**% w/w**
Hypromellose	60
glyceryl behenate	26
ethyl cellulose	14
TOTAL	100
Layering	**% w/w**
hydrocodone bitartrate	10
polymer granules (EC, HPMC and Compritol)	85
Hypromellose 2910	5
TOTAL	100
Coating	**% w/w**
hydrocodone bitartrate layered granules	50
Eudragit E-100	33
magnesium stearate	17
TOTAL	100

Example 67: Hydrocodone bitartrate tablets

Coated granules containing hydrocodone bitartrate are prepared as per the process described in Example 1 and Example 66 above. The coated granules are subsequently mixed with other components (carbomer, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose) and blended in a V-blender for 30 minutes. Magnesium stearate is added to lubricate the blend and blended for additional 5 minutes prior to compressing into tablets.

Table 100: Hydrocodone Tablet Formulations

Components	5 mg (mg/tablet)	10 mg (mg/tablet)
hypromellose	25.5	51.1
glyceryl behenate	11	21.9
ethyl cellulose	6	12.04
hydrocodone bitartrate	5	10
Hypromellose 2910	2.5	5
Eudragit E-100	33.4	66.7
mannitol	70	70
carbopol	50	50
microcrystalline cellulose	95	95
crospovidone	100	120
sodium bicarbonate	30	30
magnesium stearate	21.6	39.3
Total Tablet Weight	450	571.04

Example 68: Oxycodone hydrochloride Coated Granules

Table 201: Granule Formulation

Component	% w/w
Hypromellose K100M	60
glyceryl behenate	26
ethyl cellulose (10 cP)	14
TOTAL	100

Table 102: Layered Granule Formulation

Component	% w/w
oxycodone hydrochloride	10
polymer granules (EC, HPMC and Compritol)	85
Hypromellose 2910 E3	5
TOTAL	100

Table 103: Coated Granules Formulation

Component	**% w/w**
oxycodone hydrochloride layered granules, 10%	50
Eudragit E-100	33
magnesium stearate	17
TOTAL	100

Granules were manufactured in a high shear granulator, where hypromellose, glyceryl behenate, and a portion (67%) of the ethylcellulose were dry mixed for 3 minutes. Then, a hydroalcoholic (~28 parts of water and ~72 parts of alcohol) solution of ethylcellulose (10% wt/wt) was slowly added while maintaining the granulator impeller and chopper speed at pre-selected values that provide enough shear for granule formation and growth. Solution addition was continued until the entire amount of ethylcellulose was added. The granules were then wet milled using a size reduction mill (Granumill) and were subsequently loaded into fluid bed for drying.

The prepared granules were then layered in a bottom spray fluid bed coater with a 12% wt/wt aqueous solution of oxycodone hydrochloride and HPMC.

The oxycodone bitartrate layered granules were then coated in a bottom spray fluid bed coater with 25 % alcoholic suspension of Eudragit E-100 copolymer and magnesium stearate. The resulting coated granules were subsequently blended for homogeneity and used for further blending and compression process.

Example 69: Oxycodone Acetaminophen Tablet Formation

Coated granules were prepared according to the Example 68 above, and mixed with Paracetamol (manufactured using acetaminophen and gelatin) and other excipients (as listed in Table 104 below), and blended for approximately 270 revolutions. Magnesium stearate was then added to lubricate the blend and blended for additional 45 revolutions. The blend was then compressed into oxycodone/acetaminophen tablets.

Table 104: Tablet Formulation

Component	**% w/w**	**mg/tablet**
Oxycodone hydrochloride coated granules, 5%	20.0	200
paracetamol	33.7	337*
mannitol	10.3	103
Carbopol	5.0	50
microcrystalline cellulose	12.0	120
Crospovidone	15.0	150
sodium bicarbonate	3.0	30
magnesium stearate	1.0	10
Total	**100**	**1000**

*contains 325 mg of acetaminophen

Example 70: Coated Oxycodone Granules, 5%

Granules were prepared, layered with API and subsequently coated. These coated particles were then blended with other components and compressed into tablets.

Table 305: Granules Formulation

Component	**% w/w**
Hypromellose K100M	60
Glyceryl behenate	26
Ethyl cellulose (10 cP)	14
TOTAL	100

Table 106: Layered Granules Formulation

Component	**% w/w**
Oxycodone Hydrochloride	10
Polymer granules (EC, HPMC and Compritol)	85
Hypromellose 2910 (HPMC 2910 E3)	5
TOTAL	100

Table 107: Coated Granules Formulation

Component	**% w/w**
Oxycodone hydrochloride layered granules, 10%	50
Eudragit E-100	33
Magnesium stearate	17
TOTAL	100

Granules were manufactured in a high shear granulator, where hypromellose, a portion of ethyl cellulose and glyceryl behenate were dry mixed for 3 minutes. Then a 10% w/w hydroalcoholic (~28 parts of water and ~72 parts of ethanol) solution of ethyl cellulose 10 cP was slowly added while maintaining the granulator impeller and chopper speed at pre-selected values that provide enough shear for granule formation and growth. Solution addition was continued until the entire amount of ethyl cellulose was added. The granules were then wet milled using a size reduction mill (Granumill) and were subsequently loaded into fluid bed for drying.

The prepared granules were then layered in a bottom spray fluid bed coater with a 12% w/w aqueous solution of oxycodone hydrochloride and HPMC 2910 E3.

The oxycodone hydrochloride layered granules were then coated in a bottom spray fluid bed coater with 25 % alcoholic suspension of Eudragit E-100 copolymer and magnesium stearate. The resulting coated granules were subsequently blended for homogeneity and used for further blending and compression process.

Example 71: Coated polymer granules

Granules were manufactured in a high shear granulator, where hypromellose, a portion of ethyl cellulose and glyceryl behenate were dry mixed for 3 minutes. Then a 10% w/w hydroalcoholic (~28 parts of water and ~72 parts of ethanol) solution of ethyl cellulose 10 cP was slowly added while maintaining the granulator impeller and chopper speed at pre-selected values that provide enough shear for granule formation and growth. Solution addition was continued until the entire amount of ethyl cellulose was added. The granules were then wet milled using a size reduction mill (Granumill) and were subsequently loaded into fluid bed for drying.

The granules were then coated in a bottom spray fluid bed coater with 25 % alcoholic suspension of Eudragit E-100 copolymer and magnesium stearate.

Table 108: Granules Formulation

Component	**% w/w**
Hypromellose K100M	60
Glyceryl behenate	26
Ethyl cellulose (10 cP)	14
TOTAL	100

Table 109: Coated Polymer Granules Formulation

Component	**% w/w**
Polymer granules	50
Eudragit E-100	33
Magnesium stearate	17
TOTAL	100

Example 72A and Example 72B:

The oxycodone hydrochloride coated granules were prepared according to the Example 70 and mixed with coated polymer granules prepared according to Example 71. Another active agent i.e. Paracetamol (manufactured using acetaminophen and gelatin) and other excipients such as carbomer, crospovidone, sodium bicarbonate, mannitol and microcrystalline cellulose were added and blended for approximately 270 revolutions. Magnesium stearate was then added to lubricate the blend and blended for additional 45 revolutions prior to compressing into oxycodone/acetaminophen tablets.

Table 110: Tablet Formulation

Component	Example 72A		Example 72B	
	% w/w	mg/tablet	% w/w	mg/tablet
Oxycodone hydrochloride coated granules, 5%	10.87	108.7	16.3	163
Coated Polymer granules	9.13	91.3	3.7	37
Paracetamol	33.7	337*	33.71	337.1*
Mannitol	4.29	42.9	4.29	42.9
Carbopol	5.0	50.0	5.0	50
Microcrystalline cellulose	13.0	130.0	13.0	130
Crospovidone	20.0	200.	20.0	200
Sodium bicarbonate	3.0	30	3.0	30
Magnesium stearate	1.0	10	1.0	10
Total	100	1000	100	1000

*contains 325 mg of acetaminophen

Example 73: *In vitro* Analysis of multiple tablet oral abuse resistance

The dosage form prepared according to Example 72A and Example 72B was evaluated for *in vitro* multiple tablet oral abuse resistance by stirring the selected number of tablets in 300 mL of 0.1N HCl. Dissolution was performed using USP apparatus II at 50 RPM and 37 °C. One to twelve tablets were added to the vessel simultaneously and aliquots were removed periodically and analyzed for oxycodone hydrochloride (Figure 10) and Acetaminophen (APAP) [Figure 11] by HPLC. The results were plotted against time and appear in Figure 10 and Figure 11.

Example 74: Polymer Granules

Table 111: Granules Formulation

Component	**% w/w**
Hypromellose K100M	60
Glyceryl behenate	26
Ethyl cellulose (10 cP)	14
TOTAL	100

Granules were manufactured in a high shear granulator, where hypromellose, a portion of ethyl cellulose and glyceryl behenate were dry mixed for 3 minutes. Then a

10% w/w hydroalcoholic (~28 parts of water and ~72 parts of ethanol) solution of ethyl cellulose 10 cP was slowly added while maintaining the granulator impeller and chopper speed at pre-selected values that provide enough shear for granule formation and growth. Solution addition was continued until the entire amount of ethyl cellulose was added. The granules were then wet milled using a size reduction mill (Granumill) and were subsequently loaded into fluid bed for drying.

Example 75: Hydrocodone bitartrate Coated Granules, 5%

The granules prepared according to Example 74 were then layered in a bottom spray fluid bed coater with a 12% w/w aqueous solution of hydrocodone bitartate and HPMC 2910 E3. The hydrocodone bitartrate layered granules were then coated in a bottom spray fluid bed coater with 25 % alcoholic suspension of Eudragit E-100 copolymer and magnesium stearate.

Table 112: Layered Granules Formulation

Component	**% w/w**
Hydrocodone bitartrate	10
Polymer granules (EC, HPMC and Compritol)	85
Hypromellose 2910	5
TOTAL	100

Table 113: Coated Granules Formulation

Component	**% w/w**
Hydrocodone bitartrate layered granules, 10%	50
Eudragit E-100	33
Magnesium stearate	17
TOTAL	100

Example 76: Hydrocodone bitartrate tablets

The hydrocodone bitartrate coated granules were prepared according to the Example 75 above and mixed with polymer granules prepared according to Example 74. Another active agent i.e. Paracetamol (manufactured using acetaminophen and gelatin) and other excipients such as carbomer, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose were added and blended for approximately 270 revolutions.

Magnesium stearate was then added to lubricate the blend and blended for additional 45 revolutions prior to compressing into hydrocodone/acetaminophen tablets.

Table 114: Tablet Formulation

Component	**% w/w**	**mg/tablet**
Hydrocodone bitartrate coated granules, 5%	9.62	96.2
Polymer granules	5.38	53.8
Paracetamol	33.71	337.1*
Mannitol	9.29	92.9
Carbopol	5.0	50
Microcrystalline cellulose	13.0	130
Crospovidone	20.0	200
Sodium bicarbonate	3.0	30
Magnesium stearate	1.0	10
Total	**100**	1000

*contains 325 mg of acetaminophen

Example 77A and Example 77B: Hydrocodone bitartrate tablets

The hydrocodone bitartrate coated granules, 5% were prepared according to the Example 75 above and mixed with coated polymer granules prepared according to Example 71. Another active agent i.e. Paracetamol (manufactured using acetaminophen and gelatin) and other excipients such as carbomer, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose were added to the blender and blended for approximately 270 revolutions. Magnesium stearate was then added to lubricate the blend and blended for additional 45 revolutions prior to compressing into hydrocodone/ acetaminophen tablets.

Table 115: Tablet Formulation

Component	Example 77A		Example 77B	
	% w/w	mg/tab	% w/w	mg/tab
Hydrocodone bitartrate coated granules, 5%	9.62	96.2	14.42	96.2
Coated Polymer granules	10.38	103.8	5.58	103.8
Paracetamol	33.71	337.1*	33.71	337.1*
Mannitol	4.29	42.9	4.29	42.9
Carbopol	5.0	50	5.0	50
Microcrystalline cellulose	13.0	130	13.0	130
Crospovidone	20.0	200	20.0	200
Sodium bicarbonate	3.0	30	3.0	30
Magnesium stearate	1.0	10	1.0	10
Total	**100**	**1000**	**100**	**1000**

*contains 325 mg of acetaminophen

Example 78: *In vitro* Analysis of multiple tablet oral abuse resistance

The dosage form prepared according to Example 76 and Example 77A and Example 77B was evaluated for *in vitro* multiple tablet oral abuse resistance by stirring the selected number of tablets in 300 mL of 0.1N HCl. Dissolution was performed using USP apparatus II at 50 RPM and 37 °C. One to twelve tablets were added to the vessel simultaneously and aliquots were removed periodically and analyzed for hydrocodone bitartrate (Figure 12) and APAP (Figure 13) by HPLC. The results were plotted against time and appear in Figure 12 and Figure 13.

Example 79: Coated Oxycodone Granules, 5%

Granules are prepared and subsequently coated. These coated particles are then blended with other components and compressed into tablets.

Table 116: Granules Formulation

Component	% w/w
Hypromellose K100M	54
Glyceryl behenate	23
Ethyl cellulose (10 cP)	13
Oxycodone Hydrochloride	10
TOTAL	100

Table 117: Coated Granules Formulation

Component	**% w/w**
Oxycodone hydrochloride granules, 10%	50
Eudragit E-100	33
Magnesium stearate	17
TOTAL	100

Granules are manufactured in a high shear granulator, where oxycodone hydrochloride, hypromellose, a portion of ethyl cellulose and glyceryl behenate is dry mixed for 3 minutes. Then a hydroalcoholic solution of ethyl cellulose 10 cP is slowly added while maintaining the granulator impeller and chopper speed at pre-selected values that provide enough shear for granule formation and growth. Solution addition is continued until the entire amount of ethyl cellulose is added. The granules are then wet milled using a size reduction mill (Granumill) and subsequently loaded into fluid bed for drying. The oxycodone hydrochloride granules are then coated in a bottom spray fluid bed coater with 25 % alcoholic suspension of Eudragit E-100 copolymer and magnesium stearate.

Example 80: Oxycodone/acetaminophen tablets

The oxycodone hydrochloride coated granules, 5% are prepared according to the Example 79 above and mixed with another active agent i.e. Paracetamol (manufactured using acetaminophen and gelatin) and other excipients such as carbomer, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose and blended for approximately 270 revolutions. Magnesium stearate is then added to lubricate the blend and blended for additional 45 revolutions prior to compressing into oxycodone/acetaminophen tablets.

Table 118: Tablet Formulation

Component	**% w/w**	**mg/tablet**
Oxycodone hydrochloride coated granules, 5%	20	200
Paracetamol	34.2	342*
Mannitol	3.8	38
Carbopol	5.0	50
Microcrystalline cellulose	13.0	130
Crospovidone	20.0	200
Sodium bicarbonate	3.0	30
Magnesium stearate	1.0	10
Total	**100**	**1000**

*contains 325 mg of acetaminophen

Example 81: Coated Oxycodone Granules

Oxycodone hydrochloride granules are prepared and subsequently coated. These coated particles are then blended with other components and compressed into tablets.

Table 119: Granules Formulation

Component	**% w/w**
Hypromellose K100M	56
Glyceryl behenate	25
Ethyl cellulose (10 cP)	14
Oxycodone Hydrochloride	5
TOTAL	100

Table 120: Coated Granules Formulation

Component	**% w/w**
Oxycodone hydrochloride granules, 5%	50
Eudragit E-100	33
Magnesium stearate	17
TOTAL	100

Granules are manufactured in a high shear granulator, where oxycodone hydrochloride, hypromellose, a portion of ethyl cellulose and glyceryl behenate is dry mixed for 3 minutes. Then a hydroalcoholic solution of ethyl cellulose 10 cP is slowly added while maintaining the granulator impeller and chopper speed at pre-selected values that provide enough shear for granule formation and growth. Solution addition is continued until the entire amount of ethyl cellulose is added. The granules are then wet milled using a size reduction mill (Granumill) and subsequently loaded into fluid bed for drying. The oxycodone hydrochloride granules are then coated in a bottom spray fluid bed coater with 25 % alcoholic suspension of Eudragit E-100 copolymer and magnesium stearate.

Example 82: Oxycodone/acetaminophen tablets

The oxycodone hydrochloride coated granules, 2.5% are prepared according to the Example 81 above and mixed with another active agent i.e. Paracetamol (manufactured using acetaminophen and gelatin) and other excipients such as carbomer, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose and blended for approximately 270 revolutions. Magnesium stearate is then added to lubricate the blend and blended for additional 45 revolutions prior to compressing into oxycodone/acetaminophen tablets.

Table 121: Tablet Formulation

Component	**% w/w**	**mg/tablet**
Oxycodone hydrochloride coated granules, 2.5%	20	200
Paracetamol	34.2	342
Mannitol	3.8	38
Carbopol	5.0	50
Microcrystalline cellulose	13.0	130
Crospovidone	20.0	200
Sodium bicarbonate	3.0	30
Magnesium stearate	1.0	10
Total	**100**	**1000**

*contains 325 mg of acetaminophen

Example 83: Coated Oxycodone Granules

Oxycodone hydrochloride granules are prepared and subsequently coated. These coated particles are then blended with other components and compressed into tablets.

Table 122: Granules Formulation

Component	**% w/w**
Hypromellose K100M	54.5
Glyceryl behenate	24
Ethyl cellulose (10 cP)	14
Oxycodone Hydrochloride	7.5
TOTAL	100

Table 123: Coated Granules Formulation

Component	**% w/w**
Oxycodone hydrochloride granules, 7.5%	50
Eudragit E-100	33
Magnesium stearate	17
TOTAL	100

Granules are manufactured in a high shear granulator, where oxycodone hydrochloride, hypromellose, a portion of ethyl cellulose and glyceryl behenate is dry mixed for 3 minutes. Then a hydroalcoholic solution of ethyl cellulose 10 cP is slowly added while maintaining the granulator impeller and chopper speed at pre-selected values that provide enough shear for granule formation and growth. Solution addition is continued until the entire amount of ethyl cellulose is added. The granules are then wet milled using a size reduction mill (Granumill) and subsequently loaded into fluid bed for drying. The oxycodone hydrochloride granules are then coated in a bottom spray fluid bed coater with 25 % alcoholic suspension of Eudragit E-100 copolymer and magnesium stearate.

Example 84: Oxycodone/acetaminophen tablets

The oxycodone hydrochloride coated granules, 3.75% are prepared according to the Example 83 above and mixed with another active agent i.e. Paracetamol (manufactured using acetaminophen and gelatin) and other excipients such as carbomer, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose and blended for approximately 270 revolutions. Magnesium stearate is then added to lubricate the blend and blended for additional 45 revolutions prior to compressing into oxycodone/acetaminophen tablets.

Table 124: Tablet Formulation

Component	**% w/w**	**mg/tablet**
Oxycodone hydrochloride coated granules, 3.75%	20	200
Paracetamol	34.2	342*
Mannitol	3.8	38
Carbopol	5.0	50
Microcrystalline cellulose	13.0	130
Crospovidone	20.0	200
Sodium bicarbonate	3.0	30
Magnesium stearate	1.0	10
Total	**100**	1000

*contains 325 mg of acetaminophen

Example 85: Coated Oxycodone hydrochloride Granules

Oxycodone hydrochloride granules are prepared and subsequently coated. These coated particles are then blended with other components and compressed into tablets.

Table 125: Granules Formulation

Component	**% w/w**
Hypromellose K100M	54
Glyceryl behenate	23
Ethyl cellulose (10 cP)	13
Oxycodone Hydrochloride	10
TOTAL	100

Table 126: Coated Granules Formulation

Component	**% w/w**
Oxycodone hydrochloride granules, 10%	40
Eudragit E-100	40
Magnesium stearate	20
TOTAL	100

Granules are manufactured in a high shear granulator, where oxycodone hydrochloride, hypromellose, a portion of ethylcellulose and glyceryl behenate is dry mixed for 3 minutes. Then a hydroalcoholic solution of ethyl cellulose 10 cP is slowly added while maintaining the granulator impeller and chopper speed at pre-selected values that provide enough shear for granule formation and growth. Solution addition is continued until the entire amount of ethyl cellulose is added. The granules are then wet milled using a size reduction mill (Granumill) and subsequently loaded into fluid bed for drying. The oxycodone hydrochloride granules are then coated in a bottom spray fluid bed coater with 25 % alcoholic suspension of Eudragit E-100 copolymer and magnesium stearate.

Example 86: Oxycodone/acetaminophen tablets

The oxycodone hydrochloride coated granules, 4% are prepared according to Example 85 above and mixed with another active agent i.e. Paracetamol (manufactured using acetaminophen and gelatin) and other excipients such as carbomer, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose and blended for approximately 270 revolutions. Magnesium stearate is then added to lubricate the blend and blended for additional 45 revolutions prior to compressing into oxycodone/acetaminophen tablets.

Table 127: Tablet Formulation

Component	**% w/w**	**mg/tablets**
Oxycodone hydrochloride coated granules, 4%	18.8	188
Paracetamol	34.2	342*
Mannitol	5	50
Carbopol	5.0	50
Microcrystalline cellulose	13.0	130
Crospovidone	20.0	200
Sodium bicarbonate	3.0	30
Magnesium stearate	1.0	10
Total	**100**	1000

*contains 325 mg of acetaminophen

Example 87: Coated Oxycodone Granules

Oxycodone granules are prepared, and subsequently coated. These coated particles are then blended with other components and compressed into tablets.

Table 128: Granules Formulation

Component	**% w/w**
Hypromellose K100M	54
Glyceryl behenate	23
Ethyl cellulose (10 cP)	13
Oxycodone Hydrochloride	10
TOTAL	100

Table 129: Coated Granules Formulation

Component	**% w/w**
Oxycodone hydrochloride granules, 10%	30
Eudragit E-100	47
Magnesium stearate	23
TOTAL	100

Granules are manufactured in a high shear granulator, where oxycodone hydrochloride, hypromellose, a portion of ethyl cellulose and glyceryl behenate is dry mixed for 3 minutes. Then a hydroalcoholic solution of ethyl cellulose 10 cP is slowly added while maintaining the granulator impeller and chopper speed at pre-selected values that provide enough shear for granule formation and growth. Solution addition is continued until the entire amount of ethyl cellulose is added. The granules are then wet milled using a size reduction mill (Granumill) and subsequently loaded into fluid bed for drying. The oxycodone hydrochloride granules are then coated in a bottom spray fluid bed coater with 25 % alcoholic suspension of Eudragit E-100 copolymer and magnesium stearate.

Example 88: Oxycodone/acetaminophen tablets

The oxycodone hydrochloride coated granules (3%) are prepared according to Example 87 above and mixed with another active agent i.e. Paracetamol (manufactured using acetaminophen and gelatin) and other excipients such as carbomer, crospovidone,

sodium bicarbonate, mannitol, microcrystalline cellulose and blended for approximately 270 revolutions. Magnesium stearate is then added to lubricate the blend and blended for additional 45 revolutions prior to compressing into oxycodone/acetaminophen tablets.

Table 130: Tablet Formulation

Component	**% w/w**	mg/tablet
Oxycodone hydrochloride coated granules, 3%	16.7	167
Paracetamol	34.2	342*
Mannitol	7.1	71
Carbopol	5.0	50
Microcrystalline cellulose	13.0	130
Crospovidone	20.0	200
Sodium bicarbonate	3.0	30
Magnesium stearate	1.0	10
Total	**100**	**1000**

*contains 325 mg of acetaminophen

Example 89: Coated Oxycodone Granules

Oxycodone granules are prepared and subsequently coated. These coated particles are then blended with other components and compressed into tablets.

Table 131: Granules Formulation

Component	**% w/w**
Hypromellose K100M	56
Glyceryl behenate	25
Ethyl cellulose (10 cP)	14
Oxycodone Hydrochloride	5
TOTAL	100

Table 132: Coated Granules Formulation

Component	**% w/w**
Oxycodone hydrochloride granules, 5%	70
Eudragit E-100	20
Magnesium stearate	10
TOTAL	100

Granules are manufactured in a high shear granulator, where oxycodone hydrochloride, hypromellose, a portion of ethyl cellulose and glyceryl behenate is dry mixed for 3 minutes. Then a hydroalcoholic solution of ethyl cellulose 10 cP is slowly added while maintaining the granulator impeller and chopper speed at pre-selected values that provide enough shear for granule formation and growth. Solution addition is continued until the entire amount of ethyl cellulose is added. The granules are then wet milled using a size reduction mill (Granumill) and subsequently loaded into fluid bed for drying. The oxycodone hydrochloride granules are then coated in a bottom spray fluid bed coater with 25 % alcoholic suspension of Eudragit E-100 copolymer and magnesium stearate.

Example 90: Oxycodone/acetaminophen tablets

The oxycodone hydrochloride coated granules, 3.5% are prepared according to the Example 89 above and mixed with another active agent i.e. Paracetamol (manufactured using acetaminophen and gelatin) and other excipients such as carbomer, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose and blended for approximately 270 revolutions. Magnesium stearate is then added to lubricate the blend and blended for additional 45 revolutions prior to compressing into oxycodone/acetaminophen tablets.

Table 133: Tablet Formulation

Component	**% w/w**	**mg/tab**
Oxycodone hydrochloride coated granules, 3.5%	21.4	214
Paracetamol	34.2	342*
Mannitol	2.4	24
Carbopol	5.0	50
Microcrystalline cellulose	13.0	130
Crospovidone	20.0	200
Sodium bicarbonate	3.0	30
Magnesium stearate	1.0	10
Total	**100**	**1000**

*contains 325 mg of acetaminophen

Example 91: Coated Oxycodone Granules

Oxycodone hydrochloride granules are prepared and subsequently coated. These coated particles are then blended with other components and compressed into tablets.

Table 134: Granules Formulation

Component	**% w/w**
Hypromellose K100M	54.5
Glyceryl behenate	24
Ethyl cellulose (10 cP)	14
Oxycodone Hydrochloride	7.5
TOTAL	100

Table 135: Coated Granules Formulation

Component	**% w/w**
Oxycodone hydrochloride granules, 7.5%	70
Eudragit E-100	20
Magnesium stearate	10
TOTAL	100

Granules are manufactured in a high shear granulator, where oxycodone hydrochloride, hypromellose, a portion of ethyl cellulose and glyceryl behenate is dry mixed for 3 minutes. Then a hydroalcoholic solution of ethyl cellulose 10 cP is slowly added while maintaining the granulator impeller and chopper speed at pre-selected values that provide

enough shear for granule formation and growth. Solution addition is continued until the entire amount of ethyl cellulose is added. The granules are then wet milled using a size reduction mill (Granumill) and subsequently loaded into fluid bed for drying. The oxycodone hydrochloride granules are then coated in a bottom spray fluid bed coater with 25 % alcoholic suspension of Eudragit E-100 copolymer and magnesium stearate.

Example 92: Oxycodone/acetaminophen tablets

The oxycodone hydrochloride coated granules, 5.25% are prepared according to the Example 91 above and mixed with another active agent i.e. Paracetamol (manufactured using acetaminophen and gelatin) and other excipients such as carbomer, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose and blended for approximately 270 revolutions. Magnesium stearate is then added to lubricate the blend and blended for additional 45 revolutions prior to compressing into oxycodone/ acetaminophen tablets.

Table 136: Tablet Formulation

Component	**% w/w**	**mg/tablet**
Oxycodone hydrochloride coated granules, 5.25%	19.05	190.5
Paracetamol	34.2	342*
Mannitol	4.75	47.5
Carbopol	5.0	50
Microcrystalline cellulose	13.0	130
Crospovidone	20.0	200
Sodium bicarbonate	3.0	30
Magnesium stearate	1.0	10
Total	**100**	**1000**

*contains 325 mg of acetaminophen

Example 93: Hydrocodone/acetaminophen tablets

The hydrocodone bitartrate coated granules were prepared according to the Example 75 and mixed with another active agent i.e. Paracetamol (manufactured using acetaminophen and gelatin) along with other excipients such as carbomer, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose (blended for approximately 270

revolutions). Magnesium stearate was then added to lubricate the blend and blended for additional 45 revolutions prior to compressing into hydrocodone/acetaminophen tablets.

Table 137: Tablet Formulation

Component	**% w/w**	**mg/tablet**
Hydrocodone bitartrate coated granules, 5%	20.0	200
Paracetamol	34.21	342.1*
Mannitol	3.73	37.3
Carbopol	5.0	50
Microcrystalline cellulose	13.0	130
Crospovidone	20.0	200
Sodium bicarbonate	3.0	30
Magnesium stearate	1.0	10
Iron Oxide Red	0.06	0.6
Total	**100**	**1000**

*contains 325 mg of acetaminophen

Example 94: *In vitro* Analysis of multiple tablet oral abuse resistance – Crushed and Intact Tablets

The dosage form (crushed or intact) prepared according to Example 93 was evaluated for *in vitro* multiple tablet oral abuse resistance by conducting dissolution experiments in 300 mL or 900 mL of 0.1N HCl. Dissolution was performed using USP apparatus II at 50 RPM and 37 °C. Twelve tablets (crushed or intact) were added to the vessel simultaneously or sequentially and aliquots were removed periodically and were analyzed for hydrocodone bitartrate and APAP by HPLC. Crushing of the tablets was carried out using a morter and pestle (twelve strokes). The results were plotted against time and appear in Figure 14 and Figure 15.

Example 95: Esketamine HCl Tablets

Coated granules prepared per Example 31 are subsequently mixed with coated polymer granules prepared according to Example 71, and other components (carbomer, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose) and blended for 270 revolutions. Magnesium stearate is added to lubricate the blend and the resulting mixture was blended for additional 45 revolutions prior to compressing into tablets.

Table 138: Tablet Formulation

Components	**mg/tablet**	**mg/tablet**	**mg/tablet**	**mg/tablet**
Esketamine hydrochloride coated granules, 28.7%	87.1	87.1	348.4	348.4
Coated polymer granules	50	31	50	31
Mannitol	37	37	37	37
Carbopol	50	50	50	50
Microcrystalline cellulose	130	130	130	130
Crospovidone	200	200	200	200
Sodium bicarbonate	30	30	30	30
Magnesium stearate	6	6	9	8.5
Total	**590.1**	**571.1**	**854.4**	**834.9**

Example 96: Esketamine HCl Tablets

Coated granules prepared per Example 31 are subsequently mixed with polymer granules prepared according to Example 74, and other components (carbomer, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose) and blended for 270 revolutions. Magnesium stearate is added to lubricate the blend and the resulting mixture was blended for additional 45 revolutions prior to compressing into tablets.

Table 139: Tablet Formulation

Components	**mg/tablet**	**mg/tablet**	**mg/tablet**	**mg/tablet**
Esketamine hydrochloride coated granules, 28.7%	87.1	87.1	348.4	348.4
Polymer granules	50	27	50	27
Mannitol	37	37	37	37
Carbopol	50	50	50	50
Microcrystalline cellulose	130	130	130	130
Crospovidone	200	200	200	200
Sodium bicarbonate	30	30	30	30
Magnesium stearate	6	6	9	8.5
Total	590.1	567.1	854.4	830.9

Example 97: Esketamine HCl Tablets

The coated granules prepared per Example 27 are subsequently mixed with coated polymer granules prepared according to Example 71 and other components (carbomer, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose) and blended for 270 revolutions. Magnesium stearate is added to lubricate the blend and the resulting mixture was blended for additional 45 revolutions prior to compressing into tablets.

Table 140: Esketamine hydrochloride tablet compositions

Components mg/tab	**1 mg**	**2 mg**
Esketamine hydrochloride coated granules, 2.5%	40	80
Coated polymer granules	160	120
mannitol	70	70
carbopol	50	50
microcrystalline cellulose	94	95
crospovidone	200	200
sodium bicarbonate	30	30
magnesium stearate	11	18
Total Tablet Weight	655	663

Example 98: Esketamine HCl Tablets

The coated granules prepared per Example 27 above are subsequently mixed with polymer granules prepared according to Example 74 and other components (carbomer, crospovidone, sodium bicarbonate, mannitol, microcrystalline cellulose) and blended for 270 revolutions. Magnesium stearate is added to lubricate the blend and the resulting mixture was blended for additional 45 revolutions prior to compressing into tablets.

Table 141: Esketamine hydrochloride tablet compositions

Components mg/tab	**1 mg**	**2 mg**
Esketamine hydrochloride coated granules, 2.5%	40	80
polymer granules	80	60
mannitol	70	70
carbopol	50	50
microcrystalline cellulose	94	95
crospovidone	150	150
sodium bicarbonate	30	30
magnesium stearate	11	18
Total Tablet Weight	525	553

Claims:

What is claimed is:

1. An immediate release abuse deterrent dosage form comprising:

a) core-shell particles, the core-shell particles comprising:

a core, the core comprising a gelling polymer, wherein the gelling polymer in the core is selected from a natural starch, a synthetic starch, a natural cellulose, a synthetic cellulose, an acrylate, a polyalkylene oxide, a carbomer and combinations thereof;

an active pharmaceutical layer surrounding the core, the active pharmaceutical layer comprising a narcotic analgesic;

at least one layer surrounding the active pharmaceutical layer, the at least one layer comprising a pH-sensitive film comprising pH-sensitive polymer that is insoluble in water at a pH greater than 5 and is soluble in water at a pH below 5; and

b) a matrix comprising a disintegrant and a gelling polymer; wherein the gelling polymer in the matrix is selected from a natural starch, a synthetic starch, a natural cellulose, a synthetic cellulose, an acrylate, a polyalkylene oxide, a carbomer, and combinations thereof.

2. The immediate release abuse deterrent dosage form according to claim 1, wherein less than 5 weight percent of the total amount of the narcotic analgesic in the core shell particles is contained in the core.

3. The immediate release abuse deterrent dosage form according to claim 1, wherein at least 90 percent of the total amount of the narcotic analgesic in the core shell particles is contained in the active pharmaceutical layer.

4. The immediate release abuse deterrent dosage form according to claim 1, further comprising a second type of core-shell particles that do not contain an active pharmaceutical layer, the second type of core-shell particles comprising:

a core, the core comprising a gelling polymer, wherein the gelling polymer in the core is selected from a natural starch, a synthetic starch, a natural cellulose, a synthetic cellulose, an acrylate, a polyalkylene oxide, a carbomer and combinations thereof; and

at least one layer surrounding the core, the at least one layer comprising a pH-sensitive film comprising pH-sensitive polymer that is insoluble at a pH greater than 5 and is soluble at a pH below 5.

5. The immediate release abuse deterrent dosage form according to claim 1, wherein the narcotic analgesic is an opioid.

6. The immediate release abuse deterrent dosage form according to claim 5, further comprising a nonsteroidal analgesic drug.

7. The immediate release abuse deterrent dosage form according to claim 5, wherein the opioid is selected from buprenorphine, codeine, dihydrocodeine, dihydromorphine, hydrocodone, hydromorphone, morphine, oxycodone, oxymorphone, and pharmaceutically acceptable salts thereof.

8. The immediate release abuse deterrent dosage form according to claim 6, wherein the nonsteroidal analgesic drug is selected from acetaminophen, aspirin, ibuprofen and naproxen.

9. The immediate release abuse deterrent dosage form according to claim 1, wherein the gelling polymer in the core is selected from ethylcellulose, cellulose acetate, cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate, cellulose ether, cellulose ester, cellulose ester ether, cellulose, an acrylic acid and methacrylic acid copolymer, a methyl methacrylate copolymer, an ethoxyethyl methacrylate, a cyanoethyl methacrylate, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamide copolymer, poly(methyl methacrylate), polymethacrylate, poly(methyl methacrylate) copolymer, polyacrylamide, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride), glycidyl methacrylate copolymer, agar, acacia, karaya, tragacanth, algin, guar; polyacrylamide; water-swellable indene maleic anhydride polymer, hydroxypropyl methyl cellulose, hydroxy methyl cellulose, methyl cellulose, hydroxyethylmethyl cellulose, sodium carboxymethyl cellulose, a carbomer polymer, polyethylene oxide, polyvinyl alcohol and combinations thereof.

10. The immediate release abuse deterrent dosage form according to claim 9, wherein the gelling polymer in the core is selected from hydroxypropyl methyl cellulose, hydroxy methyl cellulose, methyl cellulose, hydroxyethylmethyl cellulose, sodium carboxymethyl cellulose, a carbomer polymer, polyethylene oxide, polyvinyl alcohol and combinations thereof.

11. The immediate release abuse deterrent dosage form according to claim 1, wherein the gelling polymer in the core is present in an amount from 0.5 to 15 weight percent based on the total weight of the dosage form.

12. The immediate release abuse deterrent dosage form according to claim 1, wherein the gelling polymer in the matrix is selected from ethyl cellulose, cellulose acetate, cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate, cellulose ether, cellulose ester, cellulose ester ether, cellulose, an acrylic acid and methacrylic acid copolymer, a methyl methacrylate copolymer, an ethoxyethyl methacrylate, a cyanoethyl methacrylate, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamide copolymer, poly(methyl methacrylate), polymethacrylate, poly(methyl methacrylate) copolymer, polyacrylamide, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride), glycidyl methacrylate copolymer, agar, acacia, karaya, tragacanth, algin, guar; polyacrylamide; water-swellable indene maleic anhydride polymer, hydroxypropyl methyl cellulose, hydroxy methyl cellulose, methyl cellulose, hydroxyethylmethyl cellulose, sodium carboxymethyl cellulose, a carbomer polymer, polyethylene oxide, polyvinyl alcohol and combinations thereof.

13. The immediate release abuse deterrent dosage form according to claim 12, wherein the gelling polymer in the matrix is selected from hydroxypropyl methyl cellulose, hydroxy methyl cellulose, methyl cellulose, ethyl cellulose, hydroxyethylmethyl cellulose, sodium carboxymethyl cellulose, a carbomer polymer, and combinations thereof.

14. The immediate release abuse deterrent dosage form according to claim 1, wherein the gelling polymer in the matrix is present in an amount from 0.5 to 15 weight percent based on the total weight of the dosage form.

15. The immediate release abuse deterrent dosage form according to claim 1, wherein the disintegrant in the matrix is selected from corn starch, croscarmellose sodium, crospovidone, sodium starch glycolate, and combinations thereof.

16. The immediate release abuse deterrent dosage form according to claim 15, wherein the dosage form comprises from 0.5 to 50 weight percent disintegrant based on total weight of the dosage form.

17. The immediate release abuse deterrent dosage form according to claim 1, wherein the pH-sensitive polymer is a copolymer of dimethyl aminoethyl methacrylate, butyl methacrylate, and methyl methacrylate monomers.

18. The immediate release abuse deterrent dosage form according to claim 1, wherein the dosage form excludes an emetic, a nasal irritant, an opioid antagonist, and an effervescent.

19. The dosage form according to claim 1, wherein the dosage form, if ground and combined with a small volume of a solvent selected from ethanol, methanol, water, or a mixture thereof forms a composition having a viscosity that prevents uptake of the composition by a hypodermic syringe.

20. The dosage form according to claim 1, wherein the dosage form reduces the risk of an overdose of the narcotic analgesic by simultaneous oral ingestion of multiple units of the oral dosage form.

21. The dosage form according to claim 1, wherein the dosage form reduces the potential for abuse by simultaneous oral ingestion of multiple units of the oral dosage form.

22. The dosage form of claim 1, wherein the dosage form is capable of releasing at least 75 weight percent of the narcotic analgesic into an aqueous hydrochloric acid solution within 240 minutes, the solution having a pH between 1 and 2 and a temperature of about 37 degrees Celsius.

23. An immediate release abuse deterrent dosage form according to claim 1, that demonstrates an immediate release profile when administered in therapeutic doses, but which demonstrates an extended release profile when administered in supratherapeutic doses.

24. The immediate release abuse deterrent dosage form according to claim 23, wherein the immediate release profile is defined as not less than 90% of API released in 60 minutes, and the extended release profile is defined as not more than 95% released in 60 minutes, wherein the release profiles may be evaluated by dissolution in 300 mL of 0.1N HCl media using USP II apparatus at 50 RPM paddle speed and 37°C.

25. The immediate release abuse deterrent dosage form according to claim 23, wherein the supratherapeutic dose is five or more tablets.

26. The immediate release abuse deterrent dosage form according to claim 1, wherein the dosage form is in a suppository, capsule, caplet, pill, gel, soft gelatin capsule, or compressed tablet form.

27. The immediate release abuse deterrent dosage form according to claim 26, wherein the dosage form is in a compressed tablet form.

28. A method of preventing, alleviating, or ameliorating a level of pain in a subject, the method comprising administering to the subject a dosage form as recited at claim 1.

29. A method of preventing abuse of a narcotic analgesic drug comprising providing an immediate release abuse deterrent dosage form according to claim 1.

30. A method of preventing overdose by accidental or intentional administration of a supratherapeutic dose of a narcotic analgesic drug, comprising providing an immediate release abuse deterrent dosage form according to claim 1.

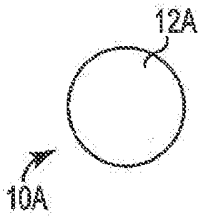


Fig. 1A

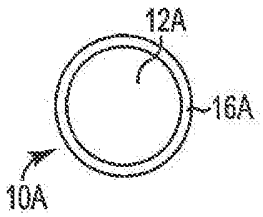


Fig. 1B

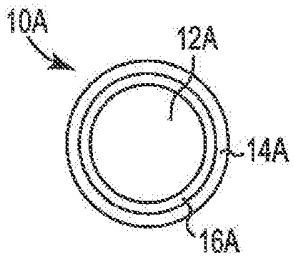


Fig. 1C

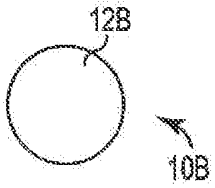


Fig. 2A

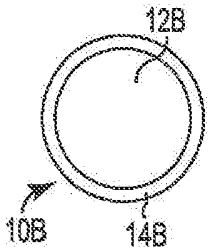


Fig. 2B

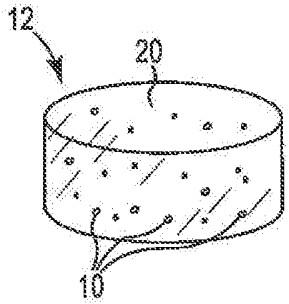


Fig. 3

Fig. 4

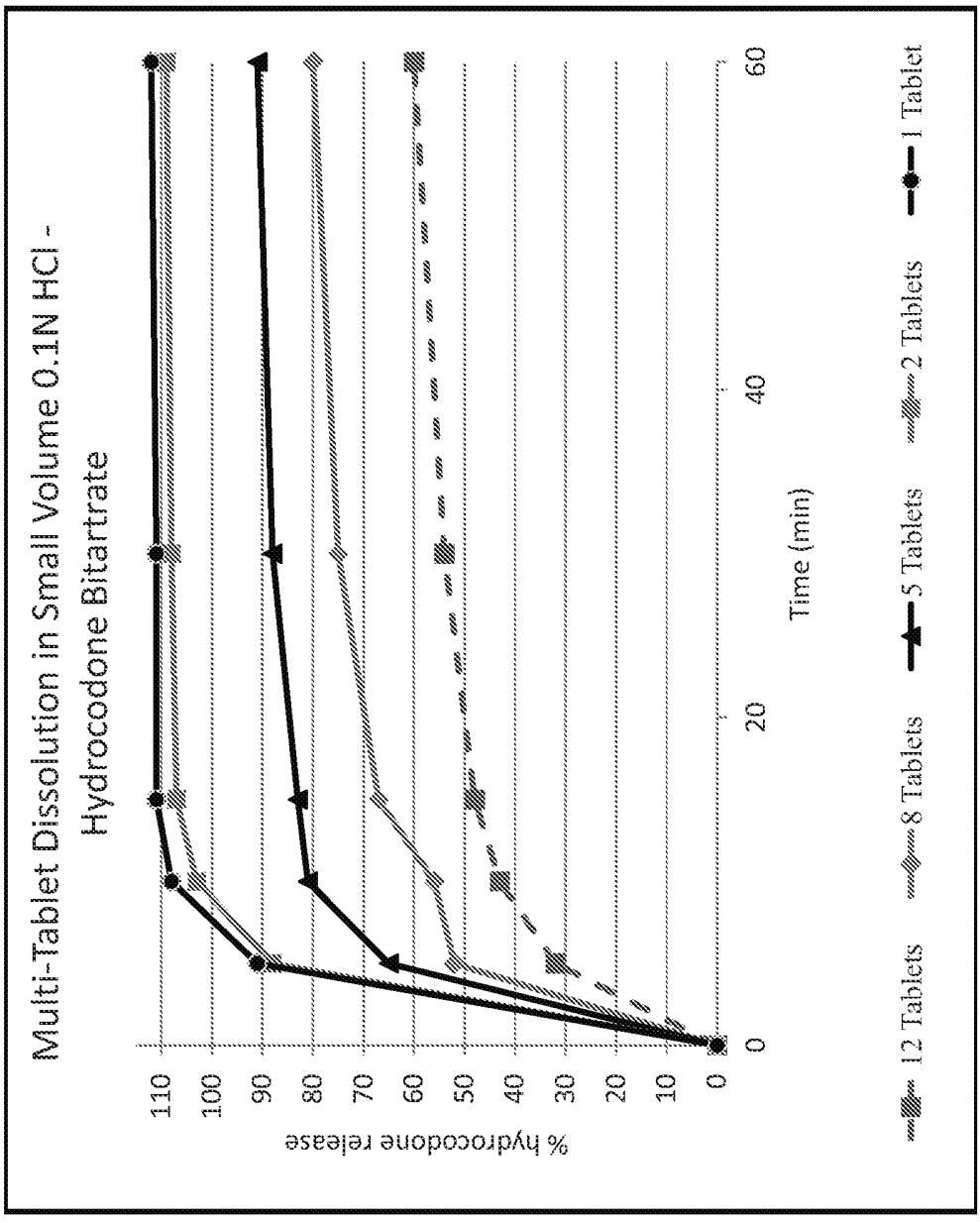

Multi-Tablet Dissolution in Small Volume 0.1N HCl - Hydrocodone Bitartrate
% hydrocodone release
0
10
20
30
40
50
60
70
80
90
100
110
0
20
40
60
Time (min)
12 Tablets
8 Tablets
5 Tablets
2 Tablets
1 Tablet

Fig. 5

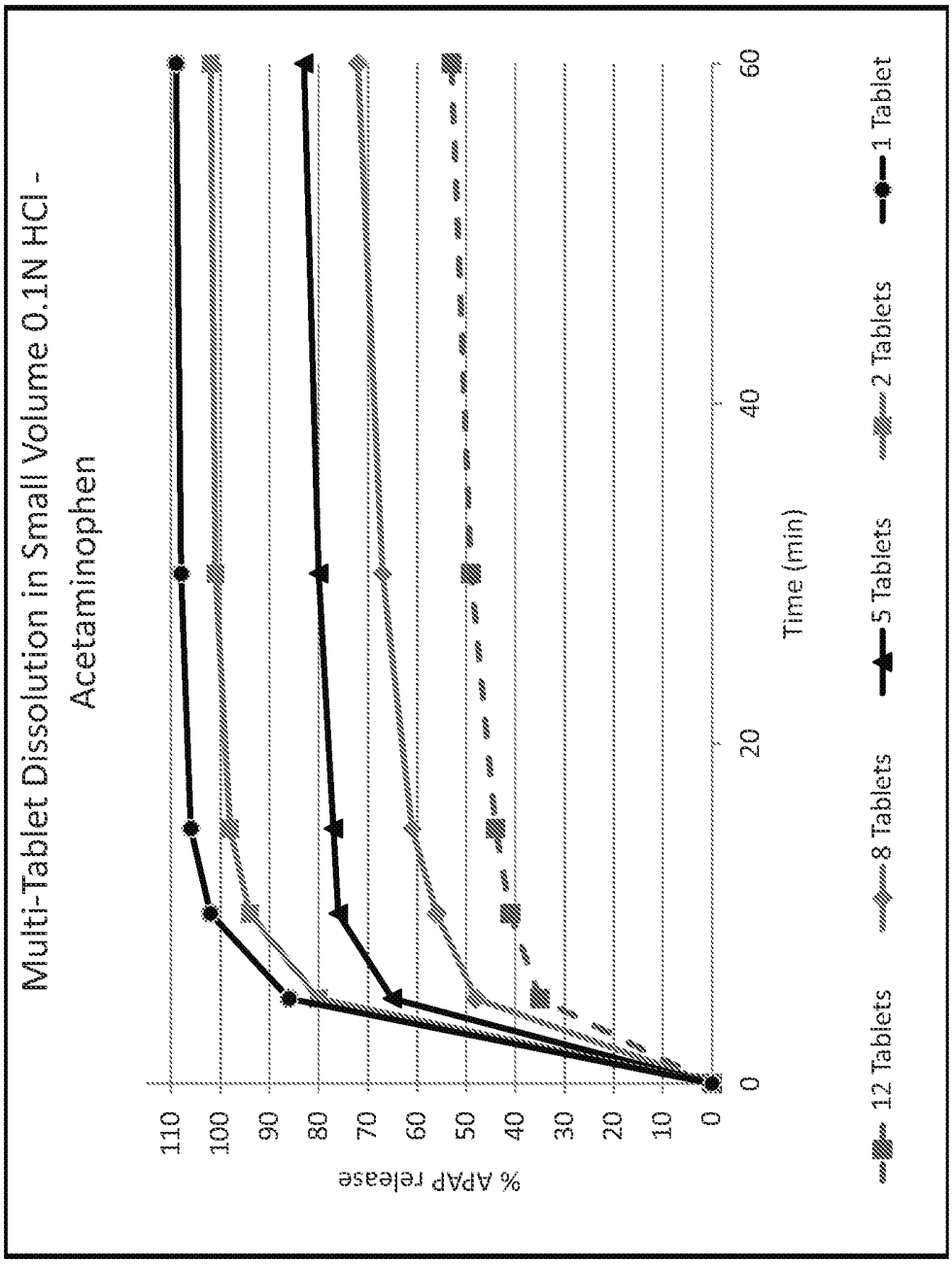

Multi-Tablet Dissolution in Small Volume 0.1N HCl - Acetaminophen
% APAP release
110
100
90
80
70
60
50
40
30
20
10
0
0
20
40
60
Time (min)
12 Tablets
8 Tablets
5 Tablets
2 Tablets
1 Tablet

Fig. 6

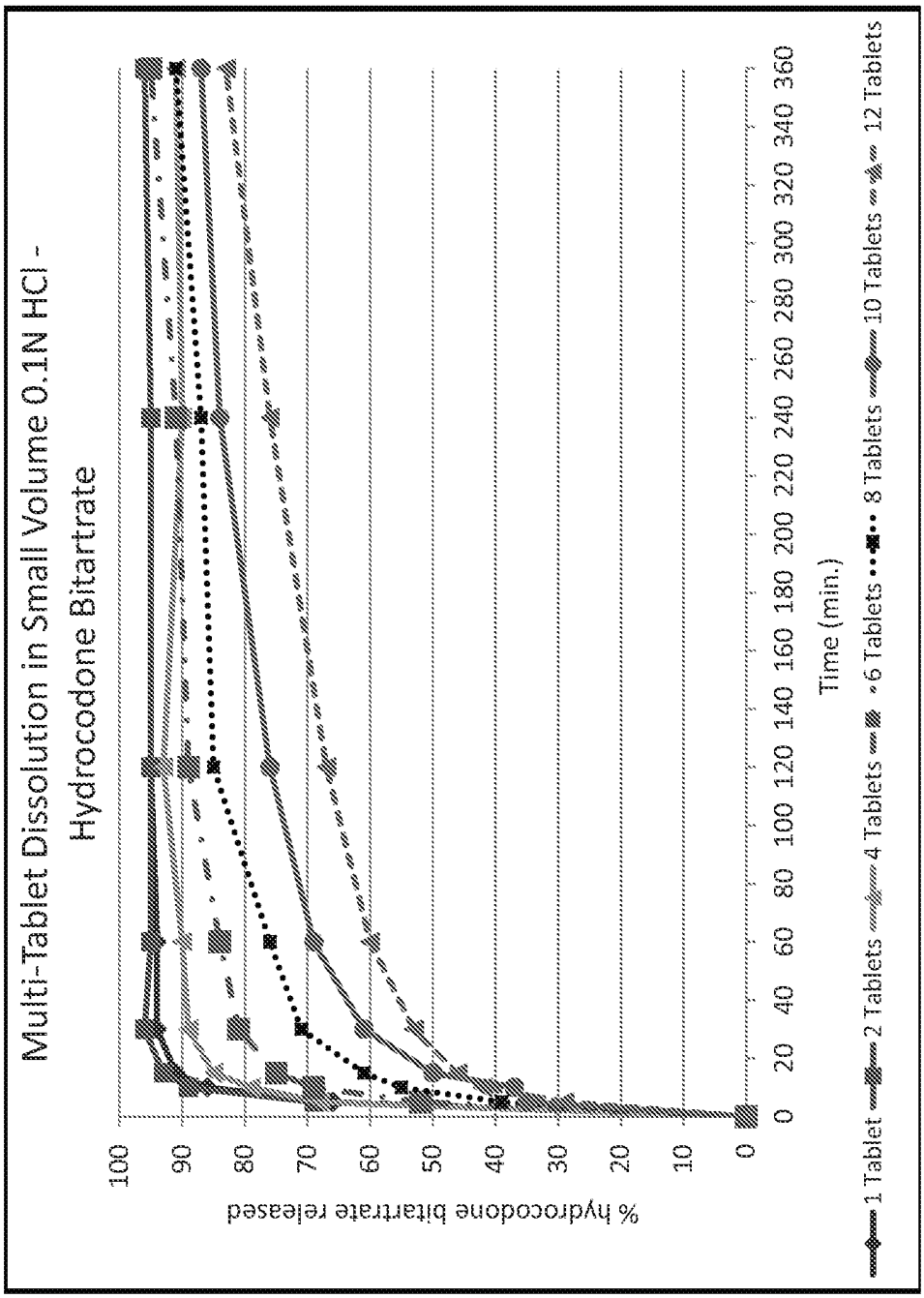

Multi-Tablet Dissolution in Small Volume 0.1N HCl -
Hydrocodone Bitartrate
% hydrocodone bitartrate released
100
90
80
70
60
50
40
30
20
10
0
0 20 40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 360
Time (min.)
1 Tablet
2 Tablets
4 Tablets
6 Tablets
8 Tablets
10 Tablets
12 Tablets

Fig. 7

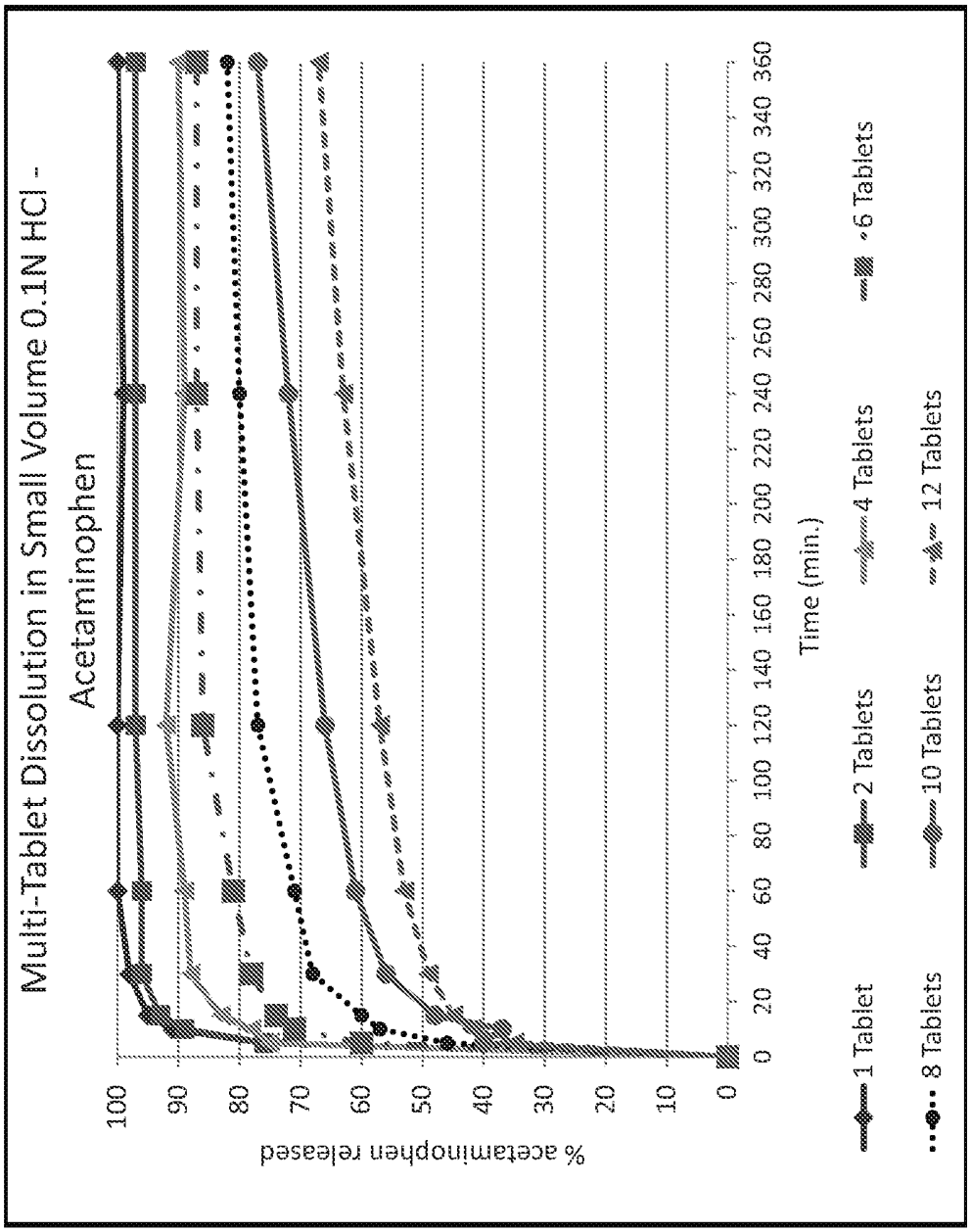

Multi-Tablet Dissolution in Small Volume 0.1N HCl - Acetaminophen
% acetaminophen released
100
90
80
70
60
50
40
30
20
10
0
0 20 40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 360
Time (min.)
1 Tablet
2 Tablets
4 Tablets
6 Tablets
8 Tablets
10 Tablets
12 Tablets

Fig. 8

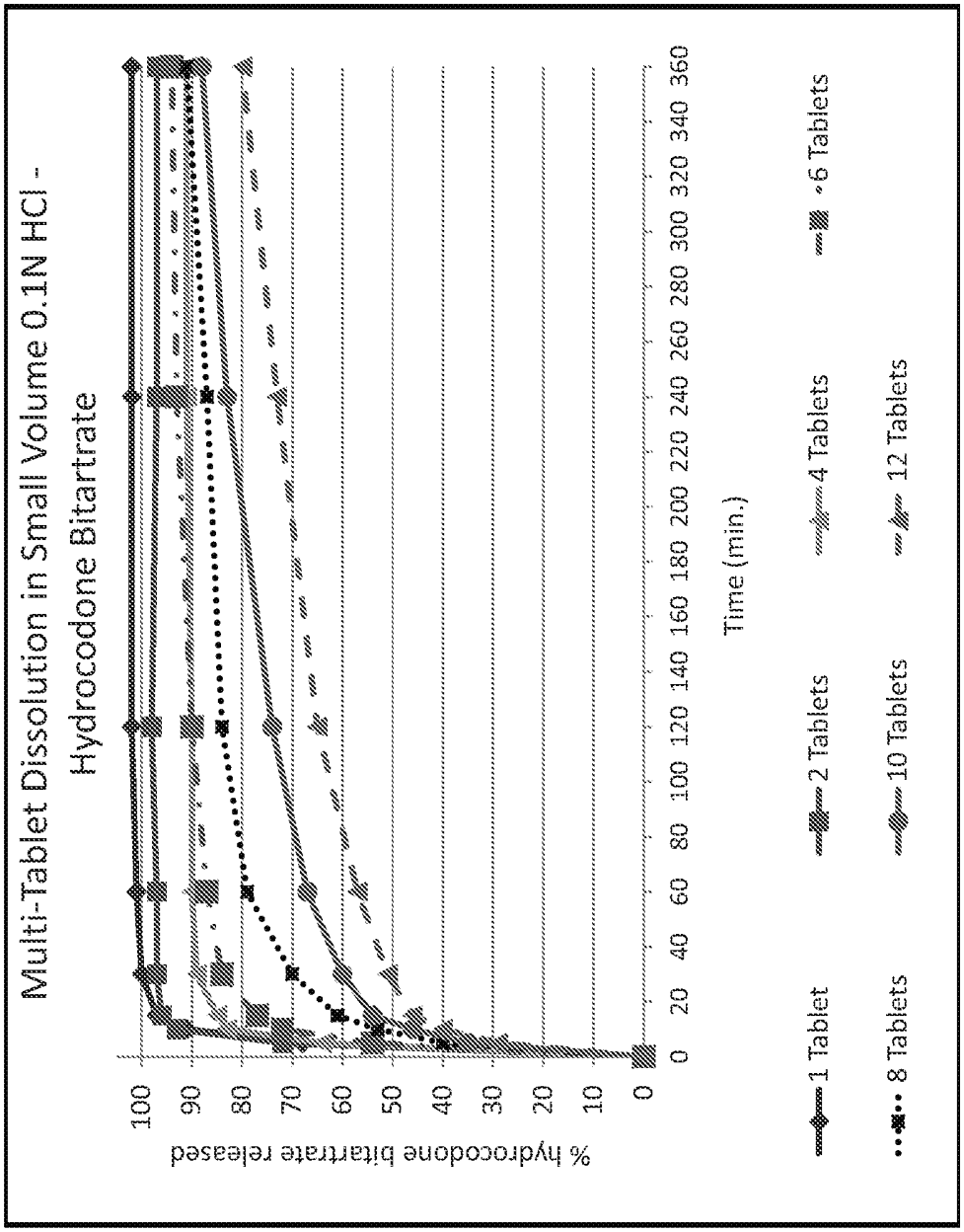

Multi-Tablet Dissolution in Small Volume 0.1N HCl - Hydrocodone Bitartrate
% hydrocodone bitartrate released
0
10
20
30
40
50
60
70
80
90
100
0 20 40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 360
Time (min.)
1 Tablet
2 Tablets
4 Tablets
6 Tablets
8 Tablets
10 Tablets
12 Tablets

Fig. 9

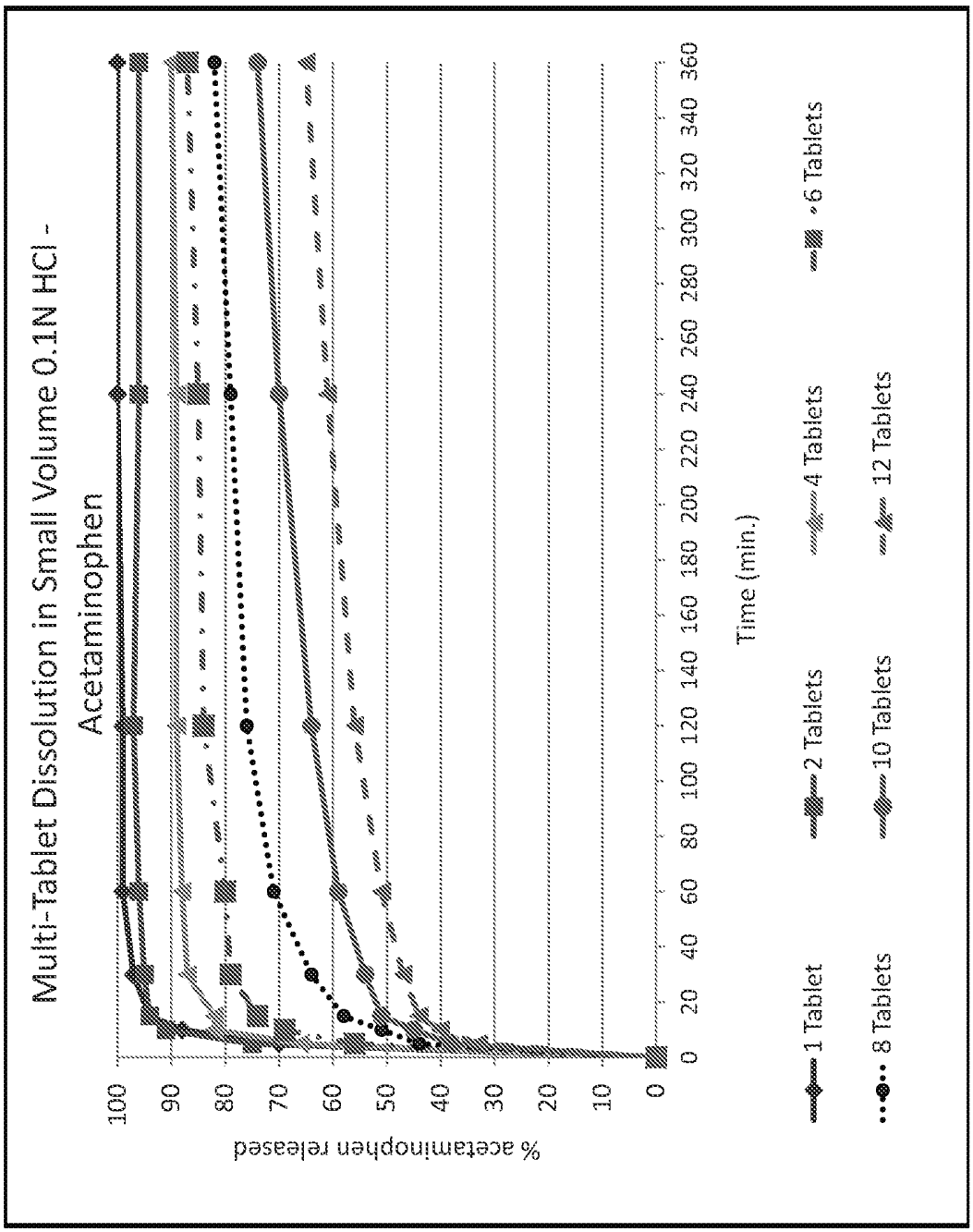

Multi-Tablet Dissolution in Small Volume 0.1N HCl - Acetaminophen
% acetaminophen released
0
10
20
30
40
50
60
70
80
90
100
Time (min.)
0 20 40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 360
1 Tablet
2 Tablets
4 Tablets
6 Tablets
8 Tablets
10 Tablets
12 Tablets

Fig. 10

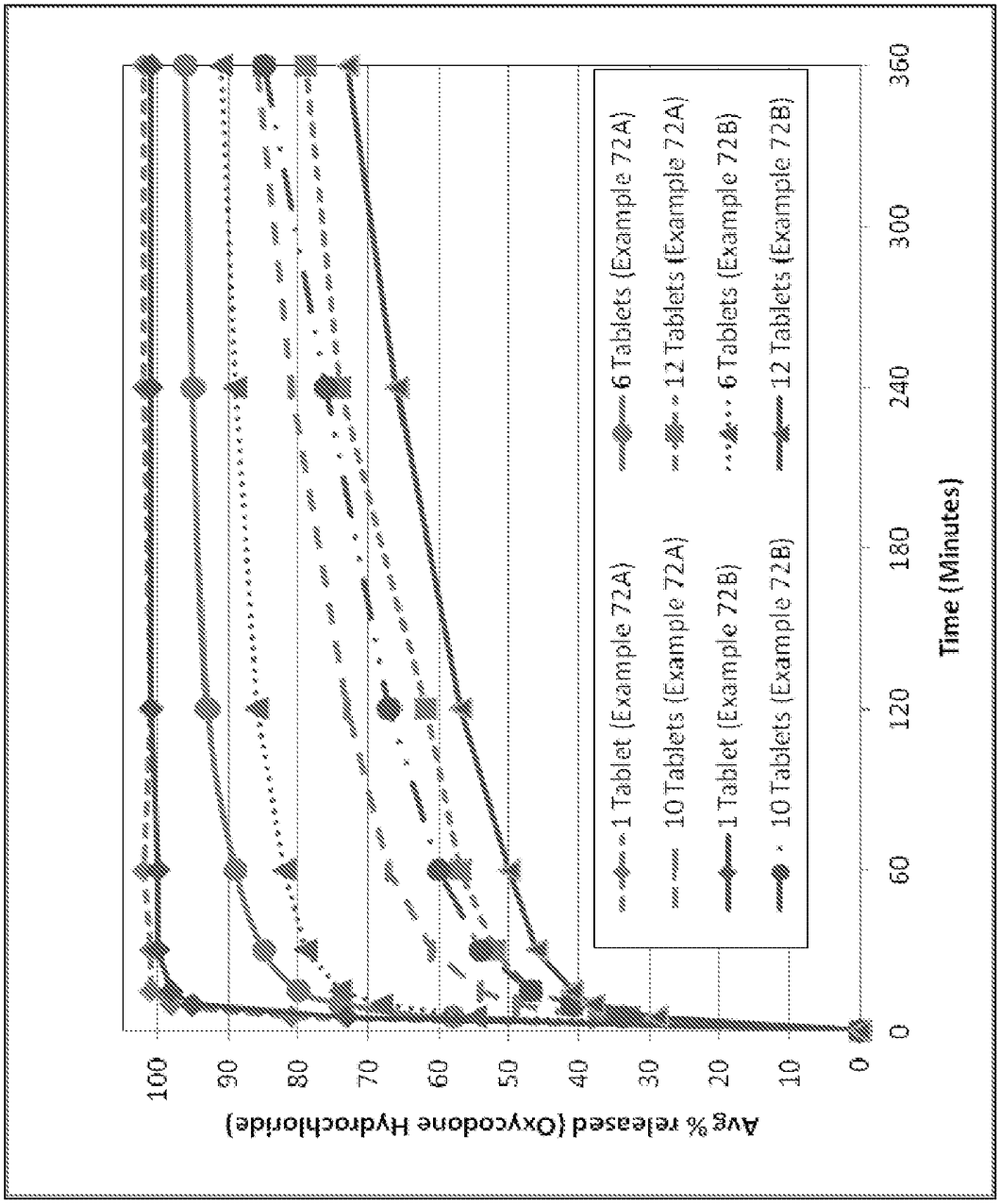

Avg % released (Oxycodone Hydrochloride)
100
90
80
70
60
50
40
30
20
10
0
0
60
120
180
240
300
360
Time (Minutes)
1 Tablet (Example 72A)
10 Tablets (Example 72A)
1 Tablet (Example 72B)
10 Tablets (Example 72B)
6 Tablets (Example 72A)
12 Tablets (Example 72A)
6 Tablets (Example 72B)
12 Tablets (Example 72B)

Fig. 11

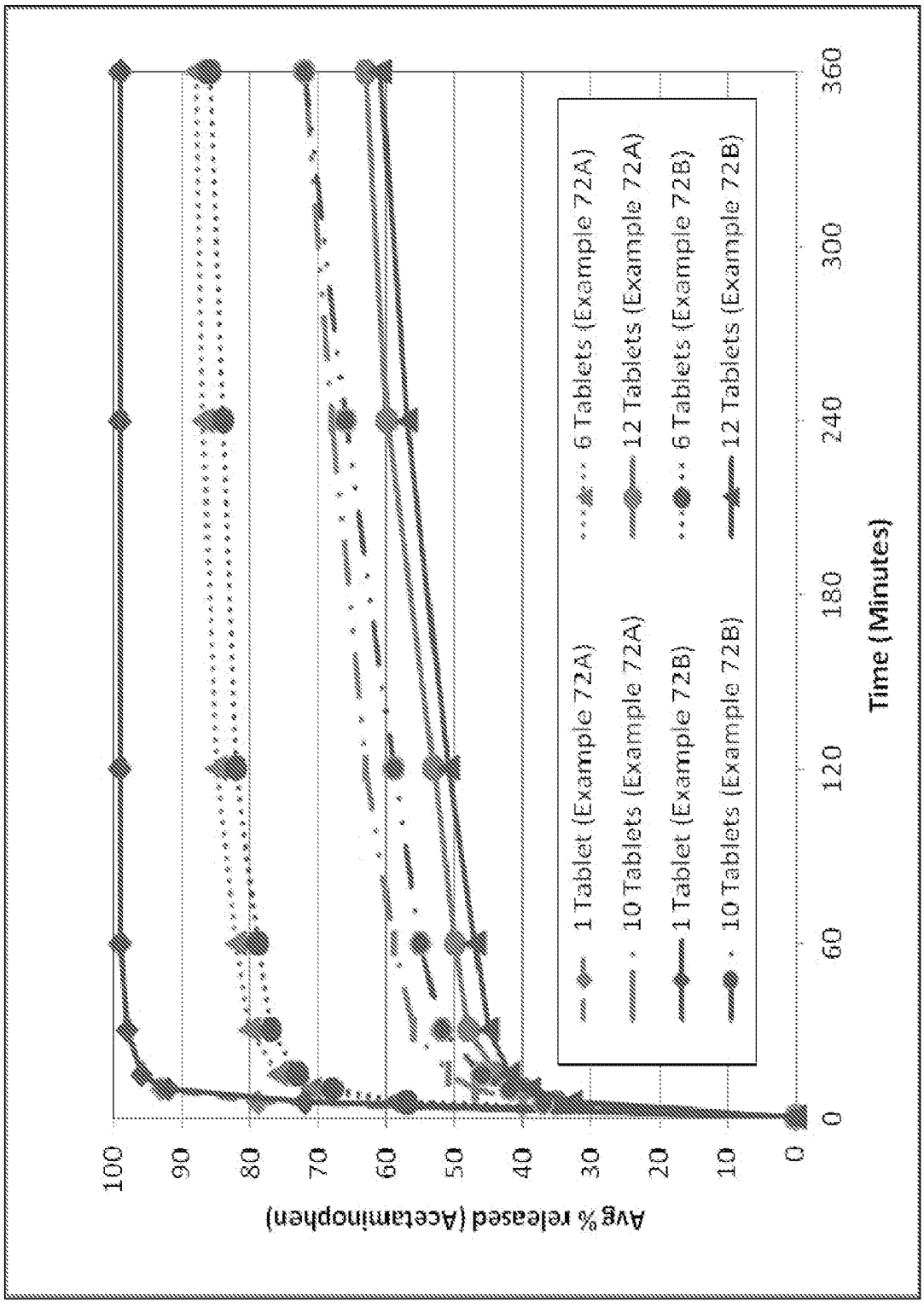

Avg % released (Acetaminophen)
100
90
80
70
60
50
40
30
20
10
0
0
60
120
180
240
300
360
Time (Minutes)
1 Tablet (Example 72A)
10 Tablets (Example 72A)
1 Tablet (Example 72B)
10 Tablets (Example 72B)
6 Tablets (Example 72A)
12 Tablets (Example 72A)
6 Tablets (Example 72B)
12 Tablets (Example 72B)

Fig. 12

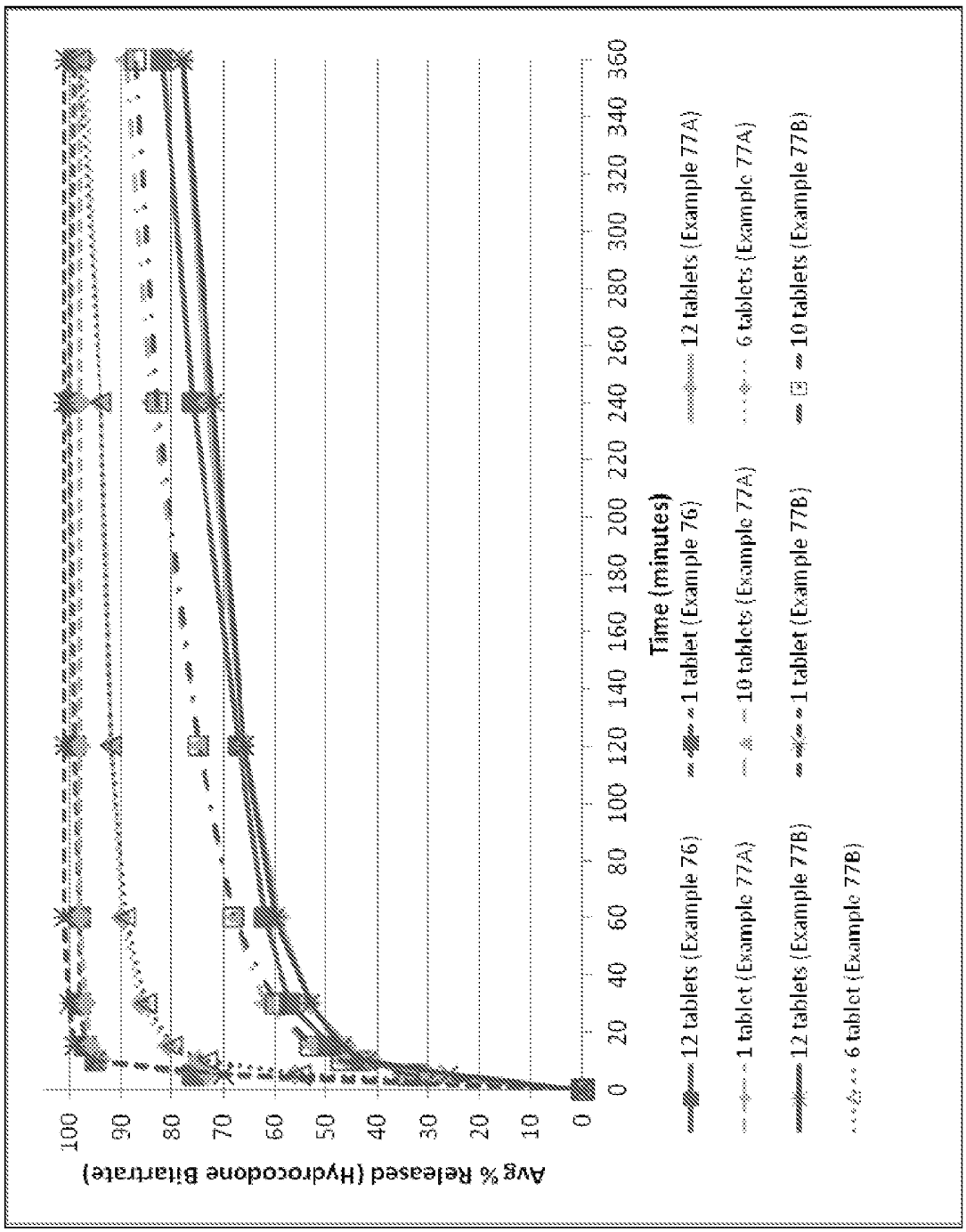

Avg % Released (Hydrocodone Bitartrate)
100
90
80
70
60
50
40
30
20
10
0
0 20 40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 360
Time (minutes)
12 tablets (Example 76)
1 tablet (Example 76)
12 tablets (Example 77A)
1 tablet (Example 77A)
10 tablets (Example 77A)
6 tablets (Example 77A)
12 tablets (Example 77B)
1 tablet (Example 77B)
10 tablets (Example 77B)
6 tablet (Example 77B)

Fig. 13

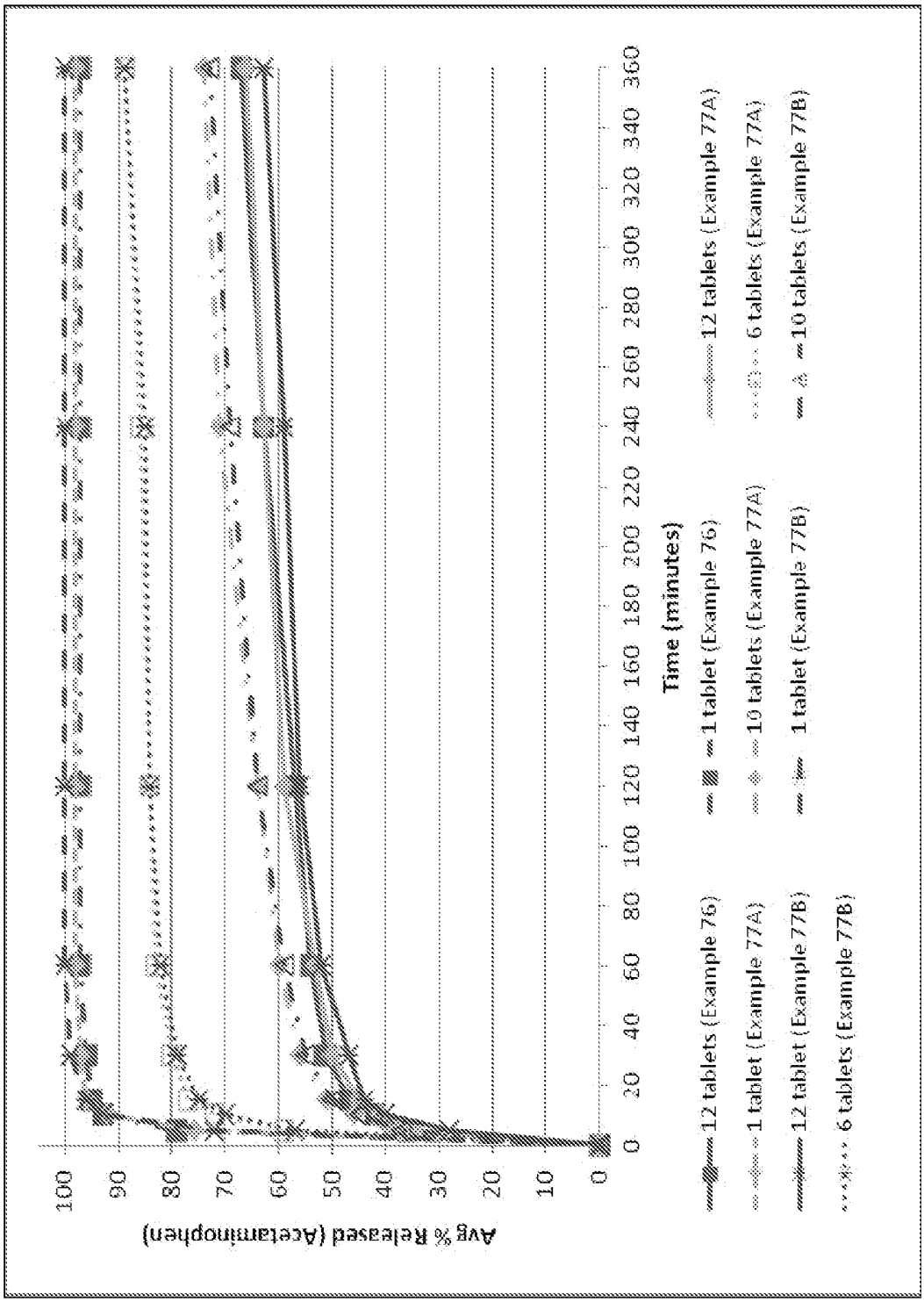

Avg % Released (Acetaminophen)
100
90
80
70
60
50
40
30
20
10
0
0 20 40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 360
Time (minutes)
12 tablets (Example 76)
1 tablet (Example 76)
12 tablets (Example 77A)
1 tablet (Example 77A)
10 tablets (Example 77A)
6 tablets (Example 77A)
12 tablet (Example 77B)
1 tablet (Example 77B)
10 tablets (Example 77B)
6 tablets (Example 77B)

Fig. 14

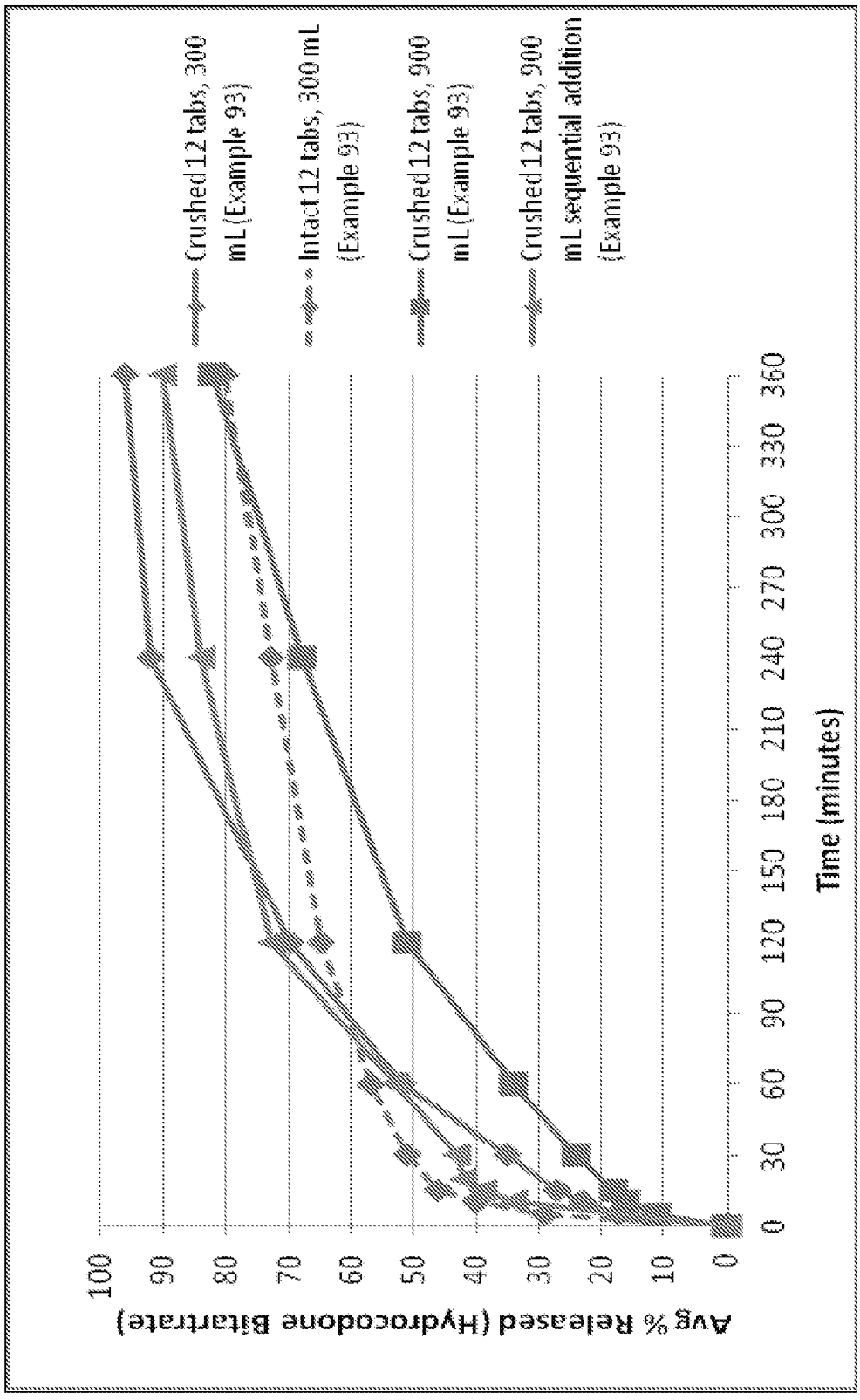
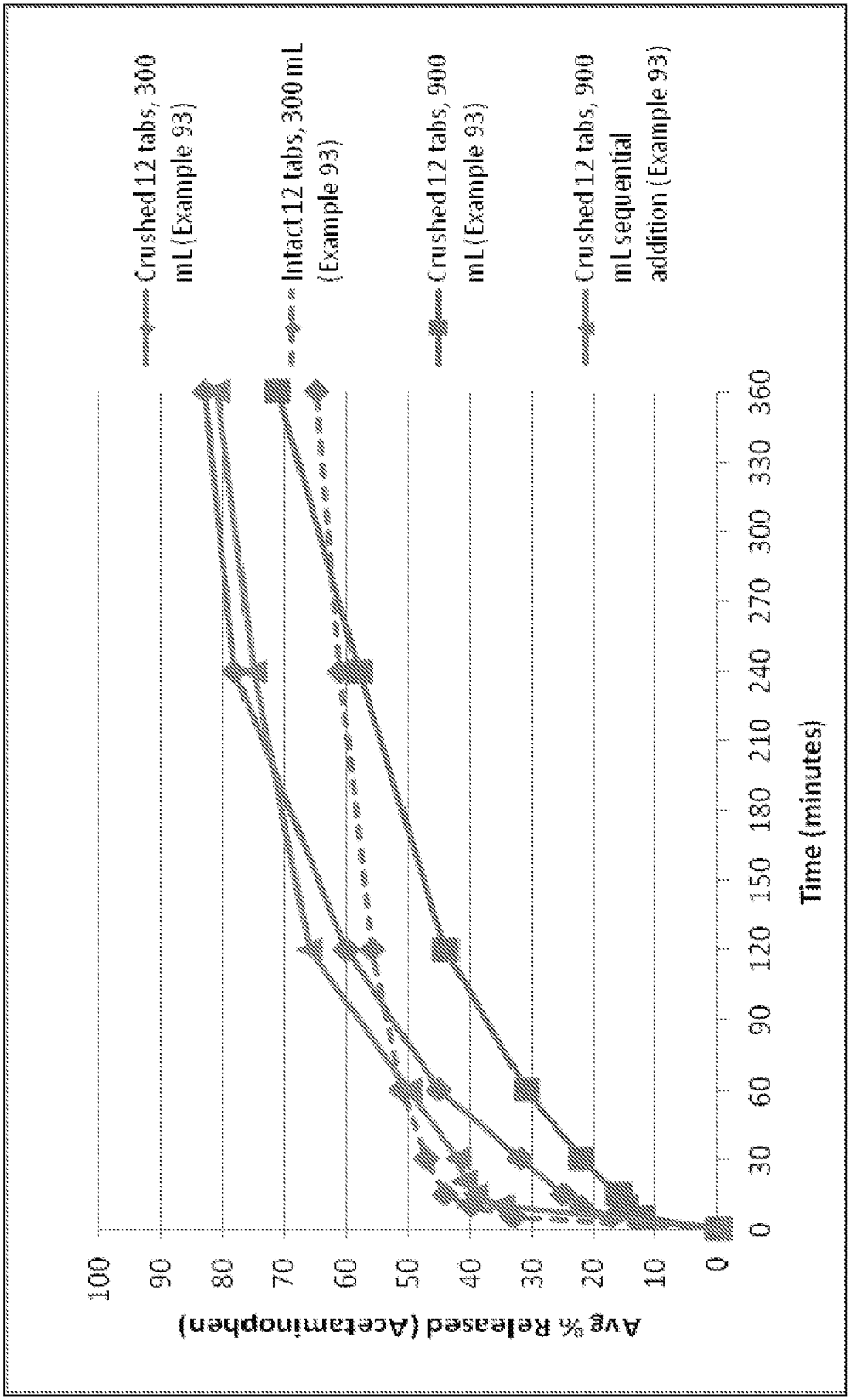

Avg % Released (Hydrocodone Bitartrate)
100
90
80
70
60
50
40
30
20
10
0
0 30 60 90 120 150 180 210 240 270 300 330 360
Time (minutes)
Crushed 12 tabs, 300 mL (Example 93)
Intact 12 tabs, 300 mL (Example 93)
Crushed 12 tabs, 900 mL (Example 93)
Crushed 12 tabs, 900 mL sequential addition (Example 93)

Fig. 15


Crushed 12 tabs, 300 mL (Example 93)
Intact 12 tabs, 300 mL (Example 93)
Crushed 12 tabs, 900 mL (Example 93)
Crushed 12 tabs, 900 mL sequential addition (Example 93)
Avg % Released (Acetaminophen)
100
90
80
70
60
50
40
30
20
10
0
0 30 60 90 120 150 180 210 240 270 300 330 360
Time (minutes)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 14/62887

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 9/20; A61P 25/04; A61K 31/485; A61K 9/22 (2014.01)
CPC - A61K 9/20; 9/0007; 31/485; 9/2018; 9/2054; 9/2031; 9/2059; 9/2013
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8): A61K 9/20; A61P 25/04; A61K 31/485; A61K 9/22 (2014.01)
CPC: A61K 9/20; 9/0007; 31/485; 9/2018; 9/2054; 9/2031; 9/2059; 9/2013

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 424/468; 424/400; 514/289; 514/777; 546/44 (keyword limited; see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Google Patents, Google Scholar
Search terms used: opioid/narcotic, dosage form, abuse deterrant/resistant, tamper-proof, core-shell particles, matrix, polysaccharide, enteric coating, pH dependent

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6,309,668 B1 (Bastin et al.) 30 October 2001 (30.10.2001), col 1 ln 9-51; col 2 ln 1-49; col 3 ln 41-53; col 3 ln 58 - col 4 ln 8; col 14 ln 63	1-30
Y	WO 2001/080826 A2 (Corbo et al.) 01 November 2001 (01.11.2001), pg 7-8	1-30
Y	US 2010/0099696 A1 (Soscia et al.) 22 April 2010 (22.04.2010), para [0044], [0046], [0055]	4
Y	US 2009/0022798 A1 (Rosenberg et al.) 22 January 2009 (22.01.2009), para [0009], [0021]	6, 8
Y	US 2012/0202838 A1 (Ghosh et al.) 09 August 2012 (09.08.2012), para [0152], [0185]	14
Y	US 2011/0002985 A1 (Shah et al.) 06 January 2011 (06.01.2011), para [0034]	22-25
Y	WO 2008/134071 A1 (Najib) 06 November 2008 (06.11.2008), para [0252], [0541]	24
Y	US 2003/0065002 A1 (Caruso et al.) 03 April 2003 (03.04.2003), para [0026]	25

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search
12 December 2014 (12.12.2014)

Date of mailing of the international search report
07 JAN 2015

Name and mailing address of the ISA/US
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P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-3201

Authorized officer:
Lee W. Young
PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

(19)中华人民共和国国家知识产权局

(12)发明专利申请

(10)申请公布号 CN 105682647 A
(43)申请公布日 2016.06.15

(21)申请号 201480059281.6

(22)申请日 2014.10.29

(30)优先权数据
61/898,207 2013.10.31 US
14/333,986 2014.07.17 US
PCT/US2014/047014 2014.07.17 US
14/477,354 2014.09.04 US
PCT/US2014/054061 2014.09.04 US
14/484,793 2014.09.12 US

(85)PCT国际申请进入国家阶段日
2016.04.28

(86)PCT国际申请的申请数据
PCT/US2014/062887 2014.10.29

(87)PCT国际申请的公布数据
WO2015/066172 EN 2015.05.07

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(51)Int.Cl.
A61K 9/20(2006.01)
A61P 25/04(2006.01)
A61K 31/485(2006.01)
A61K 9/22(2006.01)

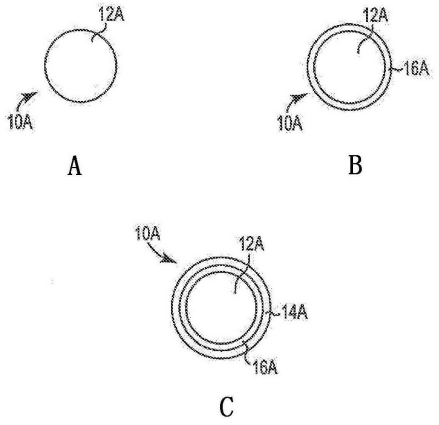
权利要求书3页 说明书91页 附图13页

(54)发明名称

立即释放型滥用制止粒状剂型

(57)摘要

本发明描述了含有滥用制止特征的立即释放型口服剂型。具体而言,所公开的剂型提供了通过摄入多个单剂量进行滥用的制止物。另外,所公开的剂型提供了对在意外或有意摄入多个单剂量的情况下过量用药的防护。



CN 105682647 A

1.立即释放型滥用制止剂型,其包含:

a)核-壳粒子,所述核-壳粒子包含:

核,所述核包含胶凝聚合物,其中在所述核中的胶凝聚合物选自天然淀粉、合成淀粉、天然纤维素、合成纤维素、丙烯酸酯、聚氧化烯烃、卡波姆及其组合;

包围所述核的活性药物层,所述活性药物层包含麻醉止痛剂;

包围所述活性药物层的至少一个层,所述至少一个层包含pH敏感膜,所述膜包含在pH高于5时不溶于水以及在pH低于5时溶于水的pH敏感聚合物;和

b)包含崩解剂和胶凝聚合物的基质;其中在所述基质中的胶凝聚合物选自天然淀粉、合成淀粉、天然纤维素、合成纤维素、丙烯酸酯、聚氧化烯烃、卡波姆及其组合。

2.根据权利要求1所述的立即释放型滥用制止剂型,其中在所述核壳粒子中,麻醉止痛剂总量的小于5重量%的麻醉止痛剂被包含在所述核中。

3.根据权利要求1所述的立即释放型滥用制止剂型,其中在所述核壳粒子中,麻醉止痛剂总量的至少90%的麻醉止痛剂被包含在所述活性药物层中。

4.根据权利要求1所述的立即释放型滥用制止剂型,其还包含第二种类型的核-壳粒子,所述第二种类型的核-壳粒子不包括活性药物层,所述第二种类型的核-壳粒子包含:

核,所述核包含胶凝聚合物,其中在所述核中的胶凝聚合物选自天然淀粉、合成淀粉、天然纤维素、合成纤维素、丙烯酸酯、聚氧化烯烃、卡波姆及其组合;和

包围所述核的至少一个层,所述至少一个层包含pH敏感膜,所述膜包含在pH高于5时不溶以及在pH低于5时可溶的pH敏感聚合物。

5.根据权利要求1所述的立即释放型滥用制止剂型,其中所述麻醉止痛剂是阿片样物质。

6.根据权利要求5所述的立即释放型滥用制止剂型,其还包含非甾体止痛药。

7.根据权利要求5所述的立即释放型滥用制止剂型,其中所述阿片样物质选自丁丙诺啡、可待因、二氢可待因、二氢吗啡、氢可酮、氢吗啡酮、吗啡、羟考酮、羟吗啡酮及其可药用盐。

8.根据权利要求6所述的立即释放型滥用制止剂型,其中所述非甾体止痛药选自对乙酰氨基酚、阿司匹灵、布洛芬和萘普生。

9.根据权利要求1所述的立即释放型滥用制止剂型,其中在核中的所述胶凝聚合物选自乙基纤维素、乙酸纤维素、乙酸丙酸纤维素、乙酸丁酸纤维素、乙酸邻苯二甲酸纤维素、三乙酸纤维素、纤维素醚、纤维素酯、纤维素酯醚、纤维素、丙烯酸和甲基丙烯酸共聚物、甲基丙烯酸甲酯共聚物、甲基丙烯酸乙氧基乙酯、甲基丙烯酸氰乙酯、聚丙烯酸、聚甲基丙烯酸、甲基丙烯酸烷基酰胺共聚物、聚甲基丙烯酸甲酯、聚甲基丙烯酸酯、聚甲基丙烯酸甲酯共聚物、聚丙烯酰胺、甲基丙烯酸氨基烷基酯共聚物、聚甲基丙烯酸酐、甲基丙烯酸缩水甘油酯共聚物、琼脂、阿拉伯胶、卡拉牙胶、黄蓍胶、褐藻胶、瓜尔胶;聚丙烯酰胺;水溶胀型茚马来酸酐聚合物、羟丙基甲基纤维素、羟甲基纤维素、甲基纤维素、羟乙基甲基纤维素、羧甲基纤维素钠、卡波姆聚合物、聚环氧乙烷、聚乙烯醇及其组合。

10.根据权利要求9所述的立即释放型滥用制止剂型,其中在核中的所述胶凝聚合物选自羟丙基甲基纤维素、羟甲基纤维素、甲基纤维素、羟乙基甲基纤维素、羧甲基纤维素钠、卡波姆聚合物、聚环氧乙烷、聚乙烯醇及其组合。

11.根据权利要求1所述的立即释放型滥用制止剂型，其中在核中的所述胶凝聚合物以基于所述剂型总重量从0.5重量％至15重量％的量存在。

12.根据权利要求1所述的立即释放型滥用制止剂型，其中在基质中的所述胶凝聚合物选自乙基纤维素、乙酸纤维素、乙酸丙酸纤维素、乙酸丁酸纤维素、乙酸邻苯二甲酸纤维素、三乙酸纤维素、纤维素醚、纤维素酯、纤维素酯醚、纤维素、丙烯酸和甲基丙烯酸共聚物、甲基丙烯酸甲酯共聚物、甲基丙烯酸乙氧基乙酯、甲基丙烯酸氰乙酯、聚丙烯酸、聚甲基丙烯酸、甲基丙烯酸烷基酰胺共聚物、聚甲基丙烯酸甲酯、聚甲基丙烯酸酯、聚甲基丙烯酸甲酯共聚物、聚丙烯酰胺、甲基丙烯酸氨基烷基酯共聚物、聚甲基丙烯酸酐、甲基丙烯酸缩水甘油酯共聚物、琼脂、阿拉伯胶、卡拉牙胶、黄蓍胶、褐藻胶、瓜尔胶；聚丙烯酰胺；水溶胀型茚马来酸酐聚合物、羟丙基甲基纤维素、羟甲基纤维素、甲基纤维素、羟乙基甲基纤维素、羧甲基纤维素钠、卡波姆聚合物、聚环氧乙烷、聚乙烯醇及其组合。

13.根据权利要求12所述的立即释放型滥用制止剂型，其中在基质中的所述胶凝聚合物选自羟丙基甲基纤维素、羟甲基纤维素、甲基纤维素、乙基纤维素、羟乙基甲基纤维素、羧甲基纤维素钠、卡波姆聚合物、及其组合。

14.根据权利要求1所述的立即释放型滥用制止剂型，其中在基质中的所述胶凝聚合物以基于所述剂型总重量从0.5重量％至15重量％的量存在。

15.根据权利要求1所述的立即释放型滥用制止剂型，其中在基质中的所述崩解剂选自玉米淀粉、交联羧甲基纤维素钠、交聚维酮、羧甲基淀粉钠、及其组合。

16.根据权利要求15所述的立即释放型滥用制止剂型，其中所述剂型包含基于所述剂型的总重量从0.5重量％至50重量％的崩解剂。

17.根据权利要求1所述的立即释放型滥用制止剂型，其中所述pH敏感聚合物是甲基丙烯酸二甲氨基乙酯单体、甲基丙烯酸丁酯单体和甲基丙烯酸甲酯单体的共聚物。

18.根据权利要求1所述的立即释放型滥用制止剂型，其中所述剂型不包括催吐剂、鼻刺激剂、阿片样物质拮抗剂和泡腾剂。

19.根据权利要求1所述的剂型，其中所述剂型，如果磨碎并与小体积的选自乙醇、甲醇、水或其混合物的溶剂相结合形成组合物，所述组合物具有防止通过皮下注射器摄取所述组合物的粘度。

20.根据权利要求1所述的剂型，其中所述剂型降低通过同时口服摄入多个所述口服剂型单位而过量用药所述麻醉止痛剂的风险。

21.根据权利要求1所述的剂型，其中所述剂型降低通过同时口服摄入多个所述口服剂型单位进行滥用的可能性。

22.权利要求1的剂型，其中所述剂型能够在240分钟内将至少75重量％的所述麻醉止痛剂释放到盐酸水溶液中，所述溶液具有1和2之间的pH和约37℃的温度。

23.根据权利要求1所述的立即释放型滥用制止剂型，其当以治疗剂量给药时表现出立即释放特性，但当以超治疗剂量给药时表现出延长释放特性。

24.根据权利要求23所述的立即释放型滥用制止剂型，其中所述立即释放特性被定义为在60分钟内释放不少于90％的API，而所述延长释放特性被定义为在60分钟内释放不超过95％的API，其中所述释放特性可以通过使用USP II设备在50RPM叶片速度和37℃在300mL的0.1N HCl介质中的溶出率来评价。

25.根据权利要求23所述的立即释放型滥用制止剂型，其中所述超治疗剂量是五片或更多片。

26.根据权利要求1所述的立即释放型滥用制止剂型，其中所述剂型是栓剂、胶囊、囊片、丸剂、凝胶、软明胶胶囊或压制片剂的形式。

27.根据权利要求26所述的立即释放型滥用制止剂型，其中所述剂型是压制片剂的形式。

28.预防、缓解、或改善对象的疼痛程度的方法，所述方法包括向所述对象给药权利要求1所述的剂型。

29.防止麻醉止痛药物滥用的方法，所述方法包括提供权利要求1所述的立即释放型滥用制止剂型。

30.防止通过意外或有意给药超治疗剂量的麻醉止痛药物的过量用药的方法，所述方法包括提供权利要求1所述的立即释放型滥用制止剂型。

立即释放型滥用制止粒状剂型

[0001] 相关申请的交叉参考

[0002] 本申请是2014年9月12日提交的序号为14/484,793的美国申请和2014年9月4日提交的序号为PCT/US 2014/054061的PCT申请的部分继续申请,这两个申请都要求2013年10月31日提交的美国临时申请No.61/898,207的权益,所述美国申请是2014年9月4日提交的序号为14/477,354的美国申请的继续申请,而序号为14/477,354的美国申请是2014年7月17日提交的序号为14/333,986的美国申请的部分继续申请;并且所述PCT申请是2014年7月17日提交的序号为PCT/US 2014/047014的PCT申请的部分继续申请;所述申请的公开内容以其全文在此引为参考。

技术领域

[0003] 本发明涉及含有滥用制止特征的口服剂型领域,特别是包括含有通常容易受到滥用的药物的立即释放剂型。

背景技术

[0004] 药品,包括处方药和非处方药二者,虽然可用于改善有需要的人的健康,但也容易受到有意和无意的滥用和过量用药。常被滥用的活性药物成分的例子包括精神药物、抗焦虑药、镇静催眠药、兴奋剂、镇静剂和止痛剂例如麻醉止痛剂,等等。常被滥用的具体药物化合物的完整列表将很长;常被滥用的一些药物类别的短名单包括阿片样物质和吗啡衍生物、巴比妥类、安非他明、氯胺酮、并且可以引起心理或身体依赖性的其他药物。

[0005] 有意滥用药物的一些常见技术始于滥用者得到固体剂型例如口服给药的片剂或胶囊,并将所述固体剂型压碎成粉末。所述粉末可以由滥用者通过吹鼻(即“鼻吸”)给药以将所述药物引入到滥用者的鼻内血流。或者,所述压碎的剂型可以与能够溶解该药物(活性药物成分,或“API”)的溶剂相结合,而具有溶解药物的溶剂可以直接注射到滥用者的血流中。

[0006] 或者,用立即释放型口服剂型,滥用者可以简单地共同、例如同时摄入多个剂型单位(例如,片剂)。所述多个剂型单位的每一个单位立即释放一定量的药物,在使用者的血流中产生短期浓度尖峰并在该使用者中产生想要的“高潮”。

[0007] 制药工业已经鉴别了可能对阻止口服剂型滥用有用的各种修改药物组成和口服剂型的机制。制药公司已经研究了含有鼻刺激剂或泡腾剂的剂型,如果该剂型被压碎然后被鼻吸,其能在鼻通道中引起刺激或疼痛,从而阻止通过吹鼻滥用。制药公司研究了向剂型添加胶凝聚合物以防止通过注射滥用。如果所述剂型被压碎成粉末并与小体积溶剂结合的话,所述胶凝聚合物能引起该组合采取不能通过注射给药的高粘度液体或凝胶的形式。另一种可能的滥用制止可以添加催吐剂,其能通过在摄入多个剂量时引起呕吐而制止滥用。另一种滥用制止包括向剂型添加API的拮抗剂,其将基本阻断药物的效应。

[0008] 虽然制药工业已经鉴别了种种可用于口服剂型的滥用制止(有时称为“抗滥用”)特征,但仍然需要改善和鉴别新的滥用制止特征来抑制或防止活性药物成分的滥用或过量

用药。

发明内容

[0009] 以下描述涉及可用于活性药物成分或“API”速释的口服剂型。

[0010] 所述剂型可以设计成在立即释放剂型中根据需要释放API，并还可以包括将防止或制止所述API滥用的一个特征或特征组合。本文中描述的滥用制止特征可以单独或以任何组合包括在立即释放剂型中。

[0011] 作为第一种类型的滥用制止特征，剂型按照描述可包括胶凝聚合物以防止或破坏滥用实践，在所述滥用实践中所述剂型被压碎然后与小体积溶剂结合以产生液体组合物，所述液体组合物含有浓缩量的API并可利用注射器输送给滥用者。所述胶凝聚合物可以是可用于实现这种功能性的任何聚合物，并可以放入所述剂型中允许所述胶凝聚合物按照所描述的发挥作用并仍然允许API速释的任何位置。胶凝聚合物可以包含在包衣的核-壳粒子的核中或悬浮所述芯-壳粒子的剂型基质中。所述核可以含有任何量的胶凝聚合物，例如基于所述核的总重量从0至100％的胶凝聚合物。或者，核-壳粒子中的核可以包含填料，例如，高达100％的填料，例如糖球或微晶纤维素球(高达100％微晶纤维素球，例如以商品名Celphere®可利用的那些)。

[0012] 另一种类型的滥用制止特征可以是蜡，其单独或与其他成分例如所述胶凝聚合物一起，有效破坏滥用实践，在所述滥用实践中剂型被压碎并与溶剂结合以产生液体组合物，所述液体组合物可以通过吹鼻滥用或利用注射器输送给滥用者。所述蜡还可以抑制或防止滥用者将剂型研磨成粉，因为与碎裂或变成粉末相反，蜡在研磨后将涂抹开。与所述胶凝聚合物相似，蜡可以包含在剂型中允许所述蜡起到滥用制止特征的作用同时不干扰API的立即释放特性的任何位置。例如，蜡可以包含在包衣粒子的核中。核可以含有任何量的蜡，例如基于核的总重量从0至100％的蜡，例如基于核的总重量高达50、75或80重量％的蜡。

[0013] 又一种类型的滥用制止特征可以是填料或粘结剂，其单独或与其他成分结合可以破坏滥用实践，在所述滥用实践中剂型被压碎并与小体积溶剂结合以产生可利用注射器输送给滥用者的液体组合物。所述填料或粘结剂可以抑制或防止滥用者将所述剂型研磨成粉，因为与碎裂或变成粉末相反，所述聚合填料在研磨后将涂抹开。所述填料或粘结剂可以用允许所述填料或粘结剂起到滥用制止特征的作用同时不干扰API的立即释放特性的任何方式和任何位置中包含在剂型内。例如，填料或粘结剂可以包含在包衣粒子的核中。核可以含有任何量的聚合填料或粘结剂，例如基于核的总重量从0至100％的填料或粘结剂，或者基于核的总重量高达50、75或80重量％的填料或粘结剂。

[0014] 又一种类型的滥用制止特征可以是膜层，其在剂型中包围或覆盖API并且任选抵抗被滥用者常用于溶解API以供注射的一种或多种溶剂溶解，所述溶剂包括水和C_1-C_4醇例如乙醇、甲醇及其混合物。所述膜层可以从任何膜材料制备，所述膜材料在包衣粒子上包围和围绕API的位置处布置为连续层。膜层的例子可以任选并优选提供耐溶剂膜的性质，所述耐溶剂膜是在滥用者常用于溶解剂型中的API的某种溶剂的有限或小体积中溶解缓慢或难以溶解。为了获取剂型的API，滥用者可以研磨所述剂型并将磨碎的剂型与溶剂(如所述)结合以图产生含有浓缩的API和所述溶剂的溶液，并且该溶液可以有效注射或鼻吸。通过在水或C_1-C_4醇例如乙醇、甲醇等的一种或多种中溶解缓慢或不溶，包围剂型的API的耐溶剂膜层

可以防止滥用者容易获取和由此操纵API。

[0015] 在示例性的实施方式中，立即释放剂型可以在包衣粒子、例如核-壳粒子中包括这些特征。示例性的核-壳粒子可以包括核和包围所述核的一个或多个层。对于这样的核-壳粒子，API可以包含在核中、或在包围核的一个或多个层中、或在所述核和包围所述核的一个或多个层二者中。所述剂型可以另外含有在核中或在包围所述核的任何层中不包含API的核-壳粒子。所述核可以单独或组合地包含以下任何一种或多种：胶凝聚合物，蜡，粘结剂，或填料。或者，所述核可以包含微晶纤维素或糖球。

[0016] 膜层可以围绕和包围所述核、或围绕所述核布置的含API的层。所述膜层可以优选是以连续包衣形式的耐溶剂膜，其覆盖含有API的核、或覆盖围绕所述核布置的含API的层或包衣、或覆盖没有含API层的核或围绕所述核布置并且不含API的包衣。

[0017] 根据其他各种实施方式，如本文中所述的包衣粒子可用于包括一个或多个任选的滥用制止特征和基质例如压缩基质的剂型中，所述基质被形成为允许所述包衣粒子中存在的API速释。示例性的基质组成可以包含附加的胶凝聚合物、崩解剂、或另外的胶凝聚合物和崩解剂二者。如上文所使用的措辞“附加的胶凝聚合物”是指在所述包衣粒子中存在的胶凝聚合物的量之外的胶凝聚合物的量。与所述包衣粒子中包含的胶凝聚合物相比，所述附加的胶凝聚合物性质、化学、分子量等方面可以是相同或不同的。崩解剂作为所述基质的组分可能对促进所述剂型的API、例如存在于包衣粒子中的API的释放有用。

[0018] 所述剂型中、特别是被膜层(例如耐溶剂膜)包围的包衣粒子中包含的活性药物成分，可以是口服给药需要的任何活性药物成分，并特别可以是通常容易受到滥用的活性药物成分类型。被认为通常容易受到滥用的活性药物成分的例子包括精神药物、镇静剂、镇静催眠药、抗焦虑药、兴奋剂、镇静剂和麻醉止痛剂等等。某些更具体的通常被滥用的药物类别包括阿片样物质、巴比妥类、苯二氮卓类、安非他明、以及已知引起心理或身体依赖性的很多其他药物。

[0019] 本描述的剂型可用作立即释放剂型，并且也可以包括所描述的滥用制止特征。所述滥用制止特征可以阻止或防止通过吹鼻、通过注射滥用，并且还可以有效防止或明显限制通过同时口服多个剂型单位的常用方法(尤其使用立即释放型口服剂型的情况下)滥用奏效。该最终滥用模式(本文中有时称为“多片用药”)经常特别难以制止，尤其在立即释放型口服剂型中，使得这些描述的剂型特别可用作滥用制止型口服立即释放剂型。

[0020] 在没有其他类型的滥用制止特征例如鼻刺激物、催吐剂、苦味剂和泡腾剂抑制吹鼻或其他形式的滥用、或没有包含主题药物的药物拮抗剂的情况下，所描述的剂型的实施方式可以是有效的。

[0021] 在一个方面，本发明涉及包括核-壳粒子的立即释放剂型。所述核-壳粒子包括：含有胶凝聚合物的内核；包围所述核的至少一个层，所述至少一个层包括包围所述核的膜层；和活性药物成分。所述活性药物成分也被所述包围核的膜层所包围。

[0022] 在另一个方面，本发明涉及包括核-壳粒子的立即释放剂型。所述核-壳粒子包括核和包围所述核的活性药物层。所述活性药物层含有活性药物成分。在所述核-壳粒子中，所述核含有小于所述活性药物成分总量的5重量％的所述活性药物成分。

[0023] 在又一个方面，本发明涉及含有核-壳粒子的立即释放剂型。所述核-壳粒子包括：核和活性药物成分。所述剂型还包括基质。所述基质包括崩解剂和附加量的胶凝聚合物。

[0024] 在又一个方面，本发明涉及包括两种类型核壳粒子的立即释放剂型。一种类型的核壳粒子如上所述包括核和包围所述核的活性药物层。在该核-壳粒子中，这些粒子的核任选含有小于API总量的5重量％的API，在一些情况下，在该核-壳粒子中，这些粒子的核含有小于API总量的1重量％的API，或甚至不含明显的API量。另一个类型的核壳粒子包含核，但不包含包围所述核的活性药物层。

附图说明

[0025] 图1A、1B和1C图示了所描述的核-壳粒子的实施方式的横截面。

[0026] 图2A和2B图示了所描述的核-壳粒子的实施方式的横截面。

[0027] 图3是所描述的剂型的实施方式的透视图。

[0028] 图4显示了抗多片口服滥用(超治疗用药)的曲线-重酒石酸氢可酮在0.1N HCl介质中随时间的溶出率。

[0029] 图5显示了抗多片口服滥用(超治疗用药)的曲线-对乙酰氨基酚在0.1N HCl介质中随时间的溶出率。

[0030] 图6显示了抗多片口服滥用(超治疗用药)的曲线-重酒石酸氢可酮在0.1N HCl介质中随时间的溶出率。

[0031] 图7显示了抗多片口服滥用(超治疗用药)的曲线-对乙酰氨基酚在0.1N HCl介质中随时间的溶出率。

[0032] 图8显示了抗多片口服滥用(超治疗用药)的曲线-重酒石酸氢可酮在0.1N HCl介质中随时间的溶出率。

[0033] 图9显示了抗多片口服滥用(超治疗用药)的曲线-对乙酰氨基酚在0.1N HCl介质中随时间的溶出率。

[0034] 图10显示了抗多片口服滥用(超治疗用药)曲线-在0.1N HCl介质中盐酸羟考酮随时间从盐酸羟考酮/对乙酰氨基酚片剂(5/325mg/片和7.5/325mg/片的盐酸羟考酮/对乙酰氨基酚)的溶出率。

[0035] 图11显示了抗多片口服滥用(超治疗用药)曲线-在0.1N HCl介质中对乙酰氨基酚随时间从盐酸羟考酮/对乙酰氨基酚片剂(5/325mg/片和7.5/325mg/片的盐酸羟考酮/对乙酰氨基酚)的溶出率。

[0036] 图12显示了抗多片口服滥用(超治疗用药)曲线-在0.1N HCl介质中重酒石酸氢可酮随时间从重酒石酸氢可酮/对乙酰氨基酚片剂(5/325mg/片和7.5/325mg/片的重酒石酸氢可酮/对乙酰氨基酚)的溶出率。

[0037] 图13显示了抗多片口服滥用(超治疗用药)曲线-在0.1N HCl介质中对乙酰氨基酚随时间从重酒石酸氢可酮/对乙酰氨基酚片剂(5/325mg/片和7.5/325mg/片的重酒石酸氢可酮/对乙酰氨基酚)的溶出率。

[0038] 图14显示了抗多片口服滥用(超治疗用药)曲线-在0.1N HCl介质中重酒石酸氢可酮随时间从重酒石酸氢可酮/对乙酰氨基酚片剂(10/325mg/片的重酒石酸氢可酮/对乙酰氨基酚，按完整片剂和压碎片剂二者测试)的溶出率。

[0039] 图15显示了抗多片口服滥用(超治疗用药)曲线-在0.1N HCl介质中对乙酰氨基酚随时间从重酒石酸氢可酮/对乙酰氨基酚片剂(10/325mg/片的重酒石酸氢可酮/对乙酰氨

基酚,按完整片剂和压碎片剂二者测试)的溶出率。

[0040] 发明详述

[0041] 本描述涉及立即释放剂型,其包括一种或多种滥用制止特征用于降低下列滥用的可能性:a)胃肠外滥用,b)通过吹鼻(“鼻吸”),和c)通过同时口服摄入药物的多个口服剂型单位(片剂或胶囊)滥用。这些滥用制止特征通过制备所述剂型以包括某些结构特征和某些成分而得到,所述某些结构特征和某些成分现在已经确定有效防止滥用者通过使用某些目前常见的用于滥用API的方法实现想要的药物滥用生物效应。有利地,制备成含有一个或多个所描述的滥用制止特征作为滥用通常容易受到滥用的一种或多种API的制止物的剂型,仍然可以构造成在通过口服摄入正常治疗应用时提供所述一种或多种API的速释。

[0042] 在本文中使用时,与药物滥用和过量用药有关的措辞例如“滥用制止”和“防止”或“制止”或“抑制”实践和过程,涉及所述要求保护的制剂中的为这些实践和过程提供明显的物理和化学障碍的特征。这种制止的目的包括既使得滥用实践明显更难以实行,也使得从企图对所要求保护的制剂实行这种滥用实践所得到的任何产物,对于潜在的滥用者明显较不理想、较不有利可图、和较不可滥用。

[0043] 术语“立即释放”是指被人口服摄入后在短时间内将所包含的活性药物成分基本上全部释放到胃肠道中供生物摄取的剂型。为了确定剂型是否表现出立即释放或延长释放的溶出规律,测量剂型的释放特性的体外方法是制药领域中已知的。通过这种方法,可以测得如本文中所述的立即释放剂型的例子能够在240分钟内,例如在小于180分钟、小于90分钟、或小于60、30、15或5分钟内,将所述剂型中包含的至少一种类型的活性药物成分(例如,通常容易受到滥用的API)的总量基本上全部(例如,剂型中所述API总量的至少75、80或90重量%)释放到pH合适的溶液(例如,酸性水溶液)中。例如,本描述的剂型的释放特性可以通过下述方法测量:将所述剂型暴露于体积高达900毫升(例如,基于各种试验方法,300毫升,或900毫升)pH从1至2和37℃温度的盐酸(0.01至0.1N)(例如,盐酸水溶液)中。根据一些实施方式,本文中描述的剂型当以治疗剂量给药时显示在60分钟内释放不少于90%的API,其中所述释放特性可以通过使用USP II设备在50RPM叶片速度和37℃在300mL的0.1N HCl介质中的溶出率来评价。本描述的剂型的释放特性或者可以通过下述方法测量:将所述剂型暴露于体积高达900毫升(例如,基于各种试验方法,300毫升,或900毫升)pH约4.5(代表了进食的胃的pH条件)和37℃温度的盐酸(0.01至0.1N)(例如,盐酸水溶液)中。

[0044] 术语“延长释放”可以定义为在60分钟时所述API不超过95%释放,其中所述释放特性可以,例如,通过使用USP II设备在50RPM叶片速度和37℃在300mL 0.1N HCl介质中的溶出率来评价。根据一些实施方式,本文中描述的剂型,显示:

[0045] • 当以治疗剂量给药时在60分钟内释放的API不少于90%;和

[0046] • 当以治疗剂量给药时在60分钟时所述API释放不多于95%;

[0047] 其中所述释放特性可以通过使用USP II设备在50RPM叶片速度和37℃在300mL 0.1N HCl介质中的溶出率来评价。在这种情形下,“超治疗剂量”应理解为对应于同时给药五或更多、六或更多、七或更多、八或更多、九或更多、十或更多、十一或更多、或十二或更多单个剂量单位,例如,片。还应理解,同时给药多个单个剂量单位将合理包括在短时间间隔内,例如在小于60分钟、小于30分钟、小于15分钟、小于5分钟或小于一分钟的间隔内,相继给药那些多个剂量。

[0048] 所描述的剂型可以配制成提供API的立即释放特性，并且也可以制备成包括有效或有利的滥用制止特征，所述特征有效制止表现出立即释放特性的所述API(例如通常容易受到滥用的API)的滥用。所述API的立即释放与所述API对于多种滥用模式包括如本文中所述的多片用药的广泛抗滥用的组合，不认为是以前已知的。更具体地，如本文中所述的剂型可以提供API的立即释放特性，并可同时包括提供所述API的普遍滥用制止或滥用抵抗的滥用制止特征。所述剂型还可以更具体地以对抗某些常见的滥用方法为特征，所述方法例如1)通过注射滥用(例如，通过包括研磨剂型和溶解所述剂型的API的步骤)，2)通过吹鼻滥用(例如，也通过研磨和任选溶解剂型的API)，和3)通过口服多片用药而滥用，意味着同时口服摄入多个或过多量的口服给药剂型例如片剂或胶囊。所述第三种滥用模式，多片用药，对于立即释放剂型是特别常见的并且特别难以通过设计剂型结构或通过配制来抵御。因此，目前描述的剂型可通过有效防止或制止通过多片用药的模式滥用(或甚至意外的过量用药)，可以是本文中描述的剂型特别有用的特征。

[0049] 如本文中所述的示例性剂型的体外试验表明，示例性剂型对通过多片用药的滥用提供制止。更具体地说，示例性剂型的体外试验通过使用50RPM叶片速度在保持37℃的300毫升0.1N HCL中进行一种或多种剂型(片剂)的溶出试验来进行。参见，本文中的实施例26(a)以及图4和5。如图4、5、6、7、8和9所示，在所述介质中释放的API(阿片样物质)或APAP(对乙酰氨基酚)的量随着片数量增加而降低。所述数据还提示所测试的剂型有效防止在将意外摄入多片的个体中API摄取水平增加，防止或降低无意的API过量用药的风险。(在图4和5中，所述1片和2片剂型按下面实施例3中制备，而所述5片、8片和12片剂型按下面实施例5中制备。图6、7、8和9中使用的片剂按照实施例17制备。)

[0050] 另外，如本文中所述的体外试验表明，示例性的剂型提供了对通过多片用药的滥用的制止，即使所述剂型在给药/试验之前被压碎。具体地说，体外试验通过根据如上文对测试完整片剂(即，使用50RPM叶片速度在保持37℃的300或900毫升的0.1N HCl中)所描述的相同的方案，进行多个(十二个)压碎片剂的溶出试验而进行。参见，本文中的实施例93和图14-15。如图14-15中所示，随着压碎片剂数量增加，在所述介质中释放的API(阿片样物质和APAP)的百分比降低。该数据提示所述剂型在可能摄入多个压碎片剂的个体中防止API摄取增加，从而防止或降低所述API过量用药的风险。实施例94中使用的片剂按照实施例93制备，所述片剂提供了图14-15中显示的数据。)

[0051] 因此，在被开出所述药物处方的患者或在为了娱乐目的服食所述药物的滥用者有意或无意服食超治疗药物剂量的情况下，如本文中所述的剂型提供了在所述患者的血流中、或所述滥用者的血流中防止所述药物的短期浓度尖峰的方法。另外，如本文中所述的剂型提供了在患者有意或无意地服食超治疗药物剂量的情况下可以防止药物过量用药的方法。“超治疗“是指超过正常为了治疗开出处方的剂量，例如超过四、五、六、七、八、九、十、十一或十二个单个剂量单位(例如片剂，胶囊等)。

[0052] 作为一种类型的滥用制止特征，所描述的剂型可以包括一种或多种胶凝聚合物。如果在也存在所述胶凝聚合物时与溶剂相结合，胶凝聚合物可以通过破坏滥用实践充当滥用制止特征，在所述滥用实践中剂型的活性药物成分溶解在小体积的溶剂中或者是可获取或可容易分离的。胶凝聚合物也可以通过将磨碎的剂型与溶剂(尤其“小体积”溶剂)的组合的粘度增加到高得足以防止所述组合或API通过使用注射器注射被摄取，从而制止或防止

剂型中API的滥用。磨碎的剂型中包含的优选的胶凝聚合物，当暴露于有限体积(或“小体积”)的溶剂例如C_{1-4}醇(例如乙醇或甲醇)或水时，可以形成不可注射的物质，范围从不溶性物质到凝胶到稠浆，其各自表现出显著防止通过皮下注射器的针摄取或注射。

[0053] 合适的胶凝聚合物包括一种聚合物或聚合物的组合，其作为剂型的一部分，在所述剂型与小体积的溶剂接触后，将吸收所述溶剂并溶胀以形成粘性的或半粘稠的物质，所述物质明显减少或最小化可以含有溶解的API并可以抽入注射器中的游离溶剂的量。所述凝胶的聚合物还可以通过在凝胶基质中截留药物，降低可用所述溶剂提取的总体药物量。

[0054] 所述胶凝聚合物在所述剂型中存在的位置和量共同让所述胶凝聚合物在滥用者研磨所述剂型并将碎剂型与溶剂结合的情况下产生粘性凝胶。另一方面，所述胶凝聚合物，存在于所述剂型中时，将优选不妨碍所述剂型的预期溶出、API从所述剂型的预期释放(立即释放)、或由患者为了预定治疗目的摄入完整立即释放剂型的API摄取。所述胶凝聚合物的示例性位置是在也包含活性药物成分的包衣粒子中，例如在核中或在围绕所述核包被的层中；其中活性药物成分的量包含在所述核、或围绕所述核包被的层中、或包含在这二者中。另一个示例性的位置在用于形成压制片剂、胶囊(例如压制胶囊)、或含有包含活性药物成分的包衣粒子的其它类型剂型的基质内。胶凝聚合物也可以存在于不包含活性药物成分的包衣粒子的核中、或包围所述核的层中。

[0055] 所述胶凝聚合物可以在剂型中以任何预期的量和在剂型结构中的任何部分、位置处存在。胶凝聚合物的量可以是任何有用量，意味着如果所述剂型被压碎、磨碎、变成粉末等并与溶剂混合的话，可以产生滥用制止型粘稠混合物或凝胶。剂型中总胶凝聚合物的有用量可以基于所述剂型的总重量在0.5至90重量％胶凝聚合物的范围内，例如，基于所述剂型的总重量从0.7至20、或2至15重量％的胶凝聚合物。

[0056] 这些量的总胶凝聚合物可以存在于所述剂型的一个或多个位置中，以达到指定的总量，例如在包衣粒子(例如核)、支持和包含所述包衣粒子的基质(例如压缩基质)结构的一部分中、或在所述包衣粒子和基质二者中。

[0057] 核-壳粒子的核(未包衣)可以含有任何有用量的胶凝聚合物，例如在核-壳粒子的核中从0直至并包括100％胶凝聚合物，例如基于所述核的总重量从10至95重量％的胶凝聚合物，例如基于核总重量从40至85或50至75重量％的胶凝聚合物。

[0058] 根据剂型总重量描述，存在于核壳聚合物的核中的胶凝聚合物的量可以，例如，在0.5重量％至15重量％胶凝聚合物(存在于核中)/剂型总重量的范围内，例如1至10重量％胶凝聚合物(存在于核中)/剂型总重量。存在于剂型的基质中的胶凝聚合物的量可以是任何需要的量，例如基于所述剂型的总重量在0.5重量％至15重量％胶凝聚合物(作为基质中的赋形剂)的范围内的量，例如基于剂型总重量从1至10重量％胶凝聚合物(作为基质中的赋形剂存在)。

[0059] 有用的胶凝聚合物可以是表现出在它的分子结构中保留相当一部分吸附溶剂的能力的任何聚合材料，例如，所述溶剂是否则可被滥用者用于从剂型或者压碎的或变成粉末的剂型中提取API的溶剂，所述溶剂例如是水或C_1至C_4醇例如乙醇或甲醇等。胶凝聚合物的例子包括当与这样的溶剂发生接触时可以溶胀或膨胀到很高程度的材料。所述溶胀或膨胀可以引起所述胶凝聚合物从干燥状态经历两到一千倍的体积增加。胶凝聚合物的更具体例子包括可溶胀聚合物，有时称为渗透聚合物或水凝胶。所述胶凝聚合物可以是非交联的、

轻度交联的或高度交联的。所述交联可以包括与拥有在溶剂存在下溶胀的能力、并且当交联时不会溶于所述溶剂中的聚合物的共价或离子键。

[0060] 胶凝聚合物，在以2％w/w的浓度(基于干燥材料)溶出或分散在水溶液或分散体(例如水)中时，使用在USP 33专论中针对羟丙甲纤维素描述的分析方法(在此引为参考)在20℃(+/-0.2℃)测量时，产生粘度从约100至200,000mPa·s(例如，4,000至175,000mPa·s，和4,000至50,000mPa·s)的溶液/分散体。

[0061] 通常合适的胶凝聚合物包括如同所描述的在与溶剂接触后经历粘度增加的可药用聚合物。各种聚合物例子已知以这种方式有用，通常包括天然和合成淀粉(即改性或预胶化的改性淀粉)、天然和合成纤维素、丙烯酸酯、和聚氧化烯烃。天然淀粉的例子包括，天然淀粉包括玉米淀粉、马铃薯淀粉、米淀粉、木薯淀粉和麦淀粉，羟丙基淀粉例如羟丙基玉米淀粉、羟丙基豌豆淀粉和羟丙基马铃薯淀粉(天然淀粉的衍生物)。合成淀粉、即改性或预胶化的改性淀粉的例子包括乙酰化己二酸双淀粉、蜡质玉米基淀粉、酸处理的玉米淀粉、酸处理的蜡质玉米淀粉、磷酸双淀粉、蜡质玉米基淀粉、氧化蜡质玉米淀粉和辛烯基琥珀酸钠淀粉。纤维素的例子包括羧甲基纤维素钙、羧甲基纤维素钠、乙基纤维素、甲基纤维素、纤维素醚例如羟丙基纤维素、羟乙基纤维素、羟乙基甲基纤维素、羟丙基甲基纤维素、羧甲基纤维素钠、和低取代羟丙基纤维素。丙烯酸酯的例子包括Eudragit RS、RL、NE、NM。聚氧化烯烃的例子包括聚环氧乙烷例如POLYOX N10、N80、N60K、WSR-1105LEO、或WSR-301LEO、或WSR-303LEO。

[0062] 因此，合适的胶凝聚合物的例子包括聚环氧乙烷、聚乙烯醇、羟丙基甲基纤维素、羟丙基纤维素、甲基纤维素、羟乙基甲基纤维素、羧甲基纤维素钠、羟乙基纤维素、聚丙烯酸和聚乙烯羧基聚合物例如可在商品名卡波普®下商购的那些、和如果与所描述的小体积溶剂相结合能够达到有效防止在注射器中摄取的粘度水平的其他高分子聚合物。

[0063] 如果分子量足够高，合适的胶凝聚合物的其他例子可以包括：乙基纤维素，乙酸纤维素，乙酸丙酸纤维素，乙酸丁酸纤维素，乙酸邻苯二甲酸纤维素和三乙酸纤维素，纤维素醚，纤维素酯，纤维素酯醚，纤维素；包含从丙烯酸酯和甲基丙烯酸酯合成的丙烯酸类树脂，例如丙烯酸和甲基丙烯酸共聚物，甲基丙烯酸甲酯共聚物，甲基丙烯酸乙氧基乙酯，甲基丙烯酸氰乙基酯，聚丙烯酸，聚甲基丙烯酸，甲基丙烯酸烷基酰胺共聚物，聚甲基丙烯酸甲酯，聚甲基丙烯酸酯，聚甲基丙烯酸甲酯共聚物，聚丙烯酰胺，甲基丙烯酸氨基烷基酯共聚物，聚甲基丙烯酸酐，和甲基丙烯酸缩水甘油酯共聚物。

[0064] 示例性的胶凝聚合物可以包括天然聚合物例如来源于植物或动物的那些，以及合成制备的聚合物。例子包括分子量大于50,000的聚羟基烷基甲纤维素；分子量从5,000至5,000,000的聚甲基丙烯酸羟烷基酯；分子量从100,000至3,000,000的聚乙烯基吡咯烷酮；阴离子和阳离子型水凝胶；聚电解质复合物；具有少量乙酸酯残基的聚乙烯醇；琼脂和羧甲基纤维素的可溶胀混合物；包含甲基纤维素与交联很少的琼脂混合的可溶胀组合物；分子量从10,000至6,000,000的聚醚；由马来酸酐与苯乙烯、乙烯、丙烯或异丁烯的细碎共聚物产生的水溶胀型共聚物；N-乙烯基内酰胺的水溶胀型聚合物；等等。

[0065] 可用作胶凝聚合物的其他聚合物包括分子量从30,000至300,000的果胶；多糖例如琼脂、阿拉伯胶、卡拉牙胶、黄蓍胶、褐藻胶和瓜尔胶；聚丙烯酰胺；水溶胀型茚马来酸酐聚合物；分子量80,000至200,000的Good-rite®聚丙烯酸；分子量100,000至7,000,000的

Polyox®聚环氧乙烷聚合物;淀粉接枝共聚物;吸水性是其原重量的400倍的Aqua-Keep®丙烯酸酯聚合物;聚葡萄糖的二酯;交联聚乙烯醇和聚乙烯基-2-吡咯烷酮的混合物;分子量4,000至100,000的聚乙二醇。

[0066] 在各种具体实施方式中,胶凝聚合物可以是,或可以包括,羟丙基甲基纤维素(例如,羟丙甲纤维素或HPMC)、以及羟甲基纤维素、甲基纤维素、羟乙基甲基纤维素和羧甲基纤维素钠。所述羟丙基甲基纤维素可以具有从10,000至1,500,000的分子量。合适的、可商购的羟丙基甲基纤维素聚合物的例子包括HPMC K100M、Methocel K100LV和Methocel K4M。

[0067] 胶凝聚合物的具体类别是卡波姆聚合物类别,其是来源于丙烯酸(例如,丙烯酸均聚物)并与多元醇烯丙醚交联、例如与季戊四醇或蔗糖的聚烯基醚交联的聚合物。卡波姆聚合物是亲水性的并且基本不溶于水。相反,这些聚合物当分散在水中时溶胀,形成胶态的、粘胶样分散体。由所述聚合物骨架的丙烯酸残基提供的羧基基团担负所述聚合物的某些性状。该聚合物的粒子可以看作通过交联互连的聚合物链的网络结构。所述结构当暴露于超过4-6的pH环境时,可以在水中溶胀直至原(干燥)体积的一千倍(和聚合物粒子原直径的十倍)以形成凝胶。这些聚合物的pKa可以是6±0.5。因此,从所述聚合物骨架侧垂的羧酸酯基团在pH超过6时可以离子化,在所述带负电粒子之间产生排斥力,如果暴露于该pH范围的溶剂,这增加了所述聚合物的溶胀。为了这个原因,如本文中所述的剂型可以优选包括pH调节剂,其在所述剂型内的量和位置要将卡波姆聚合物的pH升高到至少6,以基本上中和所述羧酸酯基团。PH调节剂的合适的量可以是约1至约10毫摩尔、或约5至约9毫摩尔、或约6至约8毫摩尔、或约7至约7.5毫摩尔的所述pH调节剂/克存在于所述剂型中的卡波姆聚合物。典型地,所述pH调节剂在本发明的剂型中存在的量为基于所述剂型的总重量,从约1至约5重量%,或从约2至约4重量%,或约3至4重量%。

[0068] 卡波姆聚合物在本领域中经常使用别的术语称呼,例如,卡波姆均聚物、丙烯酸聚合物、carbomera、卡波普、羧基聚亚甲基、聚羧乙烯、Pemulen、聚丙烯酸和聚丙烯酸,USP-NF列出了三个综合性专论,即针对“卡波姆共聚物”、“卡波姆均聚物”和“卡波姆互聚物”。

[0069] 某些可以用作胶凝聚合物的卡波普(卡波姆)聚合物可具有76/羧基基团的平均当量。合适的可商购的卡波姆的例子包括卡波普®934、934P NF、卡波普®974P NF和卡波普®971P NF、卡波普®940、和卡波普®941、卡波普®71G,可从Lubrizol商购。这样的聚合物的例子在美国专利No.2,798,053和2,909,462中描述,所述专利的全文在此引为参考。卡波普®产品的理论分子量范围在700,000至30亿的理论估值范围内。对于如本文中所述的剂型,胶凝聚合物(例如,卡波普®)可具有的分子量和粘度增加性能应降低或显著抑制滥用者从如同所述的剂型和小体积溶剂的组合提取API的能力,同时还能够加工成压制剂型。

[0070] 胶凝聚合物还可以从所述胶凝聚合物制备的溶液粘度为特征。可商购的卡波普®聚合物的产品信息报告了不同的卡波普®聚合物的粘度如下:

[0071]

卡波姆的类型	规定的粘度(cP)
A 型卡波姆均聚物(卡波普 71G、卡波普 971P 和卡波普 981 的药典名称)	4,000–11,000
B 型卡波姆均聚物(卡波普 934P 和卡波普 934 的药典名称)	25,000–45,000
C 型卡波姆均聚物 (卡波普 980 的药典名称)	40,000–60,000

[0072] (A型和B型粘度使用Brookfield RVT,20rpm,中和至pH 7.3-7.8,0.5重量%粘胶,5号转轴测量。)

[0073] 优选的胶凝聚合物类型的另一个例子是黄原胶聚合物类别,其包括可用作水胶体并来源于碳水化合物发酵的天然聚合物。黄原胶的分子量可以是大约1,000,000。黄原胶已经显示出在所描述的剂型中提供特别有用的耐提取性,因此在所描述的剂型中可以是优选的,尤其是如果存在量基于剂型的总重量为至少2或3重量%。

[0074] 并非将有用的胶凝聚合物的范围限于任何特定的类型或分子量,有用的胶凝聚合物和有用的相应分子量的例子在下表显示。

[0075]

胶凝聚合物	重均分子量
卡波姆	700,000到3万亿(估计)
K型HPMC 2910	164,000-1,200,000
E型HPMC 2910	20,000-746,000
羟乙基纤维素	90,000-1,300,000
乙基纤维素	75,000-215,000
羧甲基纤维素	49,000-725,000
羧甲基纤维素钠	49,000-725,000
聚维酮	4,000-1,300,000
共聚维酮	47,000
羟丙基纤维素	40,000-1,150,000
黄原胶	1,000,000
聚环氧乙烷	平均分子量:100,000-7,000,000

[0076] 所述剂型可以任选包括以蜡的形式的另一种滥用制止物,例如如申请人的共同待决的美国专利申请2008/0311205中所述的蜡/脂肪材料,该申请的全文在此引为参考。所述蜡可以是存在于所述剂型中抑制滥用者压碎、研磨或以其他方式将所述剂型形成为碎粉末的位置,所述碎粉末可能通过吹鼻方式被滥用或从其可以容易地通过例如使用溶剂溶出或提取来获取和取出活性药剂。

[0077] 所述蜡在所述剂型中可以存在的位置和量还要不妨碍所述活性药物成分在立即释放剂型中被患者口服摄入后的预期摄取。示例性的位置是在核-壳粒子的核处,尤其是还包含胶凝聚合物并可以含或可以不含活性药物成分的核处。位于还包含活性药物成分的粒子(例如核-壳粒子)的核处(例如,在覆盖所述核的层处,或在所述核内)的蜡,将在所述粒子压碎或研磨等时变得与所述活性药物成分混合。如前面所论述,所述剂型还可以包括不含API的核壳粒子。位于不含API的这种粒子(例如核-壳粒子)的核处的蜡在所述剂型的压

碎、研磨等时也将变得与所述API(例如,也存在于所述剂型中的含API的核壳粒子中存在的API)混合。当所述蜡与所述活性药物成分混合时,抑制或防止了所述活性成分在此后变得溶解在溶剂例如水中,或以其他方式被滥用者有效获取。

[0078] 核-壳粒子的核(未包衣)可以含有任何有用量的蜡,直至并包括100%蜡,例如基于所述核的总重量从0.1至85重量%的蜡,例如基于核总重量从15至60重量%或从25至50重量%的蜡。更通常地,剂型中蜡的有用量(例如,位于所述包衣粒子中、例如核中的蜡)可以基于剂型的总重量在0.05至15重量%的范围,例如,基于所述剂型的总重量从0.1至10重量%或从2至5重量%的蜡。

[0079] 所述蜡可以是通常疏水性的并且在室温下可以是固体或液体、优选在室温下(25℃)是固体的蜡(例如脂肪)材料。通常有用的脂肪包括作为脂肪酸基化合物的那些疏水性材料,所述化合物通常具有通常为6或更低的亲水/亲脂平衡(HLB),更优选4或更低,并最优选2或更低。脂肪可具有任何熔融温度,优选的脂肪在室温下是固体并具有至少30℃的熔点,例如至少40℃,例如至少50℃。有用的脂肪包括脂肪酸和脂肪酯,其可以是取代或未取代、饱和或不饱和的,并具有至少10、12或14个碳的链长。所述酯可以包括与醇、二醇或甘油的任一种结合的脂肪酸基团。关于甘油,单、二和三脂肪取代的甘油及其混合物可以是有用的。

[0080] 合适的蜡成分包括脂肪酸酯、甘油脂肪酸酯、脂肪甘油酯衍生物、蜡和脂肪醇例如山嵛酸酯(也叫做甘油山嵛酸酯,丙三醇山嵛酸酯,甘油二十二烷酸酯)(例如,COMPRITOL®),甘油棕榈酸硬脂酸酯(PRECIROL®),甘油单硬脂酸酯,硬脂酰宏甘油酯(GELUCIRE®50/13)。其他蜡更通常地包括昆虫和动物蜡、植物蜡、矿物蜡、石油蜡和合成蜡;具体的例子包括蜂蜡、巴西棕榈蜡、小烛树蜡、褐煤蜡、小冠巴西棕蜡、稻谷麸皮蜡、西蒙得木蜡、微晶蜡、鲸蜡酯蜡、鲸蜡醇、阴离子型乳化蜡、非离子型乳化蜡和石蜡。

[0081] 所述剂型可以任选包括以填料或粘结材料形式的另一种滥用制止物,其以破坏滥用实践的方式提供,在所述滥用实践中滥用者压碎、研磨或以其他方式将所述剂型形成为碎粉末,所述碎粉末可能通过吹鼻方式被滥用或从其可以容易地通过例如使用溶剂溶出或提取来获取和取出活性药剂。

[0082] 所述粘结剂或填料可以在所述剂型中存在的位置和量还要不妨碍所述活性药物成分在立即释放剂型中被患者口服摄入后的预期摄取。示例性的位置是在核-壳粒子的核处。位于还包含活性药物成分的粒子(例如核-壳粒子)的核处(例如,在覆盖所述核的层处,或在所述核内)的合适的填料或粘结剂,将在所述粒子压碎或研磨等时变得与所述活性药物成分混合。如前面所论述,所述剂型还可以包括不含API的核壳粒子。位于不含API的这种粒子(例如核-壳粒子)的核处的填料或粘结剂在所述剂型压碎、研磨等时也将变得与所述API(例如,也存在于所述剂型中的含API的核壳粒子中存在的API)混合。当填料或粘结剂与所述活性药物成分混合时,抑制或防止了所述活性成分在此后变得溶解在溶剂例如水中,或以其他方式被滥用者有效获取。

[0083] 当在剂型的核或粒子内、例如在核-壳粒子的核处存在时,填料或粘结剂可以任何有用的量存在,例如在核-壳粒子的核中从0直至并包括100%填料或粘结剂(单独或组合),例如基于所述核的总重量从10至95重量%的填料或粘结剂(单独或组合),例如基于核总重量从40至85重量%或从50至75重量%。含有高填料水平的核的例子包括含有100%糖的球

形粒子，和含有100％微晶纤维素的球形粒子。具有有用的粒度的惰性球形填料产品，例如这些，是可在商品名Celphere®下和商品名Suglets®下(糖球，还含有淀粉)商购的，包括如下：CELPHERE SCP-100(粒度(μm)75-212)；CELPHERE SCP-102(粒度(μm)106-212)；CELPHERE SCP-203(粒度(μm)150-300)；CELPHERE SCP-305(粒度(μm)300-500)；CELPHERE SCP-507(粒度(μm)500-710)；CELPHERE SCP-708(粒度(μm)710-850)。这些的粒度可以被认为对如本文中所述的任何核是有用的，由任何单一的填料、胶凝聚合物、粘结剂、其任何组合、或与API相结合的任何单一或组合的材料制备。

[0084] 所描述的剂型中可包括的另一种任选的滥用制止特征是作为核-壳粒子的一部分的膜层或包衣，其位于API之上并包围API。所述膜层也可以在不含API或API层的核壳粒子上作为层或包衣存在。所述膜层可以是能够作为膜层施加到核-壳粒子上包围API、或施加到不含API或API层的核-壳粒子上的任何膜层。

[0085] 所述膜层可以从任何可药用的成膜聚合物材料制备，并将包含任何可药用的成膜聚合物材料，例如粘结剂(例如如本文中所述，例如羟丙基纤维素，聚甲基丙烯酸甲酯，乙基纤维素，羟丙基甲基纤维素，羟基甲基纤维素，聚乙烯醇，等等)、耐溶剂层、和pH敏感层(有时也称为反肠溶材料或层)例如Eudragit®E 100中的一种或多种。所述膜层可以单独包括这些材料的任一种(例如，膜层可以包括100％的这些材料类型的单独一种)，或者膜层可以包括这些类型材料的两种或更多种的组合。

[0086] 耐溶剂层是妨碍或防止药物在溶剂(例如水、乙醇和甲醇中的一种或多种)中释放，同时仍然允许药物当作为立即释放型口服剂型摄入时在胃肠道正常释放。这种类型的滥用制止特征，例如，耐溶剂膜，通过防止或阻碍滥用者在滥用者经常使用的溶剂类型(例如水，乙醇，甲醇)中溶解完整或变成粉末的剂型，可以抑制获取剂型的API。同时，所述耐溶剂膜可以在人胃肠道中足够迅速地溶解以允许立即释放特性。作为滥用制止特征，这种类型的耐溶剂膜覆盖和包围了核-壳粒子的API并充当膜屏障或减速剂，防止或妨碍通过使用溶剂获取API。

[0087] 耐溶剂膜是不容易或不立即溶于小体积经常被滥用者用于溶解API的溶剂类型的膜中，所述溶剂类型例如水或C_1-C_4醇例如乙醇或甲醇的任一种。“小体积”是指这种溶剂的量可以含有足够浓缩的溶解API量以对滥用者实现想要的药物滥用生物效应有用，而且也能够给药以供所述API的滥用，例如可以含有的API量(浓度)如果通过注射或吹鼻给药有效达到预期的“高潮”的体积，所述体积也小得足以允许所述体积通过注射或吹鼻给药。对于可如此用于滥用的剂型，所述剂型中的API必须能够由滥用者在不过度复杂化下以足够的浓度获取并溶解在“小体积”的溶剂中，所述小体积溶剂是可以通过注射或通过吹鼻给药的体积。通常，“小体积”的溶剂是指50毫升或更少，或20毫升或更少，或10毫升或更少，或5毫升或更少(可注射或用于吹鼻的体积)。

[0088] 耐溶剂膜层可以是位于核-壳粒子上的膜，其难以溶于“小体积”的水或C_1-C_4醇例如乙醇或甲醇中，例如，不立即溶解在水或任何一种C_1-C_4醇例如甲醇或乙醇的一种或多种中。如果核-壳粒子放入这些溶剂的一种中，所述耐溶剂膜由此妨碍或防止滥用者获取所述核-壳粒子的API部分。所述耐溶剂膜不需要完全或基本上不溶于这些溶剂的任何一种、或所有所述溶剂中，并且对于可用作立即释放剂型的剂型，它必须能够允许在胃肠道中足够迅速地获取API。

[0089] 耐溶剂膜的具体例子是表现出溶解性能取决于溶剂的pH的膜。耐溶剂膜的例子可以是这样的膜，其在高于人胃的pH条件的pH下基本上或完全不溶，而在胃(和胃肠道)的pH条件下充分可溶解以允许所述膜足够迅速地溶解和释放API，使得所述剂型可用作立即释放型口服剂型。PH敏感层是一种类型的耐溶剂膜，并可以在剂型中布置成包围活性药物成分和抑制或防止在胃外面的溶剂中(例如，在中性pH环境下)获取和溶出所述活性药物成分，同时仍然允许所述活性药物成分在使用者的胃的较低pH环境下从立即释放剂型有效释放。这种类型的滥用制止特征可以防止或明显妨碍滥用者使用在胃外面而且不具有比较酸性的pH的溶剂例如水或C_1-C_4醇例如乙醇、甲醇等或其混合物、具有高于在人胃中存在的pH的pH例如pH高于4、高于5或高于5.5或高于6的溶剂获取剂型的活性药剂(例如，在核-壳粒子的核处或在布置在所述核上的层中，或在所述核和所述布置在核上的层的二者中)。

[0090] pH敏感层可用作耐溶剂膜，作为核-壳粒子的层放在剂型中，以包围、覆盖、或围绕含有活性药物成分的所述核-壳粒子的一部分。例如在核-壳粒子中，活性药物成分可以根据需要位于核处或未包衣的或包衣的核外面的层处；以pH敏感层形式的耐溶剂膜可以布置为包围或覆盖所述含有活性药物成分的核壳粒子部分的独立层。所述pH敏感层可以直接接触(邻近于)包含活性药物成分的核或层；或者核-壳粒子可以在pH敏感层和包含活性药物成分的核或层之间包含一个或多个中间层。另外，pH敏感层可以作为不含API层或任何API的核-壳粒子层包含在所述剂型中。

[0091] 有用的pH敏感层可以包括可作为如本文中所述的粒子层布置的聚合物或其他材料，从而覆盖含有活性药物成分的更靠内的层或核，以形成包围或覆盖活性药物成分的pH敏感膜。所述pH敏感膜可通过暴露于表现出可以存在于所述剂型的使用者的胃中的pH的液体而溶解，所述pH例如pH低于6或低于5.5。为了起到滥用制止特征的作用，即，为了抑制或防止通过将所述剂型(任选磨碎或变成粉末的)暴露于可容易得到的溶剂而有效取得所述活性药物成分，所述pH敏感层可以含有在高于人胃中存在的pH的pH例如pH高于6下不容易溶解或基本不溶解的聚合物；通过在pH高于6下不溶解，所述pH敏感聚合物在可容易得到并被滥用者常用于从剂型提取水溶性药物的很多溶剂例如水、乙醇、甲醇等中不会溶解。

[0092] 可用于pH敏感层的pH敏感聚合物的例子包括反肠溶性聚合物的类别，其含有阳离子型官能团并且表现出如本文中所述的pH依赖性的溶解性。例子包括含有碱性官能团例如氨基、并且在(人)胃中存在的pH条件下表现出溶解性但在比较高的pH条件下不溶解的聚合物，所述pH条件例如不超过pH 4、5或5.5，或不超过pH 6。这种pH敏感聚合物的更具体的例子包括二甲基氨乙基甲基丙烯酸酯和中性甲基丙烯酸酯的共聚物；例如，二甲基氨乙基甲基丙烯酸酯、甲基丙烯酸丁酯和甲基丙烯酸甲酯，例如以2:1:1的比率。这样的聚合物的例子是在商品名Eudragit®E-100、Eudragit®E PO、Eudragit®E 12,5下可商购的以及类似的氨基官能的pH敏感聚合物。优选的pH敏感聚合物是聚合物Eudragit E100，但在低pH下足够亲水并在较高pH下疏水而表现出所描述的pH依赖的溶解性的任何聚合物，如果其他方面可接受用于药物剂型中、例如作为口服剂型的非毒性成分，也可以是有效的。反肠溶性组合物也描述在EP 1694724 B1中，题为“pH敏感聚合物及其制备过程(pH Sensitive Polymer and Process for Preparation Thereof)”。

[0093] 当作为含有活性药物成分的粒子的包衣存在时，耐溶剂膜层可以在可用作滥用制止特征的任何量下存在，在核-壳粒子总重量的0.1至90重量%的范围，例如按照核-壳粒子

总重量为3至50重量％或4至40重量％的耐溶剂聚合物。更通常地，剂型中耐溶剂膜层的有用量可以在基于剂型的总重量从1至50重量％耐溶剂膜层或聚合物的范围内，例如基于剂型总重量从2至30重量％或3至15重量％的耐溶剂聚合物。类似地，当作为不含API的粒子的包衣存在时，耐溶剂膜层可以存在可用作滥用制止特征的任何量，例如在如上文对于含API的包衣粒子所公开的相同数值范围内。

[0094] 如本描述的剂型还可以优选包括崩解剂，其起到在例如在人胃的条件下使用期间引起所述剂型膨胀和破碎的功能，以允许所述剂型的活性药物成分以达到立即释放特性的方式释放。崩解剂是药物剂型的已知成分，各种例子是已知的和可商购的。崩解剂的例子包括下列物质的组合物或含有下列物质：羧甲基淀粉钠、淀粉(例如玉米淀粉、马铃薯淀粉、米淀粉、木薯淀粉、麦淀粉、玉米淀粉和预胶化淀粉)、交联羧甲基纤维素钠、交聚维酮(交联聚乙烯N-吡咯烷酮或PVP)(polyplasdone XL-10)、羧甲基淀粉钠(EXPLOTAB®或PRIMOJEL®)、前述两种或更多种的任何组合，和形成为具有一定粒度、密度等的粒子的其他可药用材料，以允许将所述崩解剂加工到有用的立即释放剂型中。

[0095] 所述崩解剂可以存在于立即释放剂型中允许所述崩解剂在摄入后如预期起作用、在完整剂型内膨胀、以在胃中引起所摄入的剂型分裂和允许活性药物成分从所述剂型的预期立即释放的任何位置。崩解剂的一个有用的位置可以是在剂型例如压制片剂或胶囊中作为赋形剂的组分，所述赋形剂用于包含含有如本文中所述的活性药物成分的核-壳粒子。

[0096] 当作为剂型的赋形剂包含时，崩解剂可以在对达到剂型的API的立即释放有用的量下存在。如本文中所述的立即释放剂型中崩解剂的有用量的例子可以是基于所述剂型的总重量在0.5重量％至50重量％崩解剂的范围内，例如基于所述剂型的总重量从1至30重量％崩解剂。在剂型的基质中崩解剂的量可以符合这些量，例如，崩解剂可以在剂型的基质(例如，除所述包衣粒子或API以外总体剂型)中包含基于所述基质的总重量在0.5重量％至50重量％崩解剂范围内的量，例如基于基质总重量从1至30重量％崩解剂。

[0097] 所描述的剂型还可以包括可能对达到立即释放剂型的预期加工和工作性能有用的各种已知和常规药物赋形剂的任一种。这些赋形剂包括填充剂、粘结剂、润滑剂、助流剂、着色剂、pH调节剂等，并可包括在片剂或胶囊的核-壳粒子中或基质(例如压缩基质)中。也可以包括在本发明片剂中的药物赋形剂的更详细说明可见于《药物赋形剂手册》(Handbook of Pharmaceutical Excipients)，第五版(2006)。

[0098] PH调节剂可包括在所描述的立即释放剂型中，例如在影响所述剂型特定位置的pH的位置上，所述特定位置只是总剂型的一部分。例如，碱形式的pH调节剂可以包括在含有酸官能性的胶凝聚合物的位置处，以中和所述酸官能性。在所述胶凝聚合物的位置处包括的pH调节剂的量可以是有效中和该位置处所述胶凝聚合物的酸官能性的量。更具体地说，所描述的包括酸官能胶凝聚合物例如卡波普的剂型组分可以包括碱，其量和位置要中和该聚合物的酸官能性。所述pH调节剂可以位于有效引起这样的中和的位置处，例如，在所述剂型的含有所述酸官能胶凝聚合物的位置处，例如在核-壳粒子的核处或作为赋形剂的一部分，所述赋形剂包括酸官能胶凝聚合物并且起到将粒子共同粘结为剂型的功能。

[0099] 可用于所描述的立即释放剂型中的填料的例子包括乳糖、淀粉、右旋糖、蔗糖、果糖、麦芽糖、甘露醇、山梨糖醇、高岭土、微晶纤维素、粉末纤维素、硫酸钙、磷酸钙、磷酸二钙、乳糖醇或前述的任何组合。与非填料成分例如胶凝聚合物相比，填料将具有如果与溶剂

例如水相结合的话不导致显著粘度增加或如本文中对于胶凝聚合物所述的凝胶形成的分子量。

[0100] 填料可以存在于所描述的剂型的任何部分，包括核-壳粒子；所述填料可以存在于核中、含有布置在所述核上的含有活性药物成分的层中、耐溶剂膜中、基质中或者所述剂型的两个或更多个这些部分中。所述填料在剂型的任何一个或多个这些部分处可以存在的量要提供所述剂型的一部分和全部剂型的预期加工或功能性质。剂型中总填料量也可以根据需要提供预期的功能性，包括立即释放特性，例如基于所述剂型的总重量在0至80重量％填料范围内的量，例如基于剂型总重量从5至50％的填料。

[0101] 可以包括在所描述的剂型中的粘结剂的例子包括聚合材料例如藻酸、羧甲基纤维素钠、微晶纤维素、糊精、乙基纤维素、明胶、淀粉、预胶化淀粉、聚乙烯醇、聚环氧乙烷、聚乙烯吡咯烷酮、聚丙烯酰胺、聚乙烯恶唑烷酮、聚乙烯醇、甲基纤维素、羟丙基纤维素、羟甲基纤维素和这些中两种或更多种的任何组合。粘结剂可以是水溶性材料；与非粘结剂成分例如胶凝聚合物相比，粘结剂具有在与小体积的水结合后不导致形成凝胶或高粘性组合物的分子量。粘结剂可以表现出与胶凝聚合物相比相对低的分子量，和相对较低的粘度(例如，当在2％水溶液中测量时)。可用作粘结剂的聚合物典型地可以具有小于50,000的分子量，例如小于30,000或小于10,000。

[0102] 粘结剂可以存在于所描述的剂型的任何部分中，包括核-壳粒子的核或膜或包衣，或作为赋形剂的一部分以在剂型中包含或粘结核-壳粒子。填料可以与活性药物成分、胶凝聚合物或二者相结合包含在核-壳粒子的核中；作为包被在核上的活性药物层或核-壳粒子的另一个层的一部分；作为耐溶剂膜的一部分；或在可用于将粒子粘结在剂型中的赋形剂内。粘结剂以在所述剂型的各部分和总体剂型中提供预期的加工或功能性质的量，可以存在于所描述的立即释放剂型的这些部分中的任何一个或多个处。剂型中总粘结剂的量也可以根据需要提供预期的功能性，包括立即释放特性，例如基于所述剂型的总重量在0.1至10重量％粘结剂范围内的量，例如基于剂型总重量从0.5至7重量％的粘结剂。

[0103] 润滑剂的例子包括无机材料例如滑石粉(水合硅酸镁；聚合物，例如PEG 4000；脂肪酸，例如硬脂酸；脂肪酸酯，例如甘油酯(例如单硬脂酸甘油酯，三山嵛酸甘油酯，和二山嵛酸甘油酯)；糖酯(例如单硬脂酸失水山梨糖醇酯和单棕榈酸蔗糖酯)；二山嵛酸甘油酯(Compritol®888ATO)；和脂肪酸的金属盐(例如，硬脂酸镁，硬脂酸钙，和硬脂酸锌)。因此，常用的润滑剂包括滑石粉、单硬脂酸甘油酯、硬脂酸钙、硬脂酸镁、硬脂酸、山嵛酸甘油酯、聚乙二醇、泊洛沙姆和前述的组合。润滑剂可以任何有用的量包括在所描述的立即释放剂型中，所述量例如基于剂型的总重量在0.1至10重量％润滑剂范围内，例如基于剂型总重量从0.5至7重量％润滑剂。

[0104] 助流剂的例子包括胶体二氧化硅、未处理的气相二氧化硅(例如，如在商品名Cab-O-Sil®下可得到的)、和结晶或熔融石英。助流剂可以任何有用的量包括在所描述的立即释放剂型中。

[0105] 着色剂的例子包括FD&C-型染料和色淀、水果和蔬菜提取物、二氧化钛、氧化铁及其混合物。着色剂可以通过所述着色剂掺合任何其他成分而纳入剂型中。或者，着色剂可以施加到剂型的外表面。

[0106] 单独或组合的任何活性药物成分可以包括在如本文中所述的立即释放剂型中。关

于如本文中所述的滥用制止特征，一些是基于核-壳粒子的具体结构或组成特征起作用的，可能特别有用的API可以是可能遭受滥用、成瘾、过量用药或这些的两种或更多种的那些活性药物成分类型；这样的API可以位于所述剂型中引起所述API受所述核-壳粒子的滥用制止特征影响的位置处，例如，在核-壳粒子的核或内层处。

[0107] 通常容易受到滥用的药物包括镇静催眠药、兴奋剂(例如中枢神经系统((CNS)兴奋剂)、抗焦虑药、抗精神病药、分离麻醉剂和麻醉止痛剂，包括但不限于可以引起对所述药物的心理或身体依赖性的药物。API可以包括任何治疗上可接受的药物盐、药物衍生物、药物类似物、药物同系物、或活性药物成分的多晶型物。

[0108] 镇静催眠药包括，例如，巴比妥类，例如苯巴比妥、甲苯比妥、异戊巴比妥、戊巴比妥和西可巴比妥及其可药用盐；苯二氮卓类，例如地西泮、氯氮卓、劳拉西泮、三唑仑、替马西泮、阿普唑仑和氟西泮及其可药用盐；吩噻嗪类，例如阿利马嗪、氯丙嗪、硫利达嗪及其可药用盐，和催眠药物，例如唑吡坦、扎莱普隆和艾佐匹克隆及其可药用盐。抗焦虑药包括，例如，苯二氮卓类，例如地西泮、氯氮卓、艾司唑仑、劳拉西泮、三唑仑、阿普唑仑、氯硝西泮和氟西泮及其可药用盐。CNS兴奋剂包括，例如安非他明类，例如右旋安非他明、左旋安非他明(benzadrine)、甲基安非他明(methadrine)、伪麻黄碱、和Adderall(安非他明混盐)及其可药用盐，以及非安非他明精神兴奋剂例如哌醋甲酯、莫达非尼和阿莫达非尼及其可药用盐。麻醉止痛剂包括阿片样物质，例如，丁丙诺啡、布托啡诺、可待因、二氢可待因、二氢吗啡、氢可酮、氢吗啡酮、吗啡、羟考酮、羟吗啡酮、美沙酮、芬太尼、哌替啶、曲马多、丙氧吩、及其可药用盐。抗精神病剂可以包括，例如，如上列的吩噻嗪类，丁酰苯类例如达罗哌丁醇和氟哌啶醇，二苯氧氮杂卓类例如洛沙平，和非典型性的抗精神病剂例如阿立哌唑、氯氮平、奥氮平、喹硫平、利培酮、齐拉西酮、帕利哌酮和瑞莫必利。

[0109] 可能容易受到滥用的其他具体药物包括，例如，肌肉松弛药例如环苯扎林及其可药用盐，大麻醇(例如，Δ^1-大麻醇，Δ^2-大麻醇，Δ^3-大麻醇，$\Delta^{3,7}$-大麻醇，Δ^4-大麻醇，Δ^5-大麻醇，和Δ^6-大麻醇)；大麻素，例如屈大麻酚、Δ-9-四氢大麻酚(THC)、大麻二酚(CBD)、大麻隆、地塞比诺、ajulemic acid、cannabinor、利莫那班和它拉那班及其可药用盐；和分离麻醉剂例如氯胺酮和艾氯胺酮，及其可药用盐。

[0110] 立即释放剂型中包括的活性药物成分的量可以是任何有用的量，如已知的和可以在相关文献例如Goodman&Gillman的《治疗的药理基础》(The Pharmacological Basis of Therapeutics)，第9版，219-222、361-396、521-535页，1996中找到的。例如，羟考酮的盐酸盐的典型治疗量范围是5mg、10mg、或直至400mg。经常，当加工成合适的立即释放剂型时，所述活性药物成分可以在这样的剂型中以正常处方量存在，基于所述剂型总重量按干重计典型为0.5至25％。关于单个单位剂型中的麻醉止痛剂例如阿片样物质，例如以约1至约500mg、或约1至约250mg、或约1至约100mg的水平；例如2.5、5、7.5、10、15、20或30毫克(mg)/剂型单位。在其他实施方式中，剂型含有任何适量的API以提供治疗效应。

[0111] 本发明还涉及治疗方法，包含口服给药有效量的本文中描述的立即释放滥用制止型剂型。例如，本文中提供了通过给药有效量的含有麻醉止痛药例如阿片样物质药物的API的本文所述立即释放滥用制止型剂型，治疗或预防有需要的对象中的疼痛或不适的方法。

[0112] 本文中还提供了通过给药有效量的含有镇静催眠药例如巴比妥酸盐的API的本文所述立即释放滥用制止型剂型，在有需要的对象中治疗睡眠障碍的方法。

[0113] 本文中还提供了通过给药有效量的含有抗焦虑药例如苯二氮卓的API的本文所述立即释放滥用制止型剂型，在有需要的对象中治疗焦虑的方法。

[0114] 本文中还提供了通过给药有效量的含有抗精神病药例如喹硫平的API的本文所述立即释放滥用制止型剂型，在有需要的对象中治疗精神病的方法。

[0115] “有效量”当结合本文中描述的组合物使用时，是在有需要的对象中足以产生治疗结果的量。例如，治疗结果可以包括，但不限于治疗或预防对象的疼痛、睡眠障碍、焦虑或精神病症状。

[0116] 所描述的剂型可以任选包括通常不容易受到滥用的类型的一种或多种附加API。这些附加的API可以是任何合适的或需要的API，例如在非甾体止痛药类别中的那些。措辞“非甾体止痛药”在本文中使用时是指包括通常称为非甾类抗炎药物或“NSAIDS”和对乙酰氨基酚的那些，其是非甾类的，但不通过炎症机制起作用。因此，术语“非甾体止痛药”将包括对乙酰氨基酚，并还包括NSAIDS例如阿司匹灵、布洛芬和萘普生。所述剂型对于这些通常不受到滥用的API也表现出立即释放性质。并且这些API可以在所述剂型中以任何有用的水平存在，所述水平基于所述剂型的总重量按干重计典型是0.5至25重量％、例如1至10重量％的所述API，例如在5、25、50、75、100、125、150、175、200、300、325、500、750或者直至或超过1000毫克(mg)/剂型单位的水平或其之间。在其他实施方式中，剂型含有适量的API以提供治疗效应。

[0117] 所描述的立即释放剂型可以包括单独或组合的一种或多种所描述的滥用制止特征；例如，下列的一种或多种：胶凝聚合物，作为核-壳粒子的一部分(例如，在核-壳粒子的核处)；蜡，作为核-壳粒子的一部分(例如，在核-壳粒子的核处)；粘结剂或填料，作为核-壳粒子的一部分(例如，在核-壳粒子的核处)；膜层，可以任选是耐溶剂膜(例如，pH敏感膜)，作为核-壳层的一部分；或胶凝聚合物，作为用于将核-壳粒子保持在一起作为立即释放剂型的一部分的赋形剂或粘结剂的组分。具有这些滥用制止特征，其他类型已知的滥用制止特征可以不需要并且可以特定地从所描述的立即释放剂型中排除出去。所描述的剂型的某些实施方式可以特定排除其他类型的滥用制止物。

[0118] 具体而言，一些剂型包括鼻刺激剂以阻止或防止通过吹鼻滥用。所述鼻刺激剂可以是粘膜刺激剂或鼻通道刺激剂，其当被包含在磨碎或变成粉末的剂型中时，如果通过鼻通道吸入，可以引起滥用者的鼻通道组织疼痛或刺激。例子包括表面活性剂例如月桂基硫酸钠、泊洛沙姆、失水山梨糖醇单酯和单油酸甘油酯。本描述的剂型的某些具体实施方式不需要，并可以特定地排除，鼻刺激剂，例如上述那些。

[0119] 或者，剂型包括催吐剂以引起呕吐。本描述的剂型的某些具体实施方式不需要并可以特定地排除催吐剂。

[0120] 或者，一些剂型包括泡腾剂充当吹鼻滥用制止物。所述泡腾剂包括酸性组分和碱性组分，其当在水介质存在下结合时，例如在吹鼻时，释放气体例如氧气或二氧化碳。参见，例如，专利公布WO 2013/077851，其全文在此引为参考。所述酸源可以是，例如，柠檬酸、酒石酸、苹果酸、马来酸、乳酸、羟基乙酸、抗坏血酸、富马酸、己二酸、琥珀酸、其盐、及其组合。所述碱可以是，例如，碳酸盐或碳酸氢盐。本描述的剂型不需要，并可以特定地排除，为了气体例如氧气或二氧化碳而可以结合的酸和碱形式的泡腾剂。

[0121] 别的其他剂型包括起到活性药物成分拮抗剂作用的生物活性化合物。拮抗剂可以

防止以包括一次性服食多个或若干或更多剂型单位的方法在内的方式的潜在剂型滥用。拮抗剂是阻断或抵消活性药物成分的效应的化合物，并且各种类别的药物，包括阿片样物质和其他药剂，是可得到的和已知的。对于阿片样物质的拮抗剂的例子包括化合物例如纳曲酮、钠洛酮、纳美芬、西科拉欣(cyclazacine)、莱瓦洛芬。用于并入剂型中的拮抗剂和拮抗剂制备方法的具体例子在美国专利No.7,682,633和7,658,939中提供，其在此引为参考。根据本描述，包括阿片样物质并且包括如本文中所述的一种或多种滥用制止特征(例如，胶凝聚合物、蜡、耐溶剂膜、或其组合)的立即释放剂型，可以配制成不包含并且特定地排除也包括在所述剂型中的API的拮抗剂，例如在含有阿片样物质的剂型中的阿片样物质拮抗剂。

[0122] 参考图1A和1B，剂型剂型可以包括包含API的粒子10A。所述粒子(例如，包衣粒子或“核-壳”粒子)可以包括核12a(或“未包衣的核”)，所述核可以包被一个或多个层、膜或包衣，例如14a、16a、或包被在这些之上、之下或中间的任何附加的层或包衣。在图1B和1C中，命名为16a的层可以是含有API的层，并且命名为14a的层可以是耐溶剂的，例如pH敏感膜层。粒子10A可以包含一种或多种本文中描述的成分，例如任何一种或多种API(尤其容易受到滥用的API)、胶凝聚合物、任选的蜡、任选的耐溶剂层、以及在这些层之下、之上或中间或者在层和核之间的一个或多个附加层。每个层可以存在的大小或量(例如厚度)将产生具有一种或多种本描述的滥用制止特征的有用的立即释放剂型。粒子10a的核或层的其他任选组分可以是填料、粘结剂、其他赋形剂、或溶剂(不超过剩余量，即使有的话)例如水或乙醇，所述溶剂用于制备所述包衣粒子并且在形成所述核、包衣或包衣粒子后被基本上除去。核10A的例子可以包括任何量的下述不同成分：胶凝聚合物(例如核的0至100％)、如本文中所述的填料例如糖(甘露醇)或微晶纤维素(例如核的0至100％)、粘结剂(例如，核的0至100％)、和蜡(例如，核的0至100％)。

[0123] 虽然核-壳粒子10a被认为是新的和创造性的，但可用于制备这些新型包衣粒子的某些方法步骤可以是已知的。可利用的方法包括制药领域中已知可用于制备粒子和包衣粒子的某些方法和加工步骤。核-壳粒子10A可以通过将核12A的成分与溶剂例如水或乙醇混合并通过已知的方法将所述混合物形成为球形核粒子的初始步骤来制备。所述粒子可以干燥并按大小分开，然后以连续膜或层形式的一个或多个包衣可以施加于所述核，任选相继施加，以产生包围所述核的多个层。产生多层包衣粒子的通用加工可以包括一系列步骤例如调配、混合、造粒、湿磨、包衣(通过任何方法例如流化床包衣、喷涂等)和一个或多个干燥步骤例如利用流化床或其他干燥法。在成核和包衣步骤之间、例如在干燥步骤之后间歇性地，可以基于大小拣选或分开包衣或未包衣的粒子以产生具有所需的大小范围和分布的粒子的组合物或集合。因此，本发明的包衣的颗粒状组合物可以通过包含以下步骤的过程制备：

[0124] (i)蜡或胶凝聚合物或其混合物在包含合适的粘结剂的水醇溶液或悬液存在下造粒，以形成颗粒；

[0125] (ii)步骤(i)中形成的颗粒用包含API的溶液或悬液敷层；和

[0126] (iii)用包含成膜聚合物材料的溶液或悬液包被步骤(ii)中形成的敷层颗粒，以形成包衣的敷层颗粒。

[0127] 上述过程还可以包含研磨和干燥在步骤(i)中形成的颗粒的步骤。

[0128] 在所述核包括糖球或微晶纤维素球的情况下，上述过程的步骤将如下修改：

[0129] (i)提供糖球(或微晶纤维素球)；

[0130] (ii)所述糖球(或微晶纤维素球)用包含API的溶液或悬液敷层；和

[0131] (iii)用包含成膜聚合物材料的溶液或悬液包被步骤(ii)中形成的敷层球，以形成包衣的敷层球。

[0132] 本发明的压制片可以通过包含以下步骤的过程制备：

[0133] (i)根据上述任何一种过程制备的包衣敷层颗粒(或包衣敷层球)与第二种API(例如对乙酰氨基酚)、胶凝聚合物和崩解剂、并任选与选自填料、着色剂和pH调节剂的至少一种附加的赋形剂相结合，以形成第一混合物，然后将所述第一混合物掺合适当的时间；

[0134] (ii)向在步骤(i)中形成的掺合混合物添加润滑剂以形成第二混合物，然后将所述第二混合物掺合适当的时间；

[0135] (iii)将步骤(ii)中形成的掺合混合物利用常规压片机压制以形成压制片剂。

[0136] 步骤(i)中的适当掺合时间可以是，例如，约5至约90分钟，或约10至约60分钟，或约20至约40分钟，或约30分钟。步骤(ii)中的适当掺合时间可以是，例如，约1至约30分钟，或约5至约20分钟，或约10分钟。

[0137] 在如图1A、1B和1C所示的某些实施方式中，所描述的立即释放剂型可以包括包含核12A的核-壳粒子10A，所述核只含有少量API或含有非显著量的API。基于所述核-壳粒子的核的总重量，核12A可以包含小于5重量％、例如小于1或小于0.5重量％的活性药物成分。或者，核12A可以包含在核-壳聚合物中药物成分总量的小于5重量％，例如基于所述核-壳粒子的中API的总重量，小于5、小于1或小于0.5重量％的活性药物成分。在这些实施方式中，大部分API可以包含在核12A的外面，例如，在API层16a中，其可以包含在核-壳聚合物中的API总量的至少50、至少75、或至少90、或至少95重量％的API。

[0138] 核12A可以包括粘结剂、胶凝聚合物(例如HPMC)、蜡或填料，任选单独或组合，各自以允许所述核的材料起到如本文中所述的一种或多种滥用制止特征的作用的量。参见与其一道包括的例子作为这些成分的有用量和量的范围的例子。

[0139] 参考图1A，核12A含有胶凝聚合物、蜡、粘结剂或填料、或这些的任何组合，并且没有API(意味着不超过非显著量，例如基于核12A的重量小于0.5或小于0.1重量％)。如图1B和1C所示，不含API的核12A可以包被含有API的包衣层，例如活性药物层或API层16A。如图1B所示，核-壳粒子10A包括不含任何API的核12A、和API层16A，所述API层含有一定量的API，例如准备包含在从粒子10A制备的剂型中的API(例如通常容易受到滥用的API)的总量。API层16A可以含有可用于将API层16A形成为核12A外表面上的层的如本文中所述的一种或多种成分。(API层16A中的API可以是通常容易受到滥用的API类型，例如阿片样物质，并可以占所述核-壳粒子中和所述剂型中该类型API总量的全部或大部分(例如，至少70、至少80、至少90或至少95％)；在这种实施方式中，所述核可以含有所述核-壳粒子中API总量的小于10、小于5、或小于1％，和所述剂型中API总量的小于10、5或1％。)API层中有用的非API成分可以包括与所述API一起的粘结剂。所述API和粘结剂可以携带在溶剂(例如水、乙醇或二者)中并包被和干燥以在核12A的外表面上形成优选连续的膜层，即，API层16A。参见与其一道包括的例子作为这些成分的有用量和量的范围的例子。

[0140] 核-壳粒子10A还可以任选包括膜层，例如，如本文中所述的耐溶剂层(例如，pH敏感层)14A。

[0141] 在某些备选实施方式中，所描述的剂型可以包括包含核12B的核-壳粒子10B，所述核含有有用量的API，例如在制备成包括粒子10B并具有如本文中所述的一种或多种滥用制止特征的立即释放剂型中有用的API量。参见图2A和2B。根据这样的实施方式，粒子10B的核12B可以含有胶凝聚合物、任选的蜡、任选的粘结剂或填料、和一定量的API。

[0142] 参考图2A，核12B含有胶凝聚合物、任选的蜡、任选的粘结剂和API。参考图2B，含有API的核12B可以任选包被如本文中所述用于立即释放剂型的耐溶剂层(例如pH敏感层)14B。核12B还可以任选在施加所述耐溶剂层之前包被含有API的包衣层，例如活性药物层或API层。因此，如本文中所述的含API的核-壳粒子可以含有容易受到滥用的类型的API：

[0143] • 在包围所述核的API层中并在所述核中有显著的量；

[0144] • 在包围所述核的API层中并在所述核中有不显著的量；

[0145] • 只在包围所述核的API层中；或

[0146] • 只在所述核中。

[0147] 在某些备选实施方式中，所描述的剂型可以包括如图2B中描绘的核-壳粒子10B，其不含API层并且不含任何API。参考图2C，这种不含API的粒子10B，可以包括含有胶凝聚合物、任选的蜡和任选的粘结剂的核12B，所述核12B可以任选包被如本文中所述用于立即释放剂型的耐溶剂层(例如，pH敏感层)14B。

[0148] 包括API的包衣粒子10a或10b，和任选，不包括API的包衣粒子10B，可以包括在任何各种各样的剂型中，例子包括压制片剂或压制胶囊、栓剂、胶囊、囊片、丸剂、凝胶、软明胶胶囊等。作为一个例子，剂型12可以制备成压制片剂或压制胶囊。片剂或胶囊12可以含有分布在基质20内的核-壳粒子10(例如，10A或10B)，受压制形成压制片剂或胶囊12。核-壳粒子10A或10B大体上或具体地可以如本文中所述，并可以含有适合于提供在摄入片剂或胶囊12后提供预期剂量的API量；例如，基质20不包括任何显著的API量。

[0149] 基质20可以包括可用于与核-壳粒子10A、10B相结合以产生立即释放剂型的成分。立即释放剂型的有用赋形剂的例子可以包括允许所述剂型在摄入后破碎或崩解并促进暴露于胃内液体的成分，例如有用的量的崩解剂。用于这种剂型的这样的赋形剂的例子还可以包括充当滥用制止特征的一种或多种成分，例如如本文中所述的胶凝聚合物。其他赋形剂可以对于加工形成压制剂型有用，并且还可以允许所述压制剂型在具有一种或多种滥用制止特征下起到立即释放剂型的作用。

[0150] 以下非限制性例子显示了如本文中所述的各种剂型。所描述和例示的剂型可以由包括如下的造粒、包衣和压制步骤的过程制成。

[0151] 一般程序

[0152] 造粒

[0153] 1.山嵛酸甘油酯和羟丙甲纤维素K100M在高剪切造粒机中干混合。添加乙基纤维素的水醇溶液。或者，所述造粒可以通过在流化床造粒机中顶喷所述水醇溶液而产生。任选地，一部分乙基纤维素，例如约10至约50重量％，或约10至约40重量％，或约15至约30重量％，与所述山嵛酸甘油酯和羟丙甲纤维素K100M干混合，然后添加含有余量的所述乙基纤维素的水醇溶液。

[0154] 1.(或者，当在所述核中包括API时)山嵛酸甘油酯和羟丙甲纤维素K100M和API在高剪切造粒机中干混合。添加乙基纤维素的水醇溶液。或者，所述造粒可以通过在流化床造

粒机中顶喷所述水醇溶液而产生。任选地，一部分乙基纤维素，例如约10至约50重量％，或约10至约40重量％，或约15至约30重量％，与所述山嵛酸甘油酯和羟丙甲纤维素K100M干混合，然后添加含有余量的所述乙基纤维素的水醇溶液。

[0155] 2.所述颗粒然后使用减尺寸磨机(granumill)湿磨，然后使用流化床干燥，并任选过筛。

[0156] 敷层

[0157] 3.所述聚合物颗粒然后使用Wurster流化床敷层过程用API敷层(或者，使用高剪切造粒或顶喷式流化床造粒法造粒)。

[0158] 3.(或者当所述包衣颗粒将不含API时)所述敷层步骤被省略并且下面步骤4的包衣施加于在步骤1制备的颗粒上。

[0159] 包衣

[0160] 4.步骤3的敷层颗粒(或者，当所述包衣颗粒将不含API时，在步骤1制备的颗粒)然后使用配备了Wurster插件(底喷式组件)的流化床包衣机，用Eudragit E100共聚物和硬脂酸镁的乙醇悬液包衣。然后过筛和掺合包衣粒子。

[0161] 掺合和片剂压制

[0162] 使用所述包衣中间体制造的氢可酮和对乙酰氨基酚片剂的掺合、压制和装瓶过程如下：

[0163] 1.所述含API的包衣颗粒、APAP、交聚维酮、卡波普71g、碳酸氢钠、甘露醇、不含API的任选包衣的颗粒、和任选的所需要的着色剂，然后添加到所述掺合器中并混合。

[0164] 2.硬脂酸镁(和任选着色剂)然后添加到所述掺合器并混合。所述掺合物使用旋转压片机被压制成片剂。

[0165] 实施例1:包衣颗粒的制备

[0166] 表1:颗粒制剂的组分

[0167]

组分	%w/w
羟丙甲纤维素	60
山嵛酸甘油酯	26
乙基纤维素	14
总计	100

[0168] 在高剪切成粒机中制造颗粒，在其中羟丙甲纤维素和山嵛酸甘油酯干混合3分钟。然后，缓慢添加乙基纤维素N10的10％水醇溶液，同时将造粒机叶片和切刀速度保持在为颗粒形成和生长提供足够剪切的预选值。继续添加溶液，直至添加了全部量的乙基纤维素。所述颗粒然后使用减尺寸磨机(granumill)湿磨并随后装载到流化床中干燥。

[0169] 表2:敷层颗粒制剂的组分

[0170]

组分	%w/w
重酒石酸氢可酮	10
聚合物颗粒(EC,HPMC和Compritol)	85
羟丙甲纤维素2910	5

总计	100

[0171] 所制备的颗粒然后在底喷式流化床包衣机中用重酒石酸氢可酮和HPMC 2910的12%水溶液敷层。

[0172] 表3:包衣颗粒制剂的组分

[0173]

组分	% w/w
重酒石酸氢可酮敷层颗粒，10%	50
Eudragit E-100	33

[0174]

硬脂酸镁	17
总计	100

[0175] 所述重酒石酸氢可酮敷层颗粒然后在底喷式流化床包衣机中用Eudragit E-100共聚物和硬脂酸镁的25%醇悬液包衣。所生成的包衣颗粒随后用于进一步掺合和压制过程。

[0176] 实施例2:氢可酮/对乙酰氨基酚片剂

[0177] 表4:氢可酮/对乙酰氨基酚片剂制剂

[0178]

组分	% w/w	mg/片
重酒石酸氢可酮包衣颗粒，5%	20.0	200
扑热息痛[1]	33.7	337
甘露醇	10.3	103
卡波普	5.0	50
微晶纤维素	12.0	120
交聚维酮	15.0	150
碳酸氢钠	3.0	30
硬脂酸镁	1.0	10
总计	**100**	**1000**
[1] 含有 95% 对乙酰氨基酚(APAP)和 5%明胶		

[0179] 所述包衣颗粒根据上文实施例1制备并与对乙酰氨基酚和其他赋形剂(卡波姆,交聚维酮,碳酸氢钠,甘露醇,微晶纤维素)混合并在V-掺合器中掺合30分钟。然后添加硬脂酸镁润滑所述掺合物并将所述混合物再掺合5分钟,然后压制成氢可酮/对乙酰氨基酚片剂。

[0180] 实施例3:重酒石酸氢可酮/对乙酰氨基酚

[0181] 表5:氢可酮/对乙酰氨基酚颗粒制剂

[0182]

核壳组成		
组分	**位置**	**mg/片**
HPMC K100M	核	51.1
compritol	核	21.9
乙基纤维素	核	12
重酒石酸氢可酮	API 层	10
HPMC 2910	API 层	5
Eudragit E-100	膜	66.7
硬脂酸镁	膜	33.3
总计		200

[0183] 表6:氢可酮/对乙酰氨基酚片剂制剂

[0184]

组分	mg/片
核壳组成(上述)	200
APAP	325
明胶	12.1
甘露醇	42.9
卡波普	50
微晶纤维素	130
交聚维酮	200
碳酸氢钠	30
硬脂酸镁	10
总计	1000

[0185] 表7:氢可酮/对乙酰氨基酚全片剂组成

[0186]

全片剂组成	
组分	**mg/片**
HPMC K100M	51.1
compritol	21.9
乙基纤维素	12
重酒石酸氢可酮	10
HPMC 2910	5
Eudragit E-100	66.7
APAP*	325
明胶	12.1
甘露醇	42.9
卡波普	50
微晶纤维素	130
交聚维酮	200
碳酸氢钠	30
硬脂酸镁	43.3
总计	**1000**
* 对乙酰氨基酚(乙酰基-对氨基酚)	

[0187] 包衣颗粒根据实施例1中描述的程序制备。所制备的包衣颗粒然后与对乙酰氨基酚和其他赋形剂(卡波姆,交聚维酮,碳酸氢钠,甘露醇,微晶纤维素)混合并在V-掺合器中掺合30分钟。然后添加硬脂酸镁润滑所述掺合物并将所述混合物再掺合5分钟,然后压制成氢可酮/对乙酰氨基酚片剂。

[0188] 实施例4:重酒石酸氢可酮/对乙酰氨基酚

[0189] 表8:氢可酮/对乙酰氨基酚颗粒组成

[0190]

核壳组成		
组分	**位置**	**mg/片**
HPMC K100M	核	25.5
compritol	核	10.9
乙基纤维素	核	6
重酒石酸氢可酮	API 层	5
HPMC 2910	API 层	2.5
Eudragit E-100	膜	33.4
硬脂酸镁	膜	16.7
总计		100

[0191] 表9:氢可酮/对乙酰氨基酚片剂

[0192]

组分	mg/片
核壳组成(上述)	100
APAP	325
明胶	12.14
甘露醇	34.88
卡波普	50
微晶纤维素	96
交聚维酮	144
碳酸氢钠	30
硬脂酸镁	8
总计	800.02

[0193] 包衣颗粒根据实施例1中描述的程序制备。所制备的包衣颗粒然后与对乙酰氨基酚和其他赋形剂(卡波姆,交聚维酮,碳酸氢钠,甘露醇,微晶纤维素)混合并在V-掺合器中掺合30分钟。然后添加硬脂酸镁润滑所述掺合物并将所述混合物再掺合5分钟,然后压制成氢可酮/对乙酰氨基酚片剂。

[0194] 表10:氢可酮/对乙酰氨基酚片剂组成

[0195]

全片剂组成	
组分	**mg/片**
HPMC K100M	25.5
compritol	10.9
乙基纤维素	6
重酒石酸氢可酮	5
HPMC 2910	2.5
Eudragit E-100	33.4
APAP	325
明胶	12.14
甘露醇	34.88
卡波普	50
微晶纤维素	96
交聚维酮	144
碳酸氢钠	30
硬脂酸镁	24.7
总计	800.02

[0196] 实施例5:重酒石酸氢可酮/对乙酰氨基酚

[0197] 表11:氢可酮/对乙酰氨基酚颗粒组成

[0198]

核壳组成		
组分	**位置**	**mg/片**
HPMC K100M	核	50.1
compritol	核	21.5
乙基纤维素	核	11.8
重酒石酸氢可酮	API 层	9.8
HPMC 2910	API 层	4.9
Eudragit E-100	膜	65.4
硬脂酸镁	膜	32.7
总计		196.2

[0199] 表12:氢可酮/对乙酰氨基酚片剂组成

[0200]

组分	mg/片
核壳组成(上述)	196.1
APAP	325
明胶	12.14
甘露醇	46.2
卡波普	50
微晶纤维素	130
交聚维酮	200
红色氧化铁	0.6
碳酸氢钠	30
硬脂酸镁	10
总计	1000

[0201] 包衣颗粒根据实施例1中描述的程序制备。所制备的包衣颗粒然后与对乙酰氨基酚和其他赋形剂(卡波姆,交聚维酮,碳酸氢钠,甘露醇,红色氧化铁,微晶纤维素)混合并在V-掺合器中掺合30分钟。然后添加硬脂酸镁润滑所述掺合物并将所述混合物再掺合5分钟,然后压制成氢可酮/对乙酰氨基酚片剂。

[0202] 表13:氢可酮/对乙酰氨基酚片剂组成

[0203]

全片剂组成	
组分	mg/片
HPMC K100M	50.1
compritol	21.5
乙基纤维素	11.8
重酒石酸氢可酮	9.8
HPMC 2910	4.9
Eudragit E-100	65.4
APAP	325
明胶	12.14
甘露醇	46.2
卡波普	50
微晶纤维素	130
交聚维酮	200
红色氧化铁	0.6
碳酸氢钠	30
硬脂酸镁	42.7
总计	1000.14

[0204] 实施例6:盐酸羟考酮(单一API)(Celphere核)

[0205] 表14:羟考酮颗粒组成

[0206]

核壳组成		
组分	**位置**	**mg/片**
Celphere (MCC)	核	42
盐酸羟考酮	API 层	5.2
HPMC 2910	API 层	1.7
Eudragit E-100	膜	1.9
硬脂酸镁	膜	0.6
总计		51.4

[0207] 微晶纤维素粒子在底喷式流化床包衣机中用盐酸羟考酮和HPMC 2910的12％水溶液敷层。所述盐酸羟考酮敷层粒子然后在底喷式流化床包衣机中用Eudragit E-100共聚物和硬脂酸镁的25％醇悬液包衣。所生成的包衣粒子随后用于进一步掺合和压制过程。

[0208] 表15:羟考酮片剂组成

[0209]

组分	mg/片

核壳组成(上述)	51.54
乳糖	96.46
微晶纤维素	40
交聚维酮	10
硬脂酸镁	2
总计	200

[0210] 所述包衣粒子然后与其他赋形剂(交聚维酮和乳糖)混合并在V-掺合器中掺合30分钟。然后添加硬脂酸镁润滑所述掺合物并将所述混合物再掺合5分钟,然后压制成羟考酮片剂。

[0211] 表16:盐酸羟考酮片剂组成

[0212]

全片剂组成	
组分	mg/片
微晶纤维素	82
盐酸羟考酮	5.2
HPMC 2910	1.7
Eudragit E-100	1.9
乳糖	96.46
交聚维酮	10
硬脂酸镁	2.6
总计	199.86

[0213] 实施例7:重酒石酸氢可酮/对乙酰氨基酚(糖球核)

[0214] 表17:重酒石酸氢可酮颗粒组成

[0215]

核壳组成		
组分	位置	mg/片
糖球	核	47.3
PEO	核	24.7
EPO	核	20.5
重酒石酸氢可酮	API层	5
HPMC 2910	API层	2.5
Eudragit E-100	膜	75
硬脂酸镁	膜	25
总计		200

[0216] 糖球粒子在底喷式流化床包衣机中用重酒石酸氢可酮和HPMC 2910的水溶液敷层。所述重酒石酸氢可酮敷层粒子然后在底喷式流化床包衣机中用Eudragit E-100共聚物和硬脂酸镁的25％醇悬液包衣。所生成的包衣粒子随后用于进一步掺合和压制过程。

[0217] 表18：重酒石酸氢可酮片剂组成

[0218]

核壳组成(上述)	mg/片
	200
APAP	325
粘结剂	17.8
甘露醇	192.2
微晶纤维素	200
交聚维酮	50
硬脂酸镁	15
总计	1000

[0219] 所述包衣球与对乙酰氨基酚和其他赋形剂(甘露醇，微晶纤维素，粘结剂和交聚维酮)混合并在V-掺合器中掺合30分钟。然后添加硬脂酸镁润滑所述掺合物并将所述混合物再掺合5分钟，然后压制成羟考酮片剂。

[0220] 表19：重酒石酸氢可酮片剂组成

[0221]

全片剂组成	
组分	**mg/片**
糖	47.3
PEO(聚环氧乙烷)	24.7
EPO(Eudragit E-PO)	20.5
重酒石酸氢可酮	5
HPMC 2910	2.5
Eudragit E-100	75
APAP	325
粘结剂	17.8
甘露醇	192.2
微晶纤维素	200
交聚维酮	50
硬脂酸镁	40
总计	1000

[0222] 实施例8:重酒石酸氢可酮/对乙酰氨基酚(Celphere核)

[0223] 表20:重酒石酸氢可酮颗粒组成

[0224]

核壳组成		
组分	**位置**	**mg/片**
Celphere (MCC)	核	117.5
重酒石酸氢可酮	API 层	5
HPMC 2910	API 层	2.5
Eudragit E-100	膜	83.4
硬脂酸镁	膜	41.6
总计		250

[0225] 表21:重酒石酸氢可酮片剂组成

[0226]

组分	mg/片
核壳组成(上述)	250
APAP	325
明胶	12.14
甘露醇	102.9
微晶纤维素	120

黄原胶	30
交聚维酮	150
硬脂酸镁	10
总计	1000.04

[0227] 所述包衣球如实施例7制备，并与对乙酰氨基酚和其他赋形剂(甘露醇，微晶纤维素，黄原胶和交聚维酮)混合并在V-掺合器中掺合30分钟。然后添加硬脂酸镁润滑所述掺合物并将所述混合物再掺合5分钟，然后压制成氢可酮片剂。

[0228] 表22：重酒石酸氢可酮颗粒组成

[0229]

全片剂组成	
组分	**mg/片**
微晶纤维素	237.5
重酒石酸氢可酮	5
HPMC 2910	2.5
Eudragit E-100	83.4
APAP	325
明胶	12.14
甘露醇	102.9
黄原胶	30
交聚维酮	150
硬脂酸镁	51.6
总计	1000.04

[0230] 实施例9：重酒石酸氢可酮/对乙酰氨基酚(Celphere核)

[0231] 表23：重酒石酸氢可酮颗粒组成

[0232]

核壳组成		
组分	**位置**	**mg/片**
Celphere (MCC)	核	117.5
重酒石酸氢可酮	API 层	5
HPMC 2910	API 层	2.5
Eudragit E-100	膜	83.4
硬脂酸镁	膜	41.6
总计		250

[0233] 表24：重酒石酸氢可酮片剂组成

[0234]

组分	mg/片
核壳组成(上述)	250

APAP	325
明胶	12.14
甘露醇	84.9
微晶纤维素	120
卡波普	30
碳酸氢钠	18
交聚维酮	150
硬脂酸镁	10
总计	1000.04

[0235] 所述包衣球如实施例7制备，并与对乙酰氨基酚和其他赋形剂(甘露醇，微晶纤维素，卡波普，碳酸氢钠和交聚维酮)混合并在V-掺合器中掺合30分钟。然后添加硬脂酸镁润滑所述掺合物并将所述混合物再掺合5分钟，然后压制成氢可酮片剂。

[0236] 表25：重酒石酸氢可酮片剂组成

[0237]

全片剂组成	
组分	**mg/片**
重酒石酸氢可酮	5
HPMC 2910	2.5
Eudragit E-100	83.4
APAP	325
明胶	12.14
甘露醇	84.9
微晶纤维素	237.5
卡波普	30
碳酸氢钠	18
交聚维酮	150
硬脂酸镁	51.6
总计	1000.04

[0238] 实施例10：盐酸羟考酮/对乙酰氨基酚

[0239] 表26：重酒石酸羟考酮颗粒组成

[0240]

核壳组成		
组分	**位置**	**mg/片**
HPMC K100M	核	71
Compritol	核	30.5
乙基纤维素	核	16.8
盐酸羟考酮	API 层	4.5
HPMC 2910	API 层	2.2
Eudragit E-100	膜	83.4
硬脂酸镁	膜	41.6
总计		250

[0241] 表27:羟考酮片剂组成

[0242]

组分	mg/片
核壳组成(上述)	250
APAP	325
明胶	12.14
乳糖	84.9
卡波普	30
微晶纤维素	120
交聚维酮	150
碳酸氢钠	18
硬脂酸镁	10
总计	1000.04

[0243] 颗粒如实施例1所述制备和包衣。所述包衣颗粒然后与对乙酰氨基酚和其他赋形剂(卡波普,交聚维酮,碳酸氢钠,甘露醇,微晶纤维素)混合并在V-掺合器中掺合30分钟。然后添加硬脂酸镁润滑所述掺合物并将所述混合物再掺合5分钟,然后压制成羟考酮/对乙酰氨基酚片剂。

[0244] 表28:羟考酮/对乙酰氨基酚片剂组成

[0245]

全片剂组成	
组分	mg/片
HPMC K100M	71
compritol	30.5
乙基纤维素	16.8
盐酸羟考酮	4.5
HPMC 2910	2.2
Eudragit E-100	83.4
APAP	325
明胶	12.14
乳糖	84.9
卡波普	30
微晶纤维素	120
交聚维酮	150
碳酸氢钠	18
硬脂酸镁	51.6
总计	1000

[0246] 实施例11:盐酸羟考酮/对乙酰氨基酚

[0247] 表29:盐酸羟考酮颗粒组成

[0248]

核壳组成		
组分	**位置**	**mg/片**
HPMC K100M	核	71
compritol	核	30.3
乙基纤维素	核	16.7
盐酸羟考酮	API 层	5
HPMC 2910	API 层	2.5
Eudragit E-100	膜	83.4
硬脂酸镁	膜	41.6
总计		250.5

[0249] 表30:羟考酮/对乙酰氨基酚片剂组成

[0250]

组分	mg/片
核壳组成(上述)	250
APAP	325
明胶	12.14
甘露醇	82.9
黄原胶	50

微晶纤维素	120
交聚维酮	150
硬脂酸镁	10
总计	1000.04

[0251] 颗粒如实施例1所述制备和包衣。所述包衣颗粒然后与对乙酰氨基酚和其他赋形剂(黄原胶,交聚维酮,碳酸氢钠,甘露醇,微晶纤维素)混合并在V-掺合器中掺合30分钟。然后添加硬脂酸镁润滑所述掺合物并将所述混合物再掺合5分钟,然后压制成羟考酮/对乙酰氨基酚片剂。

[0252] 表31:羟考酮/对乙酰氨基酚片剂组成

[0253]

全片剂组成	
组分	mg/片
HPMC K100M	71
Compritol	30.3
乙基纤维素	16.7
盐酸羟考酮	5
HPMC 2910	2.5
Eudragit E-100	83.4
APAP	325
明胶	12.14
甘露醇	82.9
黄原胶	50
微晶纤维素	120
交聚维酮	150
硬脂酸镁	51.6
总计	1000.54

[0254] 实施例12:盐酸羟考酮/对乙酰氨基酚

[0255] 表32:盐酸羟考酮颗粒组成

[0256]

核壳组成		
组分	**位置**	**mg/片**
HPMC K100M	核	71
Compritol	核	30.5
乙基纤维素	核	16.8
盐酸羟考酮	API 层	4.5
HPMC 2910	API 层	2.2
Eudragit E-100	膜	83.4
硬脂酸镁	膜	41.6
总计		250

[0257] 表33:羟考酮/对乙酰氨基酚片剂组成

[0258]

组分	mg/片
核壳组成(上述)	250
APAP	325
明胶	12.14
甘露醇	52.9
卡波普	50
微晶纤维素	120
交聚维酮	150
碳酸氢钠	30
硬脂酸镁	10
总计	1000.04

[0259] 颗粒如实施例1所述制备和包衣。所述包衣颗粒然后与对乙酰氨基酚和其他赋形剂(卡波普,交聚维酮,碳酸氢钠,甘露醇,微晶纤维素)混合并在V-掺合器中掺合30分钟。然后添加硬脂酸镁润滑所述掺合物并将所述混合物再掺合5分钟,然后压制成羟考酮/对乙酰氨基酚片剂。

[0260] 表34:羟考酮/对乙酰氨基酚片剂组成

[0261]

全片剂组成	
组分	**mg/片**
HPMC K100M	71
compritol	30.5
乙基纤维素	16.8
盐酸羟考酮	4.5
HPMC 2910	2.2
Eudragit E-100	83.4
APAP	325
明胶	12.14
甘露醇	52.9
卡波普	50
微晶纤维素	120
交聚维酮	150
碳酸氢钠	30
硬脂酸镁	51.6
总计	1000

[0262] 实施例13:重酒石酸氢可酮/对乙酰氨基酚

[0263] 表35:重酒石酸氢可酮颗粒组成

[0264]

核壳组成		
组分	位置	mg/片
HPMC K100M	核	51
compritol	核	21.9
乙基纤维素	核	12
重酒石酸氢可酮	API 层	10
HPMC 2910	API 层	5
Eudragit E-100	膜	66.7
硬脂酸镁	膜	33.3
总计		199.9

[0265] 表36:重酒石酸氢可酮/APAP片剂组成

[0266]

组分	mg/片
核壳组成(上述)	200
APAP	325

明胶	12.14
甘露醇	74.86
卡波普	80
微晶纤维素	100
交聚维酮	150
碳酸氢钠	48
硬脂酸镁	10
总计	1000

[0267] 颗粒如实施例1所述制备和包衣。所述包衣颗粒然后与对乙酰氨基酚和其他赋形剂(卡波普,交聚维酮,碳酸氢钠,甘露醇,微晶纤维素)混合并在V-掺合器中掺合30分钟。然后添加硬脂酸镁润滑所述掺合物并将所述混合物再掺合5分钟,然后压制成氢可酮/对乙酰氨基酚片剂。

[0268] 表37:重酒石酸氢可酮/APAP片剂组成

[0269]

全片剂组成	
组分	mg/片
HPMC K100M	51
Compritol	21.9
乙基纤维素	12
重酒石酸氢可酮	10
HPMC 2910	5
Eudragit E-100	66.7
APAP	325
明胶	12.14
甘露醇	74.86
卡波普	80
微晶纤维素	100
交聚维酮	150
碳酸氢钠	48
硬脂酸镁	43.3
总计	999.9

[0270] 实施例14:重酒石酸氢可酮/对乙酰氨基酚

[0271] 表38:重酒石酸氢可酮颗粒组成

[0272]

核壳组成		
组分	位置	mg/片
HPMC K100M	核	42
compritol	核	18.1
乙基纤维素	核	9.9
重酒石酸氢可酮	API 层	10
HPMC 2910	API 层	5
Eudragit E-100	膜	56.8
硬脂酸镁	膜	28.4
总计		170.2

[0273] 表39:氢可酮/APAP片剂组成

[0274]

组分	mg/片
核壳组成(上述)	170
APAP	325
明胶	12.14
甘露醇	24.905
卡波普	49.98
微晶纤维素	102
交聚维酮	127.5
碳酸氢钠	30.005
硬脂酸镁	8.5
总计	850.03

[0275] 颗粒如实施例1所述制备和包衣。所述包衣颗粒然后与对乙酰氨基酚和其他赋形剂(卡波普,交聚维酮,碳酸氢钠,甘露醇,微晶纤维素)混合并在V-掺合器中掺合30分钟。然后添加硬脂酸镁润滑所述掺合物并将所述混合物再掺合5分钟,然后压制成氢可酮/对乙酰氨基酚片剂。

[0276] 表40:氢可酮/APAP片剂组成

[0277]

全片剂组成	
组分	**mg/片**
HPMC K100M	42
compritol	18.1
乙基纤维素	9.9
重酒石酸氢可酮	10
HPMC 2910	5
Eudragit E-100	56.8
APAP	325
明胶	12.14
甘露醇	24.905
卡波普	49.98
微晶纤维素	102
交聚维酮	127.5
碳酸氢钠	30.005
硬脂酸镁	36.9
总计	850.23

[0278] 实施例15:重酒石酸氢可酮/对乙酰氨基酚

[0279] 表41:重酒石酸氢可酮颗粒组成

[0280]

核壳组成		
组分	位置	mg/片
HPMC K100M	核	51
compritol	核	21.9
乙基纤维素	核	12
重酒石酸氢可酮	API 层	10
HPMC 2910	API 层	5
Eudragit E-100	膜	66.7
硬脂酸镁	膜	33.3
总计		199.9

[0281] 表42:氢可酮/APAP片剂组成

[0282]

组分	mg/片
核壳组成(上述)	200

APAP	325
明胶	12.14
甘露醇	134.9
卡波普	30
微晶纤维素	120
交聚维酮	150
碳酸氢钠	18
硬脂酸镁	10
总计	1000.04

[0283] 颗粒如实施例1所述制备和包衣。所述包衣颗粒然后与对乙酰氨基酚和其他赋形剂(卡波普,交聚维酮,碳酸氢钠,甘露醇,微晶纤维素)混合并在V-掺合器中掺合30分钟。然后添加硬脂酸镁润滑所述掺合物并将所述混合物再掺合5分钟,然后压制成氢可酮/对乙酰氨基酚片剂。

[0284] 表43:氢可酮/APAP片剂组成

[0285]

全片剂组成	
组分	mg/片
HPMC K100M	51
compritol	21.9
乙基纤维素	12
重酒石酸氢可酮	10
HPMC 2910	5
Eudragit E-100	66.7
APAP	325
明胶	12.14
甘露醇	134.9
卡波普	30
微晶纤维素	120
交聚维酮	150
碳酸氢钠	18
硬脂酸镁	43.3
总计	999.94

[0286] 实施例16:重酒石酸氢可酮/对乙酰氨基酚

[0287] 表44:重酒石酸氢可酮颗粒组成

[0288]

核壳组成		
组分	位置	mg/片
HPMC K100M	核	51
compritol	核	21.9
乙基纤维素	核	12
重酒石酸氢可酮	API 层	10
HPMC 2910	API 层	5
Eudragit E-100	膜	66.7
硬脂酸镁	膜	33.3
总计		199.9

[0289] 表45:氢可酮/APAP片剂组成

[0290]

组分	mg/片
核壳组成(上述)	200
APAP	325
明胶	12.14
甘露醇	102.9
卡波普	50
微晶纤维素	120
交聚维酮	150
碳酸氢钠	30
硬脂酸镁	10
总计	1000.04

[0291] 颗粒如实施例1所述制备和包衣。所述包衣颗粒然后与对乙酰氨基酚和其他赋形剂(卡波普,交聚维酮,碳酸氢钠,甘露醇,微晶纤维素)混合并在V-掺合器中掺合30分钟。然后添加硬脂酸镁润滑所述掺合物并将所述混合物再掺合5分钟,然后压制成氢可酮/对乙酰氨基酚片剂。

[0292] 表46:氢可酮/APAP片剂组成

[0293]

全片剂组成	
组分	**mg/片**
HPMC K100M	51
Compritol	21.9
乙基纤维素	12
重酒石酸氢可酮	10
HPMC 2910	5
Eudragit E-100	66.7
APAP	325
明胶	12.14
甘露醇	102.9
卡波普	50
微晶纤维素	120
交聚维酮	150
碳酸氢钠	30
硬脂酸镁	43.3
总计	999.94

[0294] 实施例17:重酒石酸氢可酮/对乙酰氨基酚

[0295] 表47:氢可酮/APAP片剂组成

[0296]

组分(mg/片)	5/325mg	7.5/325mg	10/325mg
羟丙甲纤维素K100M PH	25.5	38.3	51.1
Compritol 888ATO	11	16.4	21.9
乙基纤维素	6	9	12
重酒石酸氢可酮	5	7.5	10
羟丙甲纤维素2910	2.5	3.8	5
Eudragit E-100	33.4	50	66.7
扑热息痛Dc272n**	342.11	342.11	342.11
甘露醇Ez	29.89	38.81	37.29
卡波普71g	50	50	50
微晶纤维素	96	108	130
交聚维酮	144	171	200
碳酸氢钠#1	30	30	30
FD&C蓝#2Ht铝色淀	NA	0.54	NA
氧化铁黄510p	NA	0.54	NA
氧化铁红212p	NA	NA	0.6
非牛硬脂酸镁	24.6	34	43.3
无水酒精SDA-3A*	*	*	*

纯水*	*	*	*
总片剂重量	800	900	1000

[0297] *加工期间除去

[0298] 颗粒如实施例1所述制备和包衣。所述包衣颗粒然后与扑热息痛和其他赋形剂(卡波普,交聚维酮,碳酸氢钠,甘露醇,微晶纤维素和着色剂)混合并在V-掺合器中掺合30分钟。然后添加硬脂酸镁润滑所述掺合物并将所述混合物再掺合5分钟,然后压制成氢可酮/对乙酰氨基酚片剂。

[0299] 表48:重酒石酸氢可酮颗粒组成

[0300]

	5/325 mg剂量	7.5/325 mg剂量	10/325 mg剂量
造粒	%	%	%
羟丙甲纤维素	3.19	4.26	5.11
Compritol 888 ATO	1.37	1.83	2.19
乙基纤维素	0.75	1	1.2
无水酒精SDA-3A	*	*	*
纯水	*	*	*
总计	5.31	7.09	8.5
敷层	%	%	%
重酒石酸氢可酮	0.63	0.83	1
聚合物颗粒 (EC，HPMC和Compritol)	5.31	7.09	8.5
羟丙甲纤维素2910	0.31	0.42	0.5
纯水	*	*	*
总计	6.25	8.34	10
包衣	%	%	%
氢可酮敷层颗粒，10%	6.25	8.34	10
Eudragit E-100	4.17	5.56	6.67
硬脂酸镁	2.08	2.77	3.33
无水酒精SDA-3A	*	*	*
总计	12.5	16.67	20

[0301] *加工期间除去

[0302] 实施例18:阿莫达非尼

[0303] 表49:阿莫达非尼片剂组成

[0304]

阿莫达非尼：			
组分(mg/片)	**50 mg**	**150 mg**	**200 mg**
羟丙甲纤维素	64.26	36	48
Compritol 888 ATO	17.85	10	14
乙基纤维素	10.71	10	14
阿莫达非尼	50	150	200
Eudragit E-100	21	30	40
甘露醇Ez	17	25	25
卡波普71g	50	50	50
微晶纤维素	100	125	125
交聚维酮	150	200	200
碳酸氢钠#1	30	30	30
非牛硬脂酸镁	71	25	32
Lutrol F68 (1:5)	150	200	200
月桂基硫酸钠 (3%)	23	30	40
无水酒精SDA-3A*	*	*	*
纯水*	*	*	*
总片剂重量	754.82	921	1018

[0305] *加工期间除去

[0306] 颗粒如实施例1所述制备和包衣。所述包衣颗粒然后与其他赋形剂(卡波普,交聚维酮,碳酸氢钠,甘露醇,微晶纤维素)混合并在V-掺合器中掺合30分钟。然后添加硬脂酸镁(非牛)润滑所述掺合物并将所述混合物再掺合5分钟,然后压制成阿莫达非尼片剂。

[0307] 表50:阿莫达非尼颗粒组成

[0308]

	50mg 剂量		150mg 剂量		200mg 剂量	
造粒	mg/g	mg/片	mg/g	mg/片	mg/g	mg/片
羟丙甲纤维素	450	64.26	175	36	175	48
阿莫达非尼	350	49.98	725	150	725	200
Compritol 888 ATO	125	17.85	50	10	50	14
乙基纤维素	75	10.71	50	10	50	14
无水酒精SDA-3A	*	*	*	*	*	*
纯水	*	*	*	*	*	*
总计	1000	142.8	1000	206	1000	276
包衣	mg/g	mg/片	mg/g	mg/片	mg/g	mg/片
阿莫达非尼颗粒，35%	820	142.84	820	207	820	276
Eudragit E-100	120	20.90	120	30	120	40
硬脂酸镁	60	10.45	60	15	60	20
无水酒精SDA-3A	*	*	*	*	*	*
总计	1000	174.2	1000	252	1000	336

[0309] *加工期间除去

[0310] 实施例19:苯巴比妥

[0311] 表51:苯巴比妥片剂组成

[0312]

组分(mg/片)	15mg	30mg	60mg	100mg
羟丙甲纤维素	19.3	38.6	77.2	128.52
Compritol 888ATO	5.4	10.7	21.4	35.7
乙基纤维素	3.2	6.4	12.9	21.43
苯巴比妥	15	30	60	100
Eudragit E-100	6.3	15.5	25.1	42
甘露醇Ez	20	20	20	20.1
卡波普71g	50	50	50	50
微晶纤维素	100	100	100	100
交聚维酮	130	130	130	200
碳酸氢钠#1	30	30	30	30
非牛硬脂酸镁	9.1	12.3	19.1	31
Lutrol F68(1:5)	100	100	120	200
月桂基硫酸钠(3%)	22.8	28	35	50
无水酒精SDA-3A*	*	*	*	*
纯水*	*	*	*	*

总片剂重量	511.1	571.5	700.7	1008.75

[0313] *加工期间除去

[0314] 表52:苯巴比妥颗粒组成

[0315]

	15 mg剂量		30 mg剂量		60 mg剂量		100 mg剂量	
造粒	mg/g	mg/片	mg/g	mg/片	mg/g	mg/片	mg/g	mg/片
羟丙甲纤维素	450	19.31	450	38.57	450	77.18	450	128.57
苯巴比妥	350	15.02	350	30	350	60.03	350	100
Compritol 888 ATO	125	5.36	125	10.71	125	21.44	125	35.71
乙基纤维素	75	3.22	75	6.43	75	12.86	75	21.43
无水酒精SDA-3A	*	*	*	*	*	*	*	*
纯水	*	*	*	*	*	*	*	*
总计	1000	42.91	1000	85.71	1000	171.51	1000	285.71
包衣	mg/g	mg/片	mg/g	mg/片	mg/g	mg/片	mg/g	mg/片
苯巴比妥，35%	820	42.89	820	85.69	820	171.46	820	285.69
Eudragit E-100	120	6.28	120	12.54	120	25.09	120	41.81
硬脂酸镁	60	3.14	60	6.27	60	12.55	60	20.90
无水酒精SDA-3A	*	*	*	*	*	*	*	*
总计	1000	52.3	1000	104.5	1000	209.1	1000	348.4

[0316] *加工期间除去

[0317] 颗粒如实施例1所述制备和包衣。所述包衣颗粒然后与其他赋形剂(卡波普,交聚维酮,碳酸氢钠,甘露醇,微晶纤维素)混合并在V-掺合器中掺合30分钟。然后添加硬脂酸镁(非牛)润滑所述掺合物并将所述混合物再掺合5分钟,然后压制成苯巴比妥片剂。

[0318] 实施例20:地西泮

[0319] 表53:地西泮片剂组成

[0320]

组分	2 mg (mg/片)	5 mg (mg/片)	10 mg (mg/片)
羟丙甲纤维素 K100M PH	22.2	55.6	111.2
Compritol 888 ATO	9.5	23.8	47.64
乙基纤维素 N10	5.2	13.1	26.2
地西泮	2	5	10
羟丙甲纤维素 2910	1	2.5	5
Eudragit E-100	26.7	66.7	133.4
甘露醇 Ez	70	70	70
卡波普 71g	50	50	50
微晶纤维素	95	95	94
交聚维酮	90	95	150
碳酸氢钠#1	30	30	30
非牛硬脂酸镁	18.1	38.6	74.6
无水酒精 SDA-3A*	*	*	*
纯水*	*	*	*
总片剂重量	419.7	545.3	802.04

[0321] *加工期间除去

[0322] 颗粒如实施例1所述制备和包衣。所述包衣颗粒然后与其他赋形剂(卡波普,交聚维酮,碳酸氢钠,甘露醇,微晶纤维素)混合并在V-掺合器中掺合30分钟。然后添加硬脂酸镁(非牛)润滑所述掺合物并将所述混合物再掺合5分钟,然后压制成地西泮片剂。

[0323] 表54:地西泮包衣颗粒组成

[0324]

	2 mg 剂量		5 mg 剂量		2 mg 剂量	
造粒	mg/g	mg/片	mg/g	mg/片	mg/g	mg/片
羟丙甲纤维素	600.86	22.23	600.86	55.58	600.86	111.16
Compritol 888 ATO	257.51	9.53	257.51	23.82	257.51	47.64
乙基纤维素	141.63	5.24	141.63	13.10	141.63	26.20
无水酒精SDA-3A	*	*	*	*	*	*
纯水	*	*	*	*	*	*
总计	1000	37	1000	92.5	1000	185
敷层	mg/g	mg/片	mg/g	mg/片	mg/g	mg/片
地西泮	50	2	50	5	50	10
聚合物颗粒 (EC，HPMC和Compritol)	925	37	925	92.5	925	185
羟丙甲纤维素2910	25	1	25	2.5	25	5
纯水	*	*	*	*	*	*
总计	1000	40	1000	100	1000	200
包衣的，2.5%	mg/g	mg/片	mg/g	mg/片	mg/g	mg/片
地西泮敷层颗粒，5%	500	40	500	100	500	200
Eudragit E-100	333.6	26.69	333.6	66.71	333.6	133.43
硬脂酸镁	166.4	13.31	166.4	33.29	166.4	66.57
无水酒精SDA-3A	*	*	*	*	*	*
总计	1000	80	1000	200	1000	400

[0325] 实施例21:氢可酮(单一API)

[0326] 颗粒如实施例1所述制备和包衣。所述包衣颗粒然后与其他赋形剂(卡波普,交聚维酮,碳酸氢钠,甘露醇,微晶纤维素)混合并在V-掺合器中掺合30分钟。然后添加硬脂酸镁(非牛)润滑所述掺合物并将所述混合物再掺合5分钟,然后压制成氢可酮片剂。

[0327] 实施例22:氢可酮(单一API)-(上文实施例21的继续)

[0328] 表55:氢可酮片剂组成

[0329]

组分	5mg(mg/片)	10mg(mg/片)
羟丙甲纤维素K100M PH	25.5	51.1
Compritol 888ATO	11	21.9
乙基纤维素N10	6	12.04
重酒石酸氢可酮	5	10
羟丙甲纤维素2910	2.5	5
Eudragit E-100	33.4	66.7
甘露醇Ez	70	70
卡波普71g	50	50
微晶纤维素	95	95

交聚维酮	100	120
碳酸氢钠#1	30	30
非牛硬脂酸镁	21.6	39.3
无水酒精SDA-3A*	*	*
纯水*	*	*
总片剂重量	450	571.04

[0330] *加工期间除去

[0331] 表56:重酒石酸氢可酮包衣颗粒组成

[0332]

	5 mg 剂量		10 mg 剂量	
造粒	mg/g	mg/片	mg/g	mg/片
羟丙甲纤维素	600.86	25.54	600.86	51.07
Compritol 888 ATO	257.51	10.94	257.51	21.89
乙基纤维素	141.63	6.02	141.63	12.04
无水酒精SDA-3A	*	*	*	*
纯水	*	*	*	*
总计	1000	42.5	1000	85
敷层	mg/g	mg/片	mg/g	mg/片
重酒石酸氢可酮	100	5	100	10
聚合物颗粒 (EC，HPMC和Compritol)	850	42.5	850	85
羟丙甲纤维素2910	50	2.5	50	5
纯水	*	*	*	*
总计	1000	50	1000	100
包衣	mg/g	mg/片	mg/g	mg/片
重酒石酸氢可酮敷层颗粒，10%	500	50	500	100
Eudragit E-100	333.6	33.36	333.6	66.71
硬脂酸镁	166.4	16.64	166.4	33.29
无水酒精SDA-3A	*	*	*	*
总计*(加工期间除去)	1000	100	1000	200

[0333] 实施例23:重酒石酸氢可酮/对乙酰氨基酚

[0334] 包衣颗粒如实施例1所述制备。所制备的包衣颗粒然后与扑热息痛和其他赋形剂(卡波姆、交聚维酮、碳酸氢钠、甘露醇、微晶纤维素、着色剂例如FD&C蓝、红色氧化铁或黄色氧化铁预先混合)混合并在箱式掺合器中掺合30分钟。然后添加硬脂酸镁润滑所述掺合物

并将所生成的混合物再掺合5分钟，然后压制成氢可酮/对乙酰氨基酚片剂。

[0335] 表57：氢可酮/APAP片剂组成

[0336]

组分(% w/w)	5/325 mg	7.5/325 mg	10/325 mg
重酒石酸氢可酮包衣颗粒	12.5	16.7	20.0
扑热息痛	42.76	38.0	34.21
甘露醇	3.74	4.3	3.73
卡波普	6.25	5.6	5.0
微晶纤维素	12.0	12.0	13.0
交聚维酮	18.0	19.0	20.0
碳酸氢钠	3.75	3.3	3.0
FD&C 蓝#2 HT 铝色淀	NA	0.06	NA
氧化铁红 212P	NA	NA	0.06
氧化铁黄 510P	NA	0.06	NA
硬脂酸镁	1.0	1.0	1.0
总计	**100**	**100**	**100**

[0337] 实施例24：实施例3的制剂的提取研究

[0338] 根据上文实施例3制备的剂型(完整的和压碎的)(10/325mg重酒石酸氢可酮/对乙酰氨基酚片剂)吸收在小体积的水中并提取以模拟滥用者通过静脉内(IV)途径可利用的氢可酮量。评价所生成的混合物通过过滤材料将所述混合物抽取到注射器中供IV注射的能力。评价各种针号和提取体积。滤液通过HPLC检验重酒石酸氢可酮含量。

[0339] 表58：在100℃和室温(RT)下从两批次10/325mg重酒石酸氢可酮/对乙酰氨基酚片剂提取的氢可酮量

[0340]

批次 #	完整片剂(mg)		压碎片剂 (mg)	
	100°C	RT	100°C	RT
1	0 mg	0.09 mg	0 mg	0 mg
2	0 mg	0.07 mg	0 mg	0 mg

[0341] 实施例25：实施例3的制剂的模拟鼻液提取研究

[0342] 根据上文实施例3制备的剂型(10/325mg重酒石酸氢可酮/对乙酰氨基酚片剂)利用研杵和研钵压碎并放入10mL 37℃的模拟鼻液中，伴温和搅拌来模拟对于吹鼻滥用可利用的重酒石酸氢可酮的量。在10和30分钟时取出小份用于通过HPLC分析重酒石酸氢可酮。下面表中提供就用于模拟吹鼻的从压碎片剂提取的重酒石酸氢可酮量。

[0343] 这种方法用于测定从重酒石酸氢可酮延长释放片剂的模拟鼻液提取中释放的重酒石酸氢可酮。

[0344] A.HPLC分析参数

[0345]

柱	GL Sciences Inertsil Phenyl-3，4.6 mm x 50 mm，5-μm
柱温	45°C
检测	UV，280 nm
溶剂 A	0.1% HFBA 水溶液
溶剂 B	MeOH
流动相	70: 30 溶剂 A: 溶剂 B
进样器冲洗液	50: 50 MeOH: 水
流速	2.0 mL/min
进样体积	50 μL
运行时间	4 min
峰值响应	面积
稀释剂	0.1N HCl

[0346] B.HPLC溶液制备

[0347] 溶剂A(0.1％HFBA的H_2O溶液):1mL HFBA和1L HPLC级水合并,并充分混合。溶剂A稳定14天。可以制备按比例的体积。

[0348] 流动相(70:30溶剂A:MeOH):700mL溶剂A和300mL MeOH合并,并充分混合。制备的溶液稳定1个月。可以制备按比例的体积。或者,HPLC泵可以用于混合所述流动相。

[0349] 稀释剂/介质(0.1N HCl):25mL的12N HCl和3L的DI水合并,并充分混合。0.1N HCl稳定4周。可以制备按比例的体积。

[0350] 进样器冲洗液(50:50MeOH:H_2O):500mL的MeOH和500mL的HPLC级水合并,并充分混合。50:50MeOH:H_2O稳定1个月。可以制备按比例的体积。

[0351] C.模拟鼻液(SNF)制备

[0352] 在一升水中添加8.7g氯化钠(NaCl)、3.0g氯化钾(KCl)、0.6g氯化钙($CaCl_2$)、4.4g磷酸氢二钠(Na_2HPO_4)和1.1g磷酸二氢钠(NaH_2PO_4)。充分混合。测量和记录pH(必须在6.0和7.0之间)。在室温下储存。SNF稳定2周。可以制备按比例的体积。

[0353] D.重酒石酸氢可酮标准溶液

[0354] 储备标准溶液:按照USP一份重酒石酸氢可酮标准在105℃真空干燥2小时。一式二份,精确称重30mg±5mg重酒石酸氢可酮到单独的100-mL容量瓶中。添加大约50mL的0.1N HCl稀释剂。通过声波处理溶解大约10分钟。用稀释剂稀释到体积,并充分混合。这些是大约300微克/mL(按无水重酒石酸氢可酮)的储备标准溶液并在周围实验室条件(不避光)下稳定29天。可以制备按比例的体积。

[0355] 工作标准溶液:将每种储备标准溶液15mL移液到单独的50-mL容量瓶中。用0.1N HCl稀释剂稀释到体积,并充分混合。这些工作标准溶液是大约90微克/mL(按无水重酒石酸氢可酮)并在周围实验室条件(不避光)下稳定43天。可以制备按比例的体积。

[0356] E.模拟吹鼻提取样品制备

[0357] 1.压碎一个片剂并将大约575mg精确称重的压碎材料转移到预先标记的20mL玻璃小瓶。为了药物物质对照,称重适当质量的材料并转移到预先标记的20mL玻璃小瓶中。

[0358] 2.加热水浴和模拟鼻液到37℃。

[0359] 3.将10mL所述预先加热的37℃模拟鼻液移液到含有压碎的片剂材料的每个小瓶中。

[0360] 4.加盖并颠倒两次以润湿粉末。将小瓶放在水浴内部的金属架上并以100rpm振荡。

[0361] 5.10min时,从架子中取出所述小瓶。

[0362] 6.开盖并利用微量移液器从每个小瓶抽取3-mL溶液。

[0363] 7.转移溶液到5-mL聚丙烯注射器中并通过25-mm直径、1-μm孔隙度的玻璃滤器将所述溶液过滤到玻璃试管(16x100mm)中。.

[0364] 8.将小瓶放回水浴并继续振荡。

[0365] 9.30min时,停止振荡,开盖并利用微量移液器从每个小瓶抽取3-mL溶液。

[0366] 10.转移溶液到5-mL聚丙烯注射器中并通过25-mm直径、1-μm孔隙度的玻璃滤器将所述溶液过滤到玻璃试管(16x100mm)中。

[0367] 11.从每个试管移液1mL溶液到单独的50-mL容量瓶中并用0.1N HCl稀释到体积。通过颠倒10次混合。

[0368] 12.通过25-mm直径、1-μm孔隙度的玻璃注射器式滤器传递和丢弃1-mL的样品溶液等份,然后收集第二等份到玻璃HPLC小瓶中并加盖。

[0369] 13.每个样品进样一次。

[0370] 表59:10/325mg重酒石酸氢可酮/对乙酰氨基酚片剂的模拟鼻液提取

[0371]

批次	在 10 分钟时从含有 10/325mg 重酒石酸氢可酮/对乙酰氨基酚的压碎片剂中提取的量	在 30 分钟时从含有 10/325mg 重酒石酸氢可酮/对乙酰氨基酚的压碎片剂中提取的量
1	14%	45%
2	60%	66%

[0372] 实施例26(a):通过多片摄入滥用的评价

[0373] 通过在300mL 0.1N HCl中搅拌选定数量的片剂,评价根据上文实施例3和5制备的剂型的抗多片口服滥用性。利用USP设备II在50rpm和37℃进行溶出。一到十二个片剂同时添加到容器中,在搅拌5、10、15、30、60、120、240和360分钟之后取出等份并通过HPLC分析重酒石酸氢可酮(图4)和APAP(图5)。结果对时间作图,并呈现在图4和5中。

[0374] 实施例26(b):通过多片摄入滥用的评价

[0375] 通过在300mL 0.1N HCl中搅拌选定数量的片剂,评价根据上文实施例17制备的剂型的抗多片口服滥用性。利用USP设备II在50rpm和37℃进行溶出。一到十二个片剂同时添加到容器中,在搅拌5、10、15、30、60、120、240和360分钟之后取出等份并通过HPLC分析重酒石酸氢可酮(图6)和APAP(图7)。结果对时间作图,并呈现在图6和7中。

[0376] 实施例26(c):通过多片摄入滥用的评价

[0377] 通过在300mL 0.1N HCl中搅拌选定数量的片剂,评价根据上文实施例17制备的剂型的抗多片口服滥用性。利用USP设备II在50rpm和37℃进行溶出。一到十二个片剂同时添加到容器中,在搅拌5、10、15、30、60、120、240和360分钟之后取出等份并通过HPLC分析重酒

石酸氢可酮和APAP。结果对时间作图，并呈现在图8(重酒石酸氢可酮)和图9(APAP)中。

[0378] 实施例27:包衣艾氯胺酮颗粒

[0379] 包衣艾氯胺酮颗粒按照实施例1中描述的过程制备，在组分上与实施例1略有变化，如下面所示。

[0380] 表60:盐酸艾氯胺酮颗粒组成

[0381]

造粒	%w/w
羟丙甲纤维素	60
山嵛酸甘油酯	26
乙基纤维素	14
总计	100
敷层	%w/w
盐酸艾氯胺酮	5
聚合物颗粒(EC,HPMC和Compritol)	92.5
羟丙甲纤维素2910	2.5
总计	100
包衣	%w/w
艾氯胺酮敷层颗粒	50
Eudragit E-100	33
硬脂酸镁	17
总计	100

[0382] 实施例28:艾氯胺酮HCl片剂

[0383] 按照上文实施例27制备的包衣颗粒随后与其他组分(卡波姆，交聚维酮，碳酸氢钠，甘露醇，微晶纤维素)混合并在V-掺合器中掺合30分钟。添加硬脂酸镁润滑所述掺合物并将所生成的混合物再掺合5分钟，然后压制成片剂。

[0384] 表61:盐酸艾氯胺酮片剂组成

[0385]

组分mg/片	1mg	2mg	5mg	10mg
羟丙甲纤维素	11.1	22.2	55.6	111.2
山嵛酸甘油酯	4.8	9.5	23.8	47.64
乙基纤维素	2.6	5.2	13.1	26.2
盐酸艾氯胺酮	1	2	5	10
羟丙甲纤维素2910	0.5	1	2.5	5
Eudragit E-100	13.3	26.7	66.7	133.4
甘露醇	70	70	70	70
卡波普	50	50	50	50
微晶纤维素	94	95	95	94
交聚维酮	90	90	95	150
碳酸氢钠	30	30	30	30

硬脂酸镁	11	18	38.6	74.6
总片剂重量	378.3	419.6	545.3	802.04

[0386] 实施例29:包衣艾氯胺酮颗粒

[0387] 包衣艾氯胺酮颗粒按照实施例1中描述的过程制备,在组分上与实施例1略有变化,如下表所示。

[0388] 表62:盐酸艾氯胺酮包衣颗粒组成

[0389]

造粒	%w/w
羟丙甲纤维素	60
山嵛酸甘油酯	26
乙基纤维素	14
总计	100
敷层	%w/w
盐酸艾氯胺酮	10
聚合物颗粒(EC,HPMC和Compritol)	85
羟丙甲纤维素2910	5
总计	100
包衣	%w/w
艾氯胺酮敷层颗粒	50
Eudragit E-100	33
硬脂酸镁	17
总计	100

[0390] 实施例30:艾氯胺酮HCl片剂

[0391] 按照上文实施例29制备的包衣颗粒随后与其他组分(卡波姆,交聚维酮,碳酸氢钠,甘露醇,微晶纤维素)混合并在V-掺合器中掺合30分钟。添加硬脂酸镁润滑所述掺合物并将所生成的混合物再掺合5分钟,然后压制成片剂。

[0392] 表63:盐酸艾氯胺酮片剂组成

[0393]

组分(mg/片)	14mg
羟丙甲纤维素	71.5
山嵛酸甘油酯	30.6
乙基纤维素	16.9
盐酸艾氯胺酮	14
羟丙甲纤维素2910	7
Eudragit E-100	93.4
甘露醇	70
卡波普	50
微晶纤维素	130
交聚维酮	150

碳酸氢钠	30
硬脂酸镁	55
总片剂重量	718.4

[0394] 实施例31:包衣艾氯胺酮颗粒

[0395] 艾氯胺酮颗粒利用与上文实施例1中描述的相似的过程制造,对所述过程有一些修改。所述活性成分并非在所述颗粒上敷层而是存在于核中,它在其中与按照下表的其他赋形剂一起造粒,并随后用Eudragit E-100包被。颗粒在高剪切造粒机中制造,在其中羟丙甲纤维素、盐酸艾氯胺酮和山嵛酸甘油酯干混合3分钟。然后,缓慢添加乙基纤维素的10%水醇溶液,同时将造粒机叶片和切刀速度保持在为颗粒形成和生长提供足够剪切的预选值。继续添加溶液,直至添加了全部量的乙基纤维素。所述颗粒然后使用减尺寸磨机(granumill)湿磨,随后装入流化床中干燥。

[0396] 盐酸艾氯胺酮颗粒然后在底喷式流化床包衣机中用Eudragit E-100共聚物和硬脂酸镁(2:1)的25%醇悬液包衣。所述包衣颗粒随后用于掺合和压制过程。

[0397] 表64:盐酸艾氯胺酮颗粒组成

[0398]

造粒	%w/w
盐酸艾氯胺酮	35
羟丙甲纤维素	45
山嵛酸甘油酯	12.5
乙基纤维素	7.5
总计	100
包衣	%w/w
艾氯胺酮颗粒	82
Eudragit E-100	12
硬脂酸镁	6
总计	100

[0399] 实施例32:艾氯胺酮HCl片剂

[0400] 按照上文实施例31制备的包衣颗粒随后与其他组分(卡波姆,交聚维酮,碳酸氢钠,甘露醇,微晶纤维素)混合并在V-掺合器中掺合30分钟。添加硬脂酸镁润滑所述掺合物并将所生成的混合物再掺合5分钟,然后压制成片剂。

[0401] 表65:盐酸艾氯胺酮片剂组成

[0402]

组分(mg/片)	28mg	56mg	84mg
羟丙甲纤维素	36	72	108
山嵛酸甘油酯	10	20	30
乙基纤维素	6	12	18
盐酸艾氯胺酮	28	56	84
Eudragit E-100	11.7	23.4	35.1
甘露醇	17	17	20.1

卡波普	50	50	50
微晶纤维素	100	100	100
交聚维酮	150	150	150
碳酸氢钠	30	30	30
硬脂酸镁	12	20	30
总片剂重量	450.7	550.4	655.2

[0403] 实施例33:包衣艾氯胺酮颗粒

[0404] 艾氯胺酮颗粒利用与上文实施例1和实施例32中描述的相似的过程制造,对所述过程有一些修改。所述活性成分与按照下表的其他赋形剂一起造粒,并随后用Eudragit E-100包衣。

[0405] 含有盐酸艾氯胺酮的颗粒在高剪切造粒机中制造,在其中羟丙甲纤维素、盐酸艾氯胺酮和山嵛酸甘油酯干混合3分钟。然后,缓慢添加乙基纤维素的10%水醇溶液,同时将造粒机叶片和切刀速度保持在为颗粒形成和生长提供足够剪切的预选值。继续添加溶液,直至添加了全部量的乙基纤维素。所述颗粒然后使用减尺寸磨机(granumill)湿磨,并然后装入流化床中干燥。

[0406] 所述颗粒然后在底喷式流化床包衣机中用Eudragit E-100共聚物和硬脂酸镁(2:1)的25%醇悬液包衣。所述包衣颗粒随后用于掺合和压制过程。

[0407] 表66:盐酸艾氯胺酮颗粒组成

[0408]

造粒	%w/w
盐酸艾氯胺酮	72.5
羟丙甲纤维素	17.5
山嵛酸甘油酯	5
乙基纤维素	5
总计	100
包衣	%w/w
艾氯胺酮颗粒	82
Eudragit E-100	12
硬脂酸镁	6
总计	100

[0409] 实施例34:艾氯胺酮HCl片剂

[0410] 按照上文实施例33制备的包衣颗粒随后与其他组分(卡波姆,交聚维酮,碳酸氢钠,甘露醇,微晶纤维素)混合并在V-掺合器中掺合30分钟。添加硬脂酸镁润滑所述掺合物并再掺合5分钟,然后压制成片剂。

[0411] 表67:盐酸艾氯胺酮片剂组成

[0412]

组分(mg/片)	200mg	300mg	400mg
羟丙甲纤维素	48	72	96.4
山嵛酸甘油酯	14	21	27.6

乙基纤维素	14	21	27.6
盐酸艾氯胺酮	200	300	400
Eudragit E-100	40	61	81
甘露醇	25	25	25
卡波普	75	75	75
微晶纤维素	125	125	125
交聚维酮	300	300	300
碳酸氢钠	45	45	45
硬脂酸镁	140	150	160
总片剂重量	1026	1195	1362.6

[0413] 实施例35:包衣唑吡坦颗粒

[0414] 包衣酒石酸唑吡坦颗粒按照实施例1中描述的过程按照下表中说明的组成制备。

[0415] 表68:酒石酸唑吡坦颗粒组成

[0416]

造粒	%w/w
羟丙甲纤维素	60
山嵛酸甘油酯	26
乙基纤维素	14
总计	100
敷层	%w/w
酒石酸唑吡坦	10
聚合物颗粒(EC,HPMC和Compritol)	85
羟丙甲纤维素2910	5
总计	100
包衣	%w/w
唑吡坦敷层颗粒	50
Eudragit E-100	33
硬脂酸镁	17
总计	100

[0417] 实施例36:酒石酸唑吡坦片剂

[0418] 包衣唑吡坦颗粒按照上文实施例35描述的过程制备。所述包衣颗粒与其他组分(卡波姆,交聚维酮,碳酸氢钠,甘露醇,微晶纤维素)混合并在V-掺合器中掺合30分钟。添加硬脂酸镁润滑所述掺合物并再掺合5分钟,然后压制成片剂。

[0419] 表69:酒石酸唑吡坦片剂组成

[0420]

组分(mg/片)	5mg	10mg
羟丙甲纤维素	25.5	51.1
山嵛酸甘油酯	11	21.9
乙基纤维素	6	12

酒石酸唑吡坦	5	10
羟丙甲纤维素2910	2.5	5
Eudragit E-100	33.4	66.7
甘露醇	70	70
卡波普	50	50
微晶纤维素	95	94
交聚维酮	100	100
碳酸氢钠	30	30
硬脂酸镁	21.6	39.3
总片剂重量	450	550

[0421] 实施例37:包衣富马酸喹硫平颗粒

[0422] 喹硫平颗粒利用与上文实施例1中描述的相似的过程制造,对所述过程有一些修改。所述富马酸喹硫平并非在所述颗粒上敷层而是存在于核中,它在其中与按照表70(造粒)的其他赋形剂一起造粒,并随后用Eudragit E-100包衣。

[0423] 颗粒在高剪切造粒机中制造,在其中羟丙甲纤维素、富马酸喹硫平、一部分Lutrol、月桂基硫酸钠和山嵛酸甘油酯干混合3分钟。然后,缓慢添加乙基纤维素的10%水醇溶液,同时将造粒机叶片和切刀速度保持在为颗粒形成和生长提供足够剪切的预选值。继续添加溶液,直至添加了全部量的乙基纤维素。所述颗粒然后使用减尺寸磨机(granumill)湿磨,并然后装入流化床中干燥。

[0424] 所述富马酸喹硫平颗粒然后在底喷式流化床包衣机中用Eudragit E-100共聚物和硬脂酸镁的醇悬液包衣。所生成的包衣颗粒随后用于掺合和压制过程。

[0425] 表70:富马酸喹硫平包衣颗粒组成

[0426]

造粒	%w/w
富马酸喹硫平	23.7
羟丙甲纤维素	37.6
山嵛酸甘油酯	13.4
乙基纤维素	8.1
月桂基硫酸钠	9.1
Lutrol	8.1
总计	100
包衣	%w/w
喹硫平颗粒	62.5
Eudragit E-100	25
硬脂酸镁	12.5
总计	100

[0427] 实施例38:富马酸喹硫平片剂

[0428] 按照上文实施例37制备的包衣颗粒随后与其他组分(卡波姆,交聚维酮,剩余部分的Lutrol,碳酸氢钠,甘露醇,微晶纤维素)混合,并在V-掺合器中掺合30分钟。添加硬脂酸

镁润滑所述掺合物并再掺合5分钟，然后压制成片剂。

[0429] 表71：富马酸喹硫平片剂组成

[0430]

组分 (mg/ 片)	25 mg (mg/片)	50 mg (mg/片)	100 mg (mg/片)
羟丙甲纤维素	16	32	63
山嵛酸甘油酯	9	18	36
乙基纤维素	5	11	22
富马酸喹硫平	25	50	100
Eudragit E-100	27	53	107
甘露醇	17	17	20.1
卡波普	50	50	50
微晶纤维素	100	100	100
交聚维酮	150	150	200
碳酸氢钠	30	30	30
硬脂酸镁	18	31	63
Lutrol	45	51	62
月桂基硫酸钠	6	12	24
总片剂重量	498	605	877.1

[0431] 实施例39：包衣喹硫平颗粒

[0432] 喹硫平颗粒利用与实施例1中描述的相似的过程制造，对所述过程有一些修改。所述富马酸喹硫平并非在所述颗粒上敷层而是存在于核中，它在其中与按照表72的其他赋形剂一起造粒，并随后用Eudragit E-100包衣。

[0433] 颗粒在高剪切造粒机中制造，在其中羟丙甲纤维素、富马酸喹硫平、月桂基硫酸钠、一部分Lutrol和山嵛酸甘油酯干混合3分钟。然后，缓慢添加乙基纤维素的10％水醇溶液，同时将造粒机叶片和切刀速度保持在为颗粒形成和生长提供足够剪切的预选值。继续添加溶液，直至添加了全部量的乙基纤维素。所述颗粒然后使用减尺寸磨机(granumill)湿磨，并然后装入流化床中干燥。

[0434] 富马酸喹硫平颗粒然后在底喷式流化床包衣机中用Eudragit E-100共聚物和硬脂酸镁的醇悬液包衣。所生成的包衣颗粒随后用于掺合和压制过程。

[0435] 表72：富马酸喹硫平颗粒组成

[0436]

造粒	%w/w
富马酸喹硫平	14.3
羟丙甲纤维素	59.2
山嵛酸甘油酯	4.1
乙基纤维素	4.1
月桂基硫酸钠	10.1
Lutrol	8.2
总计	100

包衣	%w/w
喹硫平颗粒	82
Eudragit E-100	12
硬脂酸镁	6
总计	100

[0437] 实施例40:富马酸喹硫平片剂

[0438] 按照上文实施例39制备的包衣颗粒随后与其他组分(卡波姆,交聚维酮,碳酸氢钠,甘露醇,微晶纤维素和剩余部分的Lutrol)混合,并在V-掺合器中掺合30分钟。添加硬脂酸镁润滑所述掺合物并再掺合5分钟,然后压制成片剂。

[0439] 表73:富马酸喹硫平片剂组成

[0440]

组分(mg/片)	200mg	300mg	400mg
羟丙甲纤维素	48	72.5	97
山嵛酸甘油酯	14	20.8	28
乙基纤维素	14	20.8	28
富马酸喹硫平	200	300	400
Eudragit E-100	40	74	99
甘露醇	25	25	25
卡波普	50	65	65
微晶纤维素	125	125	125
交聚维酮	200	275	275
碳酸氢钠	45	45	45
硬脂酸镁	36	48	64
Lutrol	78	91.6	105
月桂基硫酸钠	34	51.2	69
总片剂重量	909	1213.9	1425

[0441] 实施例41:包衣氢吗啡酮颗粒

[0442] 包衣氢吗啡酮颗粒按照实施例1中描述的过程制备,在组分上与实施例1略有变化,如下面所示。

[0443] 表74:盐酸氢吗啡酮颗粒组成

[0444]

造粒	%w/w
羟丙甲纤维素	60
山嵛酸甘油酯	26
乙基纤维素	14
总计	100
敷层	%w/w
盐酸氢吗啡酮	5
聚合物颗粒(EC,HPMC和Compritol)	92.5

羟丙甲纤维素2910	2.5
总计	100
包衣	%w/w
氢吗啡酮敷层颗粒	50
Eudragit E-100	33
硬脂酸镁	17
总计	100

[0445] 实施例42:盐酸氢吗啡酮片剂

[0446] 包衣氢吗啡酮颗粒按照上文实施例1和实施例41中描述的过程制备。所述包衣颗粒随后与其他组分(卡波姆,交聚维酮,碳酸氢钠,甘露醇,微晶纤维素)混合,并在V-掺合器中掺合30分钟。添加硬脂酸镁润滑所述掺合物并再掺合5分钟,然后压制成片剂。

[0447] 表75:盐酸氢吗啡酮片剂组成

[0448]

组分(mg/片)	2mg	4mg	8mg
羟丙甲纤维素	22.2	44.4	88.9
山嵛酸甘油酯	9.5	19.1	38.1
乙基纤维素	5.2	10.5	21
盐酸氢吗啡酮	2	4	8
羟丙甲纤维素2910	1	2	4
Eudragit E-100	26.7	53.4	106.7
甘露醇	70	70	70
卡波普	50	50	50
微晶纤维素	95	95	94
交聚维酮	90	95	150
碳酸氢钠	30	30	30
硬脂酸镁	18.1	58.3	60.4
总片剂重量	419.7	531.7	721.1

[0449] 实施例43:包衣甲基安非他明颗粒

[0450] 包衣甲基安非他明颗粒根据实施例1中描述的过程制备。

[0451] 表76:盐酸甲基安非他明颗粒组成

[0452]

造粒	%w/w
羟丙甲纤维素	60
山嵛酸甘油酯	26
乙基纤维素	14
总计	100
敷层	%w/w
盐酸甲基安非他明	5
聚合物颗粒(EC,HPMC和Compritol)	92.5

羟丙甲纤维素2910	2.5
总计	100
包衣	%w/w
甲基安非他明敷层颗粒	50
Eudragit E-100	33
硬脂酸镁	17
总计	100

[0453] 实施例44:盐酸甲基安非他明片剂

[0454] 包衣甲基安非他明颗粒按照上文实施例1和实施例43中描述的过程制备。所述包衣颗粒随后与其他组分(卡波姆,交聚维酮,碳酸氢钠,甘露醇,微晶纤维素)混合,并在V-掺合器中掺合30分钟。添加硬脂酸镁润滑所述掺合物并再掺合5分钟,然后压制成片剂。

[0455] 表77:盐酸甲基安非他明片剂组成

[0456]

组分(mg/片)	5mg
羟丙甲纤维素	55.6
山嵛酸甘油酯	23.8
乙基纤维素	13.1
盐酸安非他明	5
羟丙甲纤维素2910	2.5
Eudragit E-100	66.7
甘露醇	70
卡波普	50
微晶纤维素	95
交聚维酮	100
碳酸氢钠	30
硬脂酸镁	39
总片剂重量	550.7

[0457] 实施例45:包衣羟吗啡酮颗粒

[0458] 包衣羟吗啡酮颗粒按照实施例1中描述的过程制备。

[0459] 表78:盐酸羟吗啡酮颗粒组成

[0460]

造粒	%w/w
羟丙甲纤维素	60
山嵛酸甘油酯	26
乙基纤维素	14
总计	100
敷层	%w/w
盐酸羟吗啡酮	10
聚合物颗粒(EC,HPMC和Compritol)	85

羟丙甲纤维素2910	5
总计	100
包衣	%w/w
羟吗啡酮敷层颗粒	50
Eudragit E-100	33
硬脂酸镁	17
总计	100

[0461] 实施例46:盐酸羟吗啡酮片剂

[0462] 包衣羟吗啡酮颗粒按照上文实施例1和实施例45描述的过程制备。所述包衣颗粒随后与其他组分(卡波姆,交聚维酮,碳酸氢钠,甘露醇,微晶纤维素)混合,并在V-掺合器中掺合30分钟。添加硬脂酸镁润滑所述掺合物并再掺合5分钟,然后压制成片剂。

[0463] 表79:盐酸羟吗啡酮片剂组成

[0464]

组分s(mg/片)	5mg	10mg
羟丙甲纤维素	25.5	51.1
山嵛酸甘油酯	11	21.9
乙基纤维素	6	12
盐酸羟吗啡酮	5	10
羟丙甲纤维素2910	2.5	5
Eudragit E-100	33.4	66.7
甘露醇	70	70
卡波普	45	45
微晶纤维素	95	94
交聚维酮	100	100
碳酸氢钠	27	27
硬脂酸镁	21.6	39.3
总片剂重量	442	542

[0465] 实施例47:包衣羟考酮颗粒

[0466] 包衣羟考酮颗粒按照实施例1中描述的过程制备。

[0467] 表80:盐酸羟考酮颗粒组成

[0468]

造粒	%w/w
羟丙甲纤维素	60
山嵛酸甘油酯	26
乙基纤维素	14
总计	100
敷层	%w/w
盐酸羟考酮	10
聚合物颗粒(EC,HPMC和Compritol)	85

羟丙甲纤维素2910	5
总计	100
包衣	%w/w
羟考酮敷层颗粒	50
Eudragit E-100	33
硬脂酸镁	17
总计	100

[0469] 实施例48:盐酸羟考酮片剂

[0470] 包衣羟考酮颗粒按照上文实施例1和实施例47描述的过程制备。所述包衣颗粒随后与其他组分(卡波姆,交聚维酮,碳酸氢钠,甘露醇,微晶纤维素)混合,并在V-掺合器中掺合30分钟。添加硬脂酸镁润滑所述掺合物并再掺合5分钟,然后压制成片剂。

[0471] 表81:盐酸羟考酮片剂组成

[0472]

组分(mg/片)	5mg	15mg	30mg
羟丙甲纤维素	25.5	76.6	153.3
山嵛酸甘油酯	11	32.8	65.7
乙基纤维素	6	18.1	36.1
盐酸羟考酮	5	15	30
羟丙甲纤维素2910	2.5	7.5	15
Eudragit E-100	33.4	100.1	200.1
甘露醇	70	37.29	70
卡波普	45	50	50
微晶纤维素	95	130	94
交聚维酮	100	150	200
碳酸氢钠	27	30	30
硬脂酸镁	21.6	57	110
总片剂重量	442	704.39	1054.2

[0473] 实施例49:包衣硫酸吗啡颗粒

[0474] 包衣吗啡颗粒按照实施例1中描述的过程制备。

[0475] 表82:硫酸吗啡片剂组成

[0476]

造粒	%w/w
羟丙甲纤维素	60
山嵛酸甘油酯	26
乙基纤维素	14
总计	100
敷层	%w/w
硫酸吗啡	10
聚合物颗粒(EC,HPMC和Compritol)	85

羟丙甲纤维素2910	5
总计	100
包衣	%w/w
吗啡敷层颗粒	50
Eudragit E-100	33
硬脂酸镁	17
总计	100

[0477] 实施例50:硫酸吗啡片剂

[0478] 包衣吗啡颗粒按照上文实施例1和实施例49描述的过程制备。所述包衣颗粒随后与其他组分(卡波姆,交聚维酮,碳酸氢钠,甘露醇,微晶纤维素)混合,并在V-掺合器中掺合30分钟。添加硬脂酸镁润滑所述掺合物并再掺合5分钟,然后压制成片剂。

[0479] 表83:硫酸吗啡片剂组成

[0480]

组分(mg/片)	6mg	15mg	30mg
羟丙甲纤维素	30.6	76.6	153.3
山嵛酸甘油酯	13.1	32.8	65.7
乙基纤维素	7.2	18.1	36.1
硫酸吗啡	6	15	30
羟丙甲纤维素2910	3	7.5	15
Eudragit E-100	40.02	100.1	200.1
甘露醇	70	70	70
卡波普	45	50	50
微晶纤维素	95	130	94
交聚维酮	100	150	200
碳酸氢钠	27	30	30
硬脂酸镁	24.5	57	110
总片剂重量	461.42	737.1	1054.2

[0481] 实施例51:包衣混合安非他明盐颗粒

[0482] 含有混合安非他明盐(糖酸右旋安非他明,天冬氨酸安非他明,硫酸右旋安非他明,硫酸安非他明)的包衣颗粒按照实施例1中描述的过程制备。

[0483] 表84:混合安非他明盐颗粒配制物

[0484]

造粒	%w/w
羟丙甲纤维素	60
山嵛酸甘油酯	26
乙基纤维素	14
总计	100
敷层	%w/w
混合安非他明盐(*糖酸右旋安非他明,天冬氨酸安非他明)	10

聚合物颗粒(EC,HPMC和Compritol)	85
羟丙甲纤维素2910	5
总计	100
包衣	%w/w
混合安非他明盐敷层颗粒	50
Eudragit E-100	33
硬脂酸镁	17
总计	100

[0485] 实施例52:混合安非他明盐片剂

[0486] 含有混合安非他明盐的包衣颗粒按照上文实施例1和实施例51描述的过程制备。所述包衣颗粒随后与其他组分例如卡波姆、交聚维酮、碳酸氢钠、甘露醇、微晶纤维素混合并在V-掺合器中掺合30分钟。添加硬脂酸镁润滑所述掺合物并再掺合5分钟,然后压制成片剂。

[0487] 表85:混合安非他明盐片剂配制物

[0488]

总安非他明/基质当量	3.13 mg 5 mg	4.7 mg 7.5 mg	6.3 mg 10 mg	7.8 mg 12.5 mg	9.4 mg 15 mg	12.6 mg 20 mg	18.8 mg 30 mg
组分 (mg/片)							
羟丙甲纤维素	25.5	38.3	51.1	63.8	76.6	102.15	153.3
山嵛酸甘油酯	10.9	16.4	21.9	27.4	32.8	43.8	65.7
乙基纤维素	6.02	9.03	12.04	15.05	18.1	24.1	36.1
混合安非他明盐*	5	7.5	10	12.5	15	20	30
羟丙甲纤维素 2910	2.5	3.75	5	6.25	7.5	10	15
Eudragit E-100	33.4	50.04	66.7	83.4	100.1	133.4	200.1
甘露醇	70	70	70	70	70	70	70
卡波普	45	45	45	50	50	50	50
微晶纤维素	95	95	95	130	130	130	150
交聚维酮	100	100	100	150	150	160	200
碳酸氢钠	27	27	27	30	30	30	30
硬脂酸镁	21.5	30	38.6	48	57	75	110
总片剂重量	441.82	492.02	542.34	686.4	737.1	848.45	1110.2
*糖酸右旋安非他明，一水合天冬氨酸安非他明等同物，硫酸右旋安非他明，硫酸安非他明							

[0489] 实施例53:磷酸可待因颗粒

[0490] 含有磷酸可待因的包衣颗粒按照实施例1中描述的过程制备,对组成如下所述有一些改变。

[0491] 表86:磷酸可待因颗粒配制物

[0492]

造粒	%w/w
羟丙甲纤维素	60

山嵛酸甘油酯	26
乙基纤维素	14
总计	100
敷层	%w/w
磷酸可待因	20
聚合物颗粒(EC,HPMC和Compritol)	70
羟丙甲纤维素2910	10
总计	100
包衣	%w/w
磷酸可待因敷层颗粒	70
Eudragit E-100	20
硬脂酸镁	10
总计	100

[0493] 实施例54:磷酸可待因片剂

[0494] 含有磷酸可待因的包衣颗粒按照上文实施例1和实施例53描述的过程制备。所述包衣颗粒随后与其他活性成分(扑热息痛)和其他组分(卡波姆,交聚维酮,碳酸氢钠,甘露醇,着色剂,微晶纤维素)混合并在V-掺合器中掺合30分钟。添加硬脂酸镁润滑所述掺合物并再掺合5分钟,然后压制成片剂。

[0495] 表87:磷酸可待因/APAP片剂配制物

[0496]

组分 (mg/片)	30/300 mg	60/300 mg
羟丙甲纤维素	63.1	126.2
山嵛酸甘油酯	27	54.1
乙基纤维素	14.9	29.7
磷酸可待因	30	60
羟丙甲纤维素 2910	15	30
Eudragit E-100	42.9	85.7
扑热息痛*	315.8	315.8
甘露醇	29.4	29.4
卡波普	50	50
微晶纤维素	180	180
交聚维酮	200	200
碳酸氢钠	30	30
FD&C 蓝# 2	NA	0.6
氧化铁黄 510P	0.5	NA
硬脂酸镁	31.5	57
总片剂重量	1030.1	1248.5
*所述扑热息痛级含有 300 mg 的 APAP 和 15.8 mg 的明胶		

[0497] 实施例55:盐酸哌醋甲酯颗粒

[0498] 含有盐酸哌醋甲酯的包衣颗粒按照实施例1中描述的过程制备。

[0499] 表88:盐酸哌醋甲酯颗粒配制物

造粒	% w/w
羟丙甲纤维素	60
山嵛酸甘油酯	26
乙基纤维素	14
总计	100

[0500]

敷层	% w/w
盐酸哌醋甲酯	10
聚合物颗粒 (EC，HPMC 和 Compritol)	85
羟丙甲纤维素 2910	5
总计	100
包衣	**% w/w**
盐酸哌醋甲酯敷层颗粒	50
Eudragit E-100	33
硬脂酸镁	17
总计	100

[0501] 实施例56:盐酸哌醋甲酯片剂

[0502] 含有盐酸哌醋甲酯的包衣颗粒按照上文实施例1和实施例55描述的过程制备。所述包衣颗粒随后与其他组分(卡波姆,交聚维酮,碳酸氢钠,甘露醇,微晶纤维素)混合,并在V-掺合器中掺合30分钟。添加硬脂酸镁润滑所述掺合物并再掺合5分钟,然后压制成片剂。

[0503] 表89:盐酸哌醋甲酯片剂配制物

[0504]

组分(mg/片)	5mg	20mg
羟丙甲纤维素	25.5	102.15
山嵛酸甘油酯	10.9	43.8
乙基纤维素	6.02	24.1
盐酸哌醋甲酯	5	20
羟丙甲纤维素2910	2.5	10
Eudragit E-100	33.4	133.4
甘露醇	70	70
卡波普	45	50
微晶纤维素	95	150
交聚维酮	100	160
碳酸氢钠	27	30
硬脂酸镁	21.5	75
总片剂重量	441.82	868.45

[0505] 实施例57:盐酸羟考酮颗粒

[0506] 含有盐酸羟考酮的包衣颗粒按照实施例1中描述的过程制备和包衣。

[0507] 表90:盐酸羟考酮颗粒配制物

[0508]

造粒	%w/w
羟丙甲纤维素	60
山嵛酸甘油酯	26
乙基纤维素	14
总计	100
敷层	%w/w
盐酸羟考酮	10
聚合物颗粒(EC,HPMC和Compritol)	85
羟丙甲纤维素2910	5
总计	100
包衣	%w/w
羟考酮敷层颗粒,10%	50
Eudragit E-100	33
硬脂酸镁	17
总计	100

[0509] 颗粒在高剪切造粒机中制造,在其中羟丙甲纤维素和山嵛酸甘油酯干混合3分钟。然后,缓慢添加乙基纤维素的10%水醇溶液,同时将造粒机叶片和切刀速度保持在为颗粒形成和生长提供足够剪切的预选值。继续添加溶液,直至添加了全部量的乙基纤维素。所述颗粒然后使用减尺寸磨机(granumill)湿磨,并随后装入流化床中干燥。所制备的颗粒然后在底喷式流化床包衣机中用盐酸羟考酮和HPMC 2910(2:1)的12%水溶液敷层。

[0510] 所述盐酸羟考酮敷层颗粒然后在底喷式流化床包衣机中用Eudragit E-100共聚物和硬脂酸镁(2:1)的25%醇悬液包衣。所生成的包衣颗粒随后用于进一步的掺合和压制过程。

[0511] 实施例58:羟考酮/对乙酰氨基酚片剂

[0512] 根据上文实施例57制备的包衣颗粒与另一种活性剂扑热息痛和其他赋形剂(卡波姆,交聚维酮,碳酸氢钠,甘露醇,FD&C蓝,微晶纤维素)混合,并在V-掺合器中掺合30分钟。然后添加硬脂酸镁润滑所述掺合物并再掺合5分钟,然后压制成羟考酮/APAP片剂。

[0513] 表91:盐酸羟考酮片剂配制物

[0514]

组分	% w/w
羟考酮包衣颗粒	20.0
扑热息痛*	33.7
甘露醇	4.2
卡波普	5.0
微晶纤维素	13.0
交聚维酮	20.0
碳酸氢钠	3.0
FD&C 蓝	0.06
硬脂酸镁	1.0
总计	**100**
*含有 95%对乙酰氨基酚和 5%明胶	

[0515] 实施例59:羟考酮/对乙酰氨基酚片剂

[0516] 根据上文实施例57制备的包衣颗粒与另一种活性剂扑热息痛和其他赋形剂(卡波姆,交聚维酮,碳酸氢钠,甘露醇,FD&C蓝,微晶纤维素)混合,并在V-掺合器中掺合30分钟。然后添加硬脂酸镁润滑所述掺合物并再掺合5分钟,然后压制成羟考酮/APAP片剂。

[0517] 表92:羟考酮/对乙酰氨基酚片剂配制物

[0518]

组分 (% w/w)	5/325 mg	7.5/325 mg	10/325 mg
羟考酮包衣颗粒	12.5	16.7	20.0
扑热息痛*	42.8	38.0	34.2
甘露醇	3.7	4.37	3.79
卡波普	6.25	5.6	5
微晶纤维素	12	12	13
交聚维酮	18	19	20
碳酸氢钠	3.75	3.3	3
氧化铁黄	0.06	NA	NA
FD&C 蓝#2	NA	0.06	NA
硬脂酸镁	1.0	1.0	1.0
总计	**100**	**100**	**100**
*含有 95%对乙酰氨基酚和 5%明胶			

[0519] 实施例60:阿莫达非尼颗粒

[0520] 阿莫达非尼颗粒利用与实施例1中描述的相似的过程制造,对所述过程有一些修改。所述活性成分,阿莫达非尼,并非在所述颗粒上敷层而是存在于核中,它在其中与按照表93的其他赋形剂一起造粒,并随后用Eudragit E-100包衣。

[0521] 颗粒在高剪切造粒机中制造,在其中羟丙甲纤维素、阿莫达非尼、聚维酮和山嵛酸甘油酯干混合3分钟。然后,缓慢添加乙基纤维素的10%水醇溶液,同时将造粒机叶片和切刀速度保持在为颗粒形成和生长提供足够剪切的预选值。继续添加溶液,直至添加了全部量的乙基纤维素。所述颗粒然后使用减尺寸磨机(Granumill)湿磨,随后装入流化床中干燥。

[0522] 阿莫达非尼颗粒然后在底喷式流化床包衣机中用Eudragit E-100共聚物和硬脂酸镁的醇悬液包衣。所生成的包衣颗粒随后用于掺合和压制过程。

[0523] 表93:阿莫达非尼颗粒配制物

[0524]

造粒	%w/w
阿莫达非尼	66.99
羟丙甲纤维素	16.75
山嵛酸甘油酯	3.83
乙基纤维素	3.83
聚维酮	8.61
总计	100
包衣	%w/w
阿莫达非尼颗粒	70
Eudragit E-100	20
硬脂酸镁	10
总计	100

[0525] 实施例61:阿莫达非尼片剂

[0526] 根据上文实施例60制备的包衣颗粒随后与其他组分(卡波姆,交聚维酮,碳酸氢钠,甘露醇,微晶纤维素)混合,并在V-掺合器中掺合30分钟。添加硬脂酸镁润滑所述掺合物并再掺合5分钟,然后压制成片剂。

[0527] 表94:阿莫达非尼片剂配制物

[0528]

组分 (mg/片)	**50 mg** (mg/片)	**150 mg** (mg/片)	**200 mg** (mg/片)
羟丙甲纤维素	12.5	37.5	50
山嵛酸甘油酯	2.9	8.6	11
乙基纤维素	2.9	8.6	11
阿莫达非尼	50	150	200
Eudragit E-100	21.3	64	85
甘露醇	17	25	25
卡波普	50	50	50
微晶纤维素	100	125	125
交聚维酮	150	200	200
碳酸氢钠	30	30	30
硬脂酸镁	16	40	52
聚维酮	6.4	19.3	26
总片剂重量	459	758	865

[0529] 实施例62:苯巴比妥颗粒

[0530] 苯巴比妥颗粒利用与实施例1中描述的相似的过程制造,对所述过程有一些修改。所述活性成分,苯巴比妥,并非在所述颗粒上敷层而是存在于核中,它在其中与按照下表的其他赋形剂一起造粒,并随后用Eudragit E-100包衣。

[0531] 颗粒在高剪切造粒机中制造,在其中羟丙甲纤维素、苯巴比妥、聚维酮和山嵛酸甘

油酯干混合3分钟。然后，缓慢添加乙基纤维素的10％水醇溶液，同时将造粒机叶片和切刀速度保持在为颗粒形成和生长提供足够剪切的预选值。继续添加溶液，直至添加了全部量的乙基纤维素。所述颗粒然后使用减尺寸磨机(Granumill)湿磨，随后装入流化床中干燥。

[0532] 所述苯巴比妥颗粒然后在底喷式流化床包衣机中用Eudragit E-100共聚物和硬脂酸镁的醇悬液包衣。所生成的包衣颗粒随后用于掺合和压制过程。

[0533] 表95：苯巴比妥颗粒配制物

[0534]

造粒	％w/w
苯巴比妥	66.99
羟丙甲纤维素	16.75
山嵛酸甘油酯	3.83
乙基纤维素	3.83
聚维酮	8.61
总计	100
敷层	％w/w
苯巴比妥颗粒	50
Eudragit E-100	33
硬脂酸镁	17
总计	100

[0535] 实施例63：苯巴比妥片剂

[0536] 根据上文实施例62制备的包衣颗粒随后与其他组分(卡波姆，交聚维酮，碳酸氢钠，甘露醇，微晶纤维素)混合，并在V-掺合器中掺合30分钟。添加硬脂酸镁润滑所述掺合物并再掺合5分钟，然后压制成片剂。

[0537] 表96：苯巴比妥片剂配制物

[0538]

组分	15 mg (mg/片)	30 mg (mg/片)	60 mg (mg/片)	100 mg (mg/片)
羟丙甲纤维素	3.8	7.5	15	25.01
山嵛酸甘油酯	1	2	3.4	5.72
乙基纤维素	1	2	3.4	5.72
苯巴比妥	15	30	60	100
Eudragit E-100	15	30	59	98.5
甘露醇	20	20	20	20
卡波普	50	50	50	50
微晶纤维素	75	100	100	100
交聚维酮	130	130	200	200
碳酸氢钠	30	30	30	30
硬脂酸镁	12	20	36	59
聚维酮	2	4	7.7	12.9
总片剂重量	354.8	425.5	584.5	706.85

[0539] 实施例64：地西泮颗粒

[0540] 包衣地西泮颗粒按照实施例1中描述的过程制备，在组分上与实施例1略有变化，

如下表所示。

[0541] 表97:地西泮颗粒配制物

[0542]

造粒	%w/w
羟丙甲纤维素	60
山嵛酸甘油酯	26
乙基纤维素	14
总计	100
敷层	%w/w
地西泮	5
聚合物颗粒(EC,HPMC和Compritol)	92.5
羟丙甲纤维素2910	2.5
总计	100
包衣	%w/w
地西泮敷层颗粒	50
Eudragit E-100	33
硬脂酸镁	17
总计	100

[0543] 实施例65:地西泮片剂

[0544] 包衣地西泮颗粒根据上文实施例1和实施例64中描述的过程制备。所述包衣颗粒随后与其他组分(卡波姆,交聚维酮,碳酸氢钠,甘露醇,微晶纤维素)混合,并在V-掺合器中掺合30分钟。添加硬脂酸镁润滑所述掺合物并再掺合5分钟,然后压制成片剂。

[0545] 表98:地西泮片剂配制物

[0546]

组分(mg/片)	2mg	5mg	10mg
羟丙甲纤维素	22.2	55.6	111.2
山嵛酸甘油酯	9.5	23.8	47.64
乙基纤维素	5.2	13.1	26.2
地西泮	2	5	10
羟丙甲纤维素2910	1	2.5	5
Eudragit E-100	26.7	66.7	133.4
甘露醇	70	70	70
卡波普	50	50	50
微晶纤维素	95	95	94
交聚维酮	120	120	150
碳酸氢钠	30	30	30
硬脂酸镁	18.1	38.6	74.6
总片剂重量	449.7	570.3	802.04

[0547] 实施例66:重酒石酸氢可酮颗粒

[0548] 含有重酒石酸氢可酮的包衣颗粒根据实施例1中描述的过程制备。

[0549] 表99:重酒石酸氢可酮颗粒配制物

[0550]

造粒	%w/w
羟丙甲纤维素	60
山嵛酸甘油酯	26
乙基纤维素	14
总计	100
敷层	%w/w
重酒石酸氢可酮	10
聚合物颗粒(EC,HPMC和Compritol)	85
羟丙甲纤维素2910	5
总计	100
包衣	%w/w
重酒石酸氢可酮敷层颗粒	50
Eudragit E-100	33
硬脂酸镁	17
总计	100

[0551] 实施例67:重酒石酸氢可酮片剂

[0552] 含有重酒石酸氢可酮的包衣颗粒根据上文实施例1和实施例66中描述的过程制备。所述包衣颗粒随后与其他组分(卡波姆,交聚维酮,碳酸氢钠,甘露醇,微晶纤维素)混合,并在V-掺合器中掺合30分钟。添加硬脂酸镁润滑所述掺合物并再掺合5分钟,然后压制成片剂。

[0553] 表100:氢可酮片剂配制物

[0554]

组分	5 mg (mg/片)	10 mg (mg/片)
羟丙甲纤维素	25.5	51.1
山嵛酸甘油酯	11	21.9
乙基纤维素	6	12.04
重酒石酸氢可酮	5	10
羟丙甲纤维素 2910	2.5	5
Eudragit E-100	33.4	66.7
甘露醇	70	70
卡波普	50	50
微晶纤维素	95	95
交聚维酮	100	120
碳酸氢钠	30	30
硬脂酸镁	21.6	39.3
总片剂重量	450	571.04

[0555] 实施例68:盐酸羟考酮包衣颗粒

[0556] 表201:颗粒配制物

[0557]

组分	%w/w
羟丙甲纤维素K100M	60
山嵛酸甘油酯	26
乙基纤维素(10cP)	14
总计	100

[0558] 表102:敷层颗粒配制物

[0559]

组分	%w/w
盐酸羟考酮	10
聚合物颗粒(EC,HPMC和Compritol)	85
羟丙甲纤维素2910E3	5
总计	100

[0560] 表103:包衣颗粒配制物

[0561]

组分	%w/w
10%盐酸羟考酮敷层颗粒	50
Eudragit E-100	33
硬脂酸镁	17
总计	100

[0562] 颗粒在高剪切造粒机中制造,在其中羟丙甲纤维素、山嵛酸甘油酯和一部分(67%)的乙基纤维素干混合3分钟。然后,缓慢添加乙基纤维素的10%水醇(～28份水和～72份醇)溶液(10%wt/wt),同时将造粒机叶片和切刀速度保持在为颗粒形成和生长提供足够剪切的预选值。继续添加溶液,直至添加了全部量的乙基纤维素。所述颗粒然后使用减尺寸磨机(Granumill)湿磨,随后装入流化床中干燥。

[0563] 所制备的颗粒然后在底喷式流化床涂布机中用盐酸羟考酮和HPMC的12%wt/wt水溶液敷层。

[0564] 所述重酒石酸羟考酮敷层颗粒然后在底喷式流化床包衣机中用Eudragit E-100共聚物和硬脂酸镁的25%醇悬液包衣。所生成的包衣颗粒随后掺合均匀和用于进一步的掺合和压制过程。

[0565] 实施例69:羟考酮对乙酰氨基酚片剂制剂

[0566] 包衣颗粒根据上文实施例68制备,并与扑热息痛(使用对乙酰氨基酚和明胶制造)和其他赋形剂(如下表104中列出的)混合,并掺合大约270转。添加硬脂酸镁润滑所述掺合物并再掺合45转。所述掺合物然后压制成羟考酮/对乙酰氨基酚片剂。

[0567] 表104:片剂配制物

[0568]

组分	%w/w	mg/片
5%盐酸羟考酮包衣颗粒	20.0	200
扑热息痛	33.7	337*

甘露醇	10.3	103
卡波普	5.0	50
微晶纤维素	12.0	120
交聚维酮	15.0	150
碳酸氢钠	3.0	30
硬脂酸镁	1.0	10
总计	100	1000

[0569] *含有325mg的对乙酰氨基酚

[0570] 实施例70:包衣羟考酮颗粒,5%

[0571] 制备颗粒,用API敷层和随后包衣。这些包衣粒子然后与其他组分掺合并压制成片剂。

[0572] 表305:颗粒配制物

[0573]

组分	%w/w
羟丙甲纤维素K100M	60
山嵛酸甘油酯	26
乙基纤维素(10cP)	14
总计	100

[0574] 表106:敷层颗粒配制物

[0575]

组分	%w/w
盐酸羟考酮	10
聚合物颗粒(EC,HPMC和Compritol)	85
羟丙甲纤维素2910(HPMC 2910E3)	5
总计	100

[0576] 表107:包衣颗粒配制物

[0577]

组分	%w/w
10%盐酸羟考酮敷层颗粒	50
Eudragit E-100	33
硬脂酸镁	17
总计	100

[0578] 颗粒在高剪切造粒机中制造,在其中羟丙甲纤维素、一部分乙基纤维素和山嵛酸甘油酯干混合3分钟。然后,缓慢添加乙基纤维素10cP的10%w/w水醇(～28份水和～72份醇)溶液,同时将造粒机叶片和切刀速度保持在为颗粒形成和生长提供足够剪切的预选值。继续添加溶液,直至添加了全部量的乙基纤维素。所述颗粒然后使用减尺寸磨机(Granumill)湿磨,随后装入流化床中干燥。

[0579] 所制备的颗粒然后在底喷式流化床涂布机中用盐酸羟考酮和HPMC 2910E3的12%wt/wt水溶液敷层。

[0580] 所述盐酸羟考酮敷层颗粒然后在底喷式流化床包衣机中用Eudragit E-100共聚物和硬脂酸镁的25％醇悬液包衣。所生成的包衣颗粒随后掺合均匀和用于进一步的掺合和压制过程。

[0581] 实施例71:包衣聚合物颗粒

[0582] 颗粒在高剪切造粒机中制造,在其中羟丙甲纤维素、一部分乙基纤维素和山嵛酸甘油酯干混合3分钟。然后,缓慢添加乙基纤维素10cP的10％w/w水醇(～28份水和～72份醇)溶液,同时将造粒机叶片和切刀速度保持在为颗粒形成和生长提供足够剪切的预选值。继续添加溶液,直至添加了全部量的乙基纤维素。所述颗粒然后使用减尺寸磨机(Granumill)湿磨,随后装入流化床中干燥。

[0583] 所述颗粒然后在底喷式流化床包衣机中用Eudragit E-100共聚物和硬脂酸镁的25％醇悬液包衣。

[0584] 表108:颗粒配制物

[0585]

组分	％w/w
羟丙甲纤维素K100M	60
山嵛酸甘油酯	26
乙基纤维素(10cP)	14
总计	100

[0586] 表109:包衣聚合物颗粒配制物

[0587]

组分	％w/w
聚合物颗粒	50
Eudragit E-100	33
硬脂酸镁	17
总计	100

[0588] 实施例72A和实施例72B:

[0589] 盐酸羟考酮包衣颗粒根据实施例70制备并与根据实施例71制备的包衣聚合物颗粒混合。添加另一种活性剂、即扑热息痛(使用对乙酰氨基酚和明胶制造)和其他赋形剂例如卡波姆、交聚维酮、碳酸氢钠、甘露醇和微晶纤维素,并掺合大约270转。然后添加硬脂酸镁润滑所述掺合物并再掺合45转,然后压制成片剂。

[0590] 表110:片剂配制物

[0591]

组分	实施例 72A		实施例 72B	
	% w/w	mg/片	% w/w	mg/片
5%盐酸羟考酮包衣颗粒	10.87	108.7	16.3	163
包衣聚合物颗粒	9.13	91.3	3.7	37
扑热息痛	33.7	337*	33.71	337.1*
甘露醇	4.29	42.9	4.29	42.9
卡波普	5.0	50.0	5.0	50
微晶纤维素	13.0	130.0	13.0	130
交聚维酮	20.0	200.	20.0	200
碳酸氢钠	3.0	30	3.0	30
硬脂酸镁	1.0	10	1.0	10
总计	100	1000	100	1000

[0592] *含有325mg对乙酰氨基酚

[0593] 实施例73:抗多片口服滥用性的体外分析

[0594] 根据实施例72A和实施例72B制备的剂型通过在300mL 0.1N HCl中搅拌选定的片数来评价抗体外多片口服滥用性。利用USP设备II在50rpm和37℃下进行溶出。一到十二个片剂同时添加到容器中,定期取出等份并通过HPLC分析盐酸羟考酮(图10)和对乙酰氨基酚(APAP)[图11]。结果对时间作图,并呈现在图10和图11中。

[0595] 实施例74:聚合物颗粒

[0596] 表111:颗粒配制物

[0597]

组分	%w/w
羟丙甲纤维素K100M	60
山嵛酸甘油酯	26
乙基纤维素(10cP)	14
总计	100

[0598] 颗粒在高剪切造粒机中制造,在其中羟丙甲纤维素、一部分乙基纤维素和山嵛酸甘油酯干混合3分钟。然后,缓慢添加乙基纤维素10cP的10%w/w水醇(～28份水和～72份醇)溶液,同时将造粒机叶片和切刀速度保持在为颗粒形成和生长提供足够剪切的预选值。继续添加溶液,直至添加了全部量的乙基纤维素。所述颗粒然后使用减尺寸磨机(Granumill)湿磨,随后装入流化床中干燥。

[0599] 实施例75:5%重酒石酸氢可酮包衣颗粒

[0600] 根据实施例74制备的颗粒然后在底喷式流化床包衣机中用重酒石酸氢可酮和HPMC 2910 E3的12%w/w水溶液敷层。所述重酒石酸氢可酮敷层颗粒然后在底喷式流化床包衣机中用Eudragit E-100共聚物和硬脂酸镁的25%醇悬液包衣。

[0601] 表112:敷层颗粒配制物

[0602]

组分	%w/w
重酒石酸氢可酮	10
聚合物颗粒(EC,HPMC和Compritol)	85
羟丙甲纤维素2910	5
总计	100

[0603] 表113:包衣颗粒配制物

[0604]

组分	%w/w
10%重酒石酸氢可酮敷层颗粒	50
Eudragit E-100	33
硬脂酸镁	17
总计	100

[0605] 实施例76:重酒石酸氢可酮片剂

[0606] 重酒石酸氢可酮包衣颗粒根据上文实施例75制备并与根据实施例74制备的聚合物颗粒混合。添加另一种活性剂、即扑热息痛(使用对乙酰氨基酚和明胶制造)和其他赋形剂例如卡波姆、交聚维酮、碳酸氢钠、甘露醇、微晶纤维素,并掺合大约270转。然后添加硬脂酸镁润滑所述掺合物并再掺合45转,然后压制成氢可酮/对乙酰氨基酚片剂。

[0607] 表114:片剂配制物

[0608]

组分	%w/w	mg/片
5%重酒石酸氢可酮包衣颗粒	9.62	96.2
聚合物颗粒	5.38	53.8
扑热息痛	33.71	337.1*
甘露醇	9.29	92.9
卡波普	5.0	50
微晶纤维素	13.0	130
交聚维酮	20.0	200
碳酸氢钠	3.0	30
硬脂酸镁	1.0	10
总计	100	1000

[0609] *含有325mg对乙酰氨基酚

[0610] 实施例77A和实施例77B:重酒石酸氢可酮片剂

[0611] 5%重酒石酸氢可酮包衣颗粒根据上文实施例75制备并与根据实施例71制备的包衣聚合物颗粒混合。添加另一种活性剂、即扑热息痛(使用对乙酰氨基酚和明胶制造)和其他赋形剂例如卡波姆、交聚维酮、碳酸氢钠、甘露醇、微晶纤维素,并掺合大约270转。然后添加硬脂酸镁润滑所述掺合物并再掺合45转,然后压制成氢可酮/对乙酰氨基酚片剂。

[0612] 表115:片剂配制物

[0613]

组分	实施例 77A		实施例 77B	
	% w/w	mg/片	% w/w	mg/片
5%重酒石酸氢可酮包衣颗粒	9.62	96.2	14.42	96.2
包衣聚合物颗粒	10.38	103.8	5.58	103.8
扑热息痛	33.71	337.1*	33.71	337.1*
甘露醇	4.29	42.9	4.29	42.9
卡波普	5.0	50	5.0	50
微晶纤维素	13.0	130	13.0	130
交聚维酮	20.0	200	20.0	200
碳酸氢钠	3.0	30	3.0	30
硬脂酸镁	1.0	10	1.0	10
总计	**100**	**1000**	**100**	**1000**

[0614] *含有325mg对乙酰氨基酚

[0615] 实施例78:抗多片口服滥用性的体外分析

[0616] 根据实施例76和实施例77A和实施例77B制备的剂型通过在300mL 0.1N HCl中搅拌选定的片数来评价抗体外多片口服滥用性。利用USP设备II在50rpm和37℃下进行溶出。一到十二个片剂同时添加到容器中,定期取出等份并通过HPLC分析重酒石酸氢可酮(图11)和APAP(图13)。结果对时间作图,并呈现在图12和图13中。

[0617] 实施例79:5%包衣羟考酮颗粒

[0618] 制备颗粒并随后包衣。这些包衣粒子然后与其他组分掺合并压制成片剂。

[0619] 表116:颗粒配制物

[0620]

组分	%w/w
羟丙甲纤维素K100M	54
山嵛酸甘油酯	23
乙基纤维素(10cP)	13
盐酸羟考酮	10
总计	100

[0621] 表117:包衣颗粒配制物

[0622]

组分	%w/w
10%盐酸羟考酮颗粒	50
Eudragit E-100	33
硬脂酸镁	17
总计	100

[0623] 颗粒在高剪切造粒机中制造,在其中盐酸羟考酮、羟丙甲纤维素、一部分乙基纤维素和山嵛酸甘油酯干混合3分钟。然后,缓慢添加乙基纤维素10cP的水醇溶液,同时将造粒机叶片和切刀速度保持在为颗粒形成和生长提供足够剪切的预选值。继续添加溶液,直至添加了全部量的乙基纤维素。所述颗粒然后使用减尺寸磨机(Granumill)湿磨,随后装入流化床中干燥。所述盐酸羟考酮颗粒然后在底喷式流化床包衣机中用Eudragit E-100共聚物和硬脂酸镁的25%醇悬液包衣。

[0624] 实施例80:羟考酮/对乙酰氨基酚片剂

[0625] 5%盐酸羟考酮包衣颗粒根据上文实施例79制备并与另一种活性剂、即扑热息痛(使用对乙酰氨基酚和明胶制造)和其他赋形剂例如卡波姆、交聚维酮、碳酸氢钠、甘露醇、微晶纤维素混合,并掺合大约270转。然后添加硬脂酸镁润滑所述掺合物并再掺合45转,然后压制成羟考酮/对乙酰氨基酚片剂。

[0626] 表118:片剂配制物

[0627]

组分	%w/w	mg/片
5%盐酸羟考酮包衣颗粒	20	200
扑热息痛	34.2	342*
甘露醇	3.8	38
卡波普	5.0	50
微晶纤维素	13.0	130
交聚维酮	20.0	200
碳酸氢钠	3.0	30
硬脂酸镁	1.0	10
总计	100	1000

[0628] *含有325mg对乙酰氨基酚

[0629] 实施例81:包衣羟考酮颗粒

[0630] 制备盐酸羟考酮颗粒并随后包衣。这些包衣粒子然后与其他组分掺合并压制成片剂。

[0631] 表119:颗粒配制物

[0632]

组分	%w/w
羟丙甲纤维素K100M	56
山嵛酸甘油酯	25
乙基纤维素(10cP)	14
盐酸羟考酮	5
总计	100

[0633] 表120:包衣颗粒配制物

[0634]

组分	%w/w
5%盐酸羟考酮颗粒	50
Eudragit E-100	33
硬脂酸镁	17
总计	100

[0635] 颗粒在高剪切造粒机中制造,在其中盐酸羟考酮、羟丙甲纤维素、一部分乙基纤维素和山嵛酸甘油酯干混合3分钟。然后,缓慢添加乙基纤维素10cP的水醇溶液,同时将造粒机叶片和切刀速度保持在为颗粒形成和生长提供足够剪切的预选值。继续添加溶液,直至

添加了全部量的乙基纤维素。所述颗粒然后使用减尺寸磨机(Granumill)湿磨,随后装入流化床中干燥。所述盐酸羟考酮颗粒然后在底喷式流化床包衣机中用Eudragit E-100共聚物和硬脂酸镁的25%醇悬液包衣。

[0636] 实施例82:羟考酮/对乙酰氨基酚片剂

[0637] 2.5%盐酸羟考酮包衣颗粒根据上文实施例81制备并与另一种活性剂、即扑热息痛(使用对乙酰氨基酚和明胶制造)和其他赋形剂例如卡波姆、交聚维酮、碳酸氢钠、甘露醇、微晶纤维素混合,并掺合大约270转。然后添加硬脂酸镁润滑所述掺合物并再掺合45转,然后压制成羟考酮/对乙酰氨基酚片剂。

[0638] 表121:片剂配制物

[0639]

组分	%w/w	mg/片
2.5%盐酸羟考酮包衣颗粒	20	200
扑热息痛	34.2	342
甘露醇	3.8	38
卡波普	5.0	50
微晶纤维素	13.0	130
交聚维酮	20.0	200
碳酸氢钠	3.0	30
硬脂酸镁	1.0	10
总计	100	1000

[0640] *含有325mg对乙酰氨基酚

[0641] 实施例83:包衣羟考酮颗粒

[0642] 制备盐酸羟考酮颗粒并随后包衣。这些包衣粒子然后与其他组分掺合并压制成片剂。

[0643] 表122:颗粒配制物

[0644]

组分	%w/w
羟丙甲纤维素K100M	54.5
山嵛酸甘油酯	24
乙基纤维素(10cP)	14
盐酸羟考酮	7.5
总计	100

[0645] 表123:包衣颗粒配制物

[0646]

组分	%w/w
7.5%盐酸羟考酮颗粒	50
Eudragit E-100	33
硬脂酸镁	17
总计	100

[0647] 颗粒在高剪切造粒机中制造，在其中盐酸羟考酮、羟丙甲纤维素、一部分乙基纤维素和山嵛酸甘油酯干混合3分钟。然后，缓慢添加乙基纤维素10cP的水醇溶液，同时将造粒机叶片和切刀速度保持在为颗粒形成和生长提供足够剪切的预选值。继续添加溶液，直至添加了全部量的乙基纤维素。所述颗粒然后使用减尺寸磨机(Granumill)湿磨，随后装入流化床中干燥。所述盐酸羟考酮颗粒然后在底喷式流化床包衣机中用Eudragit E-100共聚物和硬脂酸镁的25％醇悬液包衣。

[0648] 实施例84：羟考酮/对乙酰氨基酚片剂

[0649] 3.75％盐酸羟考酮包衣颗粒根据上文实施例83制备并与另一种活性剂、即扑热息痛(使用对乙酰氨基酚和明胶制造)和其他赋形剂例如卡波姆、交聚维酮、碳酸氢钠、甘露醇、微晶纤维素混合，并掺合大约270转。然后添加硬脂酸镁润滑所述掺合物并再掺合45转，然后压制成羟考酮/对乙酰氨基酚片剂。

[0650] 表124：片剂配制物

[0651]

组分	％w/w	mg/片
3.75％盐酸羟考酮包衣颗粒	20	200
扑热息痛	34.2	342*
甘露醇	3.8	38
卡波普	5.0	50
微晶纤维素	13.0	130
交聚维酮	20.0	200
碳酸氢钠	3.0	30
硬脂酸镁	1.0	10
总计	100	1000

[0652] *含有325mg对乙酰氨基酚

[0653] 实施例85：包衣盐酸羟考酮颗粒

[0654] 制备盐酸羟考酮颗粒并随后包衣。这些包衣粒子然后与其他组分掺合并压制成片剂。

[0655] 表125：颗粒配制物

[0656]

组分	％w/w
羟丙甲纤维素K100M	54
山嵛酸甘油酯	23
乙基纤维素(10cP)	13
盐酸羟考酮	10
总计	100

[0657] 表126：包衣颗粒配制物

[0658]

组分	％w/w
10％盐酸羟考酮颗粒	40

Eudragit E-100	40
硬脂酸镁	20
总计	100

[0659] 颗粒在高剪切造粒机中制造，在其中盐酸羟考酮、羟丙甲纤维素、一部分乙基纤维素和山嵛酸甘油酯干混合3分钟。然后，缓慢添加乙基纤维素10cP的水醇溶液，同时将造粒机叶片和切刀速度保持在为颗粒形成和生长提供足够剪切的预选值。继续添加溶液，直至添加了全部量的乙基纤维素。所述颗粒然后使用减尺寸磨机(Granumill)湿磨，随后装入流化床中干燥。所述盐酸羟考酮颗粒然后在底喷式流化床包衣机中用Eudragit E-100共聚物和硬脂酸镁的25％醇悬液包衣。

[0660] 实施例86:羟考酮/对乙酰氨基酚片剂

[0661] 4％盐酸羟考酮包衣颗粒根据上文实施例83制备并与另一种活性剂、即扑热息痛(使用对乙酰氨基酚和明胶制造)和其他赋形剂例如卡波姆、交聚维酮、碳酸氢钠、甘露醇、微晶纤维素混合，并掺合大约270转。然后添加硬脂酸镁润滑所述掺合物并再掺合45转，然后压制成羟考酮/对乙酰氨基酚片剂。

[0662] 表127:片剂配制物

[0663]

组分	%w/w	mg/片
4％盐酸羟考酮包衣颗粒	18.8	188
扑热息痛	34.2	342*
甘露醇	5	50
卡波普	5.0	50
微晶纤维素	13.0	130
交聚维酮	20.0	200
碳酸氢钠	3.0	30
硬脂酸镁	1.0	10
总计	100	1000

[0664] *含有325mg对乙酰氨基酚

[0665] 实施例87:包衣羟考酮颗粒

[0666] 制备羟考酮颗粒并随后包衣。这些包衣粒子然后与其他组分掺合并压制成片剂。

[0667] 表128:颗粒配制物

[0668]

组分	%w/w
羟丙甲纤维素K100M	54
山嵛酸甘油酯	23
乙基纤维素(10cP)	13
盐酸羟考酮	10
总计	100

[0669] 表129:包衣颗粒配制物

[0670]

组分	%w/w
10%盐酸羟考酮颗粒	30
Eudragit E-100	47
硬脂酸镁	23
总计	100

[0671] 颗粒在高剪切造粒机中制造，在其中盐酸羟考酮、羟丙甲纤维素、一部分乙基纤维素和山嵛酸甘油酯干混合3分钟。然后，缓慢添加乙基纤维素10cP的水醇溶液，同时将造粒机叶片和切刀速度保持在为颗粒形成和生长提供足够剪切的预选值。继续添加溶液，直至添加了全部量的乙基纤维素。所述颗粒然后使用减尺寸磨机(Granumill)湿磨，随后装入流化床中干燥。所述盐酸羟考酮颗粒然后在底喷式流化床包衣机中用Eudragit E-100共聚物和硬脂酸镁的25%醇悬液包衣。

[0672] 实施例88:羟考酮/对乙酰氨基酚片剂

[0673] 盐酸羟考酮包衣颗粒(3%)根据上文实施例87制备并与另一种活性剂、即扑热息痛(使用对乙酰氨基酚和明胶制造)和其他赋形剂例如卡波姆、交聚维酮、碳酸氢钠、甘露醇、微晶纤维素混合，并掺合大约270转。然后添加硬脂酸镁润滑所述掺合物并再掺合45转，然后压制成羟考酮/对乙酰氨基酚片剂。

[0674] 表130:片剂配制物

[0675]

组分	%w/w	mg/片
3%盐酸羟考酮包衣颗粒	16.7	167
扑热息痛	34.2	342*
甘露醇	7.1	71
卡波普	5.0	50
微晶纤维素	13.0	130
交聚维酮	20.0	200
碳酸氢钠	3.0	30
硬脂酸镁	1.0	10
总计	100	1000

[0676] *含有325mg对乙酰氨基酚

[0677] 实施例89:包衣羟考酮颗粒

[0678] 制备羟考酮颗粒并随后包衣。这些包衣粒子然后与其他组分掺合并压制成片剂。

[0679] 表131:颗粒配制物

[0680]

组分	%w/w
羟丙甲纤维素K100M	56
山嵛酸甘油酯	25
乙基纤维素(10cP)	14
盐酸羟考酮	5

总计	100

[0681] 表132:包衣颗粒配制物

[0682]

组分	%w/w
5%盐酸羟考酮颗粒	70
Eudragit E-100	20
硬脂酸镁	10
总计	100

[0683] 颗粒在高剪切造粒机中制造,在其中盐酸羟考酮、羟丙甲纤维素、一部分乙基纤维素和山嵛酸甘油酯干混合3分钟。然后,缓慢添加乙基纤维素10cP的水醇溶液,同时将造粒机叶片和切刀速度保持在为颗粒形成和生长提供足够剪切的预选值。继续添加溶液,直至添加了全部量的乙基纤维素。所述颗粒然后使用减尺寸磨机(Granumill)湿磨,随后装入流化床中干燥。所述盐酸羟考酮颗粒然后在底喷式流化床包衣机中用Eudragit E-100共聚物和硬脂酸镁的25%醇悬液包衣。

[0684] 实施例90:羟考酮/对乙酰氨基酚片剂

[0685] 3.5%盐酸羟考酮包衣颗粒根据上文实施例89制备并与另一种活性剂、即扑热息痛(使用对乙酰氨基酚和明胶制造)和其他赋形剂例如卡波姆、交聚维酮、碳酸氢钠、甘露醇、微晶纤维素混合,并掺合大约270转。然后添加硬脂酸镁润滑所述掺合物并再掺合45转,然后压制成羟考酮/对乙酰氨基酚片剂。

[0686] 表133:片剂配制物

[0687]

组分	%w/w	mg/片
3.5%盐酸羟考酮包衣颗粒	21.4	214
扑热息痛	34.2	342*
甘露醇	2.4	24
卡波普	5.0	50
微晶纤维素	13.0	130
交聚维酮	20.0	200
碳酸氢钠	3.0	30
硬脂酸镁	1.0	10
总计	100	1000

[0688] *含有325mg对乙酰氨基酚

[0689] 实施例91:包衣羟考酮颗粒

[0690] 制备盐酸羟考酮颗粒并随后包衣。这些包衣粒子然后与其他组分掺合并压制成片剂。

[0691] 表134:颗粒配制物

[0692]

组分	%w/w
羟丙甲纤维素K100M	54.5

山嵛酸甘油酯	24
乙基纤维素(10cP)	14
盐酸羟考酮	7.5
总计	100

[0693] 表135:包衣颗粒配制物

[0694]

组分	%w/w
7.5%盐酸羟考酮颗粒	70
Eudragit E-100	20
硬脂酸镁	10
总计	100

[0695] 颗粒在高剪切造粒机中制造,在其中盐酸羟考酮、羟丙甲纤维素、一部分乙基纤维素和山嵛酸甘油酯干混合3分钟。然后,缓慢添加乙基纤维素10cP的水醇溶液,同时将造粒机叶片和切刀速度保持在为颗粒形成和生长提供足够剪切的预选值。继续添加溶液,直至添加了全部量的乙基纤维素。所述颗粒然后使用减尺寸磨机(Granumill)湿磨,随后装入流化床中干燥。所述盐酸羟考酮颗粒然后在底喷式流化床包衣机中用Eudragit E-100共聚物和硬脂酸镁的25%醇悬液包衣。

[0696] 实施例92:羟考酮/对乙酰氨基酚片剂

[0697] 5.25%盐酸羟考酮包衣颗粒根据上文实施例91制备并与另一种活性剂、即扑热息痛(使用对乙酰氨基酚和明胶制造)和其他赋形剂例如卡波姆、交聚维酮、碳酸氢钠、甘露醇、微晶纤维素混合,并掺合大约270转。然后添加硬脂酸镁润滑所述掺合物并再掺合45转,然后压制成羟考酮/对乙酰氨基酚片剂。

[0698] 表136:片剂配制物

[0699]

组分	%w/w	mg/片
5.25%盐酸羟考酮包衣颗粒	19.05	190.5
扑热息痛	34.2	342*
甘露醇	4.75	47.5
卡波普	5.0	50
微晶纤维素	13.0	130
交聚维酮	20.0	200
碳酸氢钠	3.0	30
硬脂酸镁	1.0	10
总计	100	1000

[0700] *含有325mg对乙酰氨基酚

[0701] 实施例93:氢可酮/对乙酰氨基酚片剂

[0702] 重酒石酸氢可酮包衣颗粒根据实施例75制备并与另一种活性剂、即扑热息痛(使用对乙酰氨基酚和明胶制造)和其他赋形剂例如卡波姆、交聚维酮、碳酸氢钠、甘露醇、微晶纤维素混合(掺合大约270转)。然后添加硬脂酸镁润滑所述掺合物并再掺合45转,然后压制

成氢可酮/对乙酰氨基酚片剂。

[0703] 表137:片剂配制物

[0704]

组分	%w/w	mg/片
5%重酒石酸氢可酮包衣颗粒	20.0	200
扑热息痛	34.21	342.1*
甘露醇	3.73	37.3
卡波普	5.0	50
微晶纤维素	13.0	130
交聚维酮	20.0	200
碳酸氢钠	3.0	30
硬脂酸镁	1.0	10
氧化铁红	0.06	0.6
总计	100	1000

[0705] *含有325mg对乙酰氨基酚

[0706] 实施例94:抗多片口服滥用性的体外分析-压碎的和完整的片剂

[0707] 根据实施例93制备的剂型(压碎的和完整的)通过在300mL或900mL 0.1N HCl中进行溶出试验来评价抗体外多片口服滥用性。所述溶出利用USP设备II在50rpm和37℃下进行。十二个片剂(压碎的和完整的)同时或相继添加到容器中,定期取出等份并通过HPLC分析重酒石酸氢可酮和APAP。片剂的压碎使用研钵和研杵(撞击十二次)进行。结果对时间作图,并呈现在图14和图15中。

[0708] 实施例95:艾氯胺酮HCl片剂

[0709] 按照实施例31制备的包衣颗粒随后与根据实施例71制备的包衣聚合物颗粒和其他组分(卡波姆,交聚维酮,碳酸氢钠,甘露醇,微晶纤维素)混合并掺合270转。添加硬脂酸镁润滑所述掺合物并将所生成的混合物再掺合45转,然后压制成片剂。

[0710] 表138:片剂配制物

[0711]

组分	mg/片	mg/片	mg/片	mg/片
28.7%盐酸艾氯胺酮包衣颗粒	87.1	87.1	348.4	348.4
包衣聚合物颗粒	50	31	50	31
甘露醇	37	37	37	37
卡波普	50	50	50	50
微晶纤维素	130	130	130	130
交聚维酮	200	200	200	200
碳酸氢钠	30	30	30	30
硬脂酸镁	6	6	9	8.5
总计	590.1	571.1	854.4	834.9

[0712] 实施例96:艾氯胺酮HCl片剂

[0713] 按照实施例31制备的包衣颗粒随后与根据实施例71制备的包衣聚合物颗粒和其

他组分(卡波姆,交聚维酮,碳酸氢钠,甘露醇,微晶纤维素)混合并掺合270转。添加硬脂酸镁润滑所述掺合物并将所生成的混合物再掺合45转,然后压制成片剂。

[0714] 表139:片剂配制物

[0715]

组分	mg/片	mg/片	mg/片	mg/片
28.7%盐酸艾氯胺酮包衣颗粒	87.1	87.1	348.4	348.4
聚合物颗粒	50	27	50	27
甘露醇	37	37	37	37
卡波普	50	50	50	50
微晶纤维素	130	130	130	130
交聚维酮	200	200	200	200
碳酸氢钠	30	30	30	30
硬脂酸镁	6	6	9	8.5
总计	590.1	567.1	854.4	830.9

[0716] 实施例97:艾氯胺酮HCl片剂

[0717] 按照实施例27制备的包衣颗粒随后与根据实施例71制备的包衣聚合物颗粒和其他组分(卡波姆,交聚维酮,碳酸氢钠,甘露醇,微晶纤维素)混合并掺合270转。添加硬脂酸镁润滑所述掺合物并将所生成的混合物再掺合45转,然后压制成片剂。

[0718] 表140:盐酸艾氯胺酮片剂组成

[0719]

组分mg/片	1mg	2mg
2.5%盐酸艾氯胺酮包衣颗粒	40	80
包衣聚合物颗粒	160	120
甘露醇	70	70
卡波普	50	50
微晶纤维素	94	95
交聚维酮	200	200
碳酸氢钠	30	30
硬脂酸镁	11	18
总片剂重量	655	663

[0720] 实施例98:艾氯胺酮HCl片剂

[0721] 按照实施例27制备的包衣颗粒随后与根据实施例74制备的聚合物颗粒和其他组分(卡波姆,交聚维酮,碳酸氢钠,甘露醇,微晶纤维素)混合并掺合270转。添加硬脂酸镁润滑所述掺合物并将所生成的混合物再掺合45转,然后压制成片剂。

[0722] 表141:盐酸艾氯胺酮片剂组成

[0723]

组分mg/片	1mg	2mg
2.5%盐酸艾氯胺酮包衣颗粒	40	80
聚合物颗粒	80	60

甘露醇	70	70
卡波普	50	50
微晶纤维素	94	95
交聚维酮	150	150
碳酸氢钠	30	30
硬脂酸镁	11	18
总片剂重量	525	553

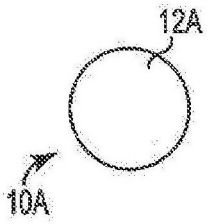


图1A

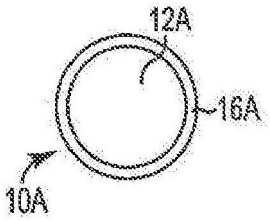


图1B

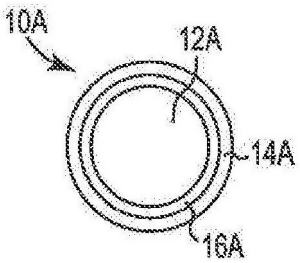


图1C

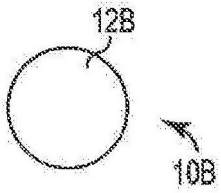


图2A

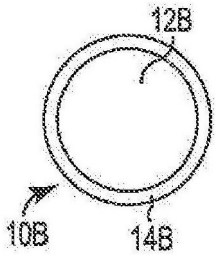


图2B

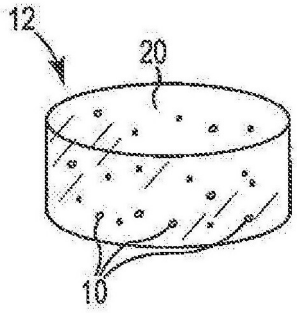


图3

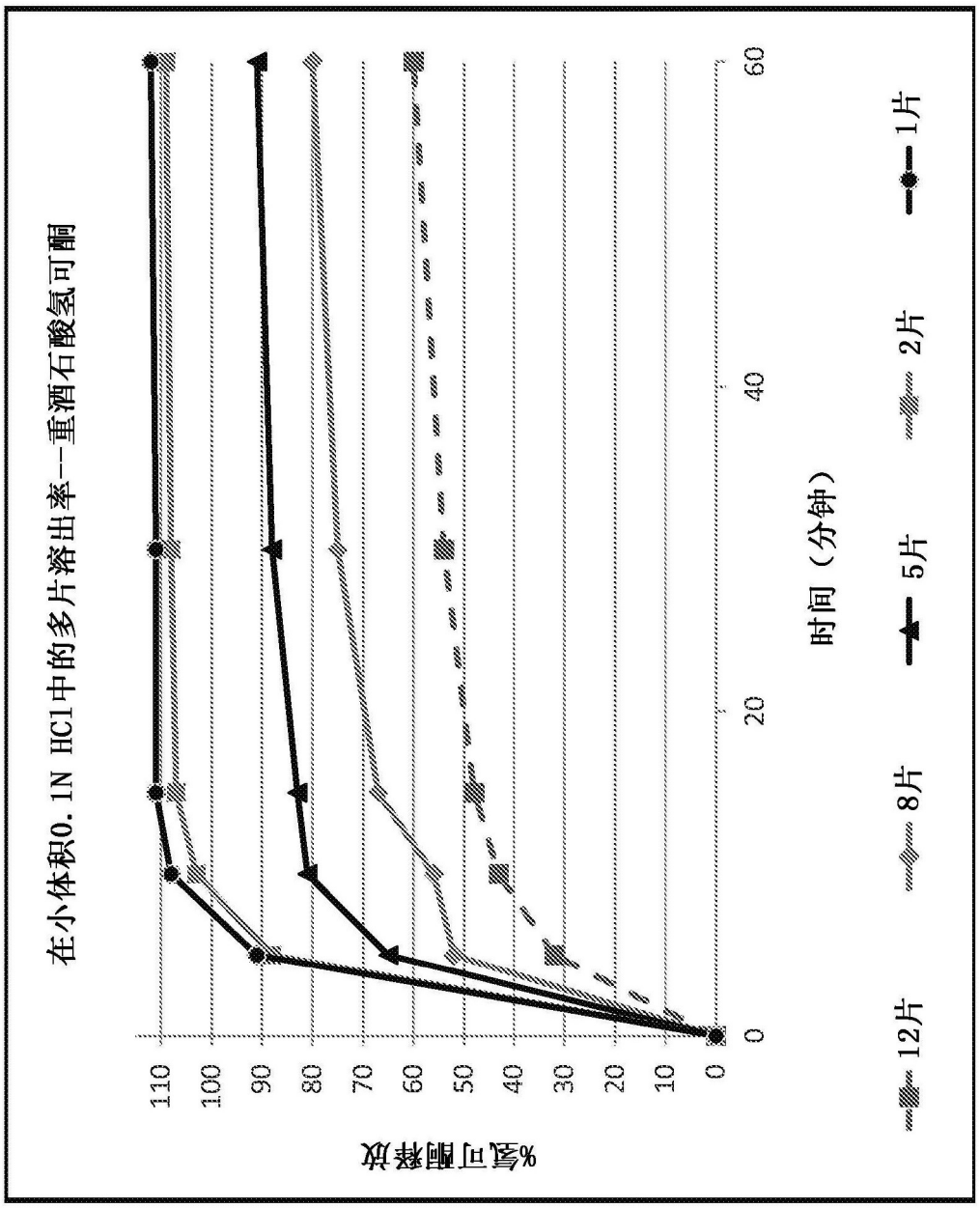

在小体积0.1N HCl中的多片溶出率—重酒石酸氢可酮
%氢可酮释放
时间（分钟）
0
10
20
30
40
50
60
70
80
90
100
110
0
20
40
60
12片
8片
5片
2片
1片

图4

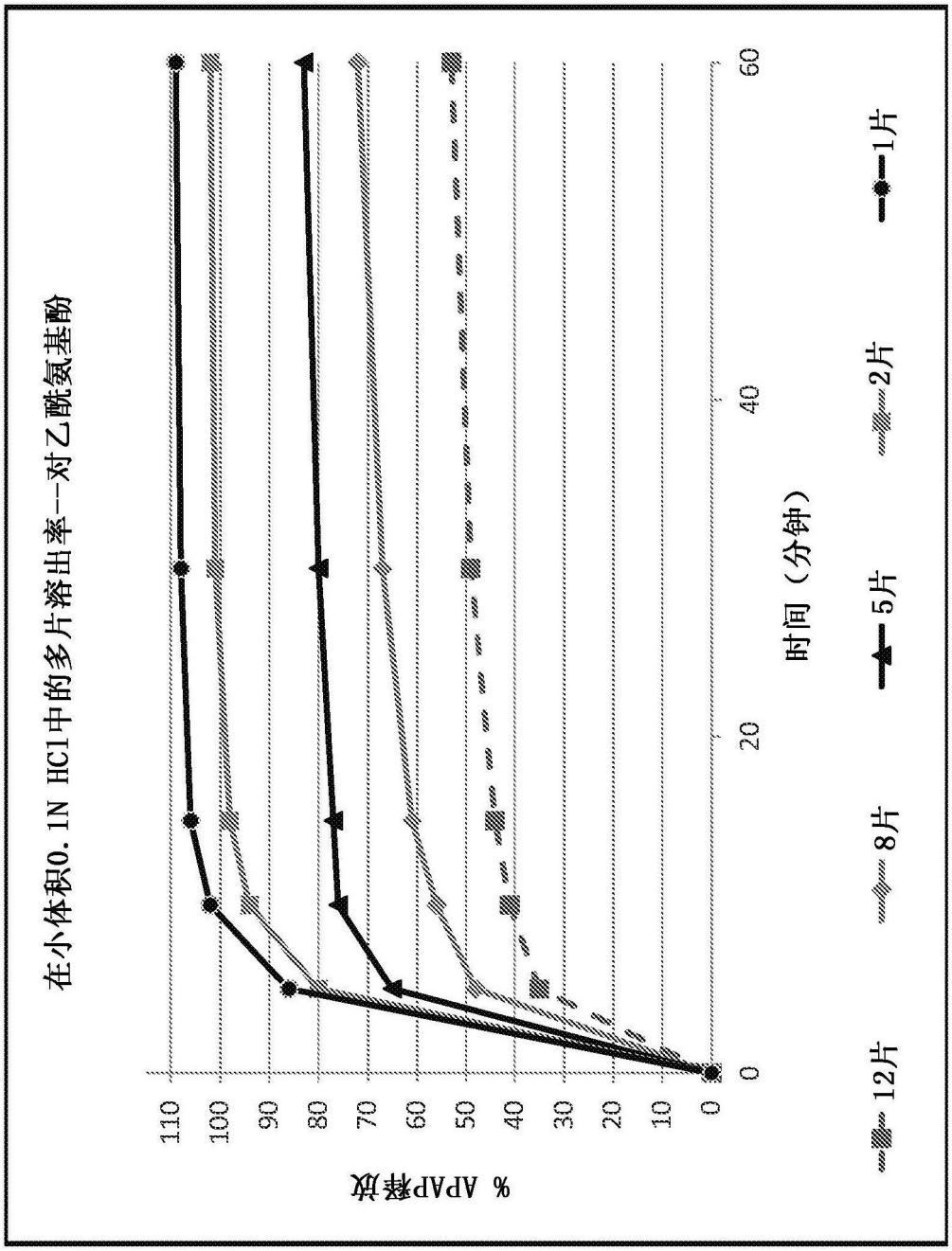

在小体积0.1N HCl中的多片溶出率—对乙酰氨基酚
% APAP释放
时间（分钟）
0
10
20
30
40
50
60
70
80
90
100
110
0
20
40
60
1片
2片
5片
8片
12片

图5

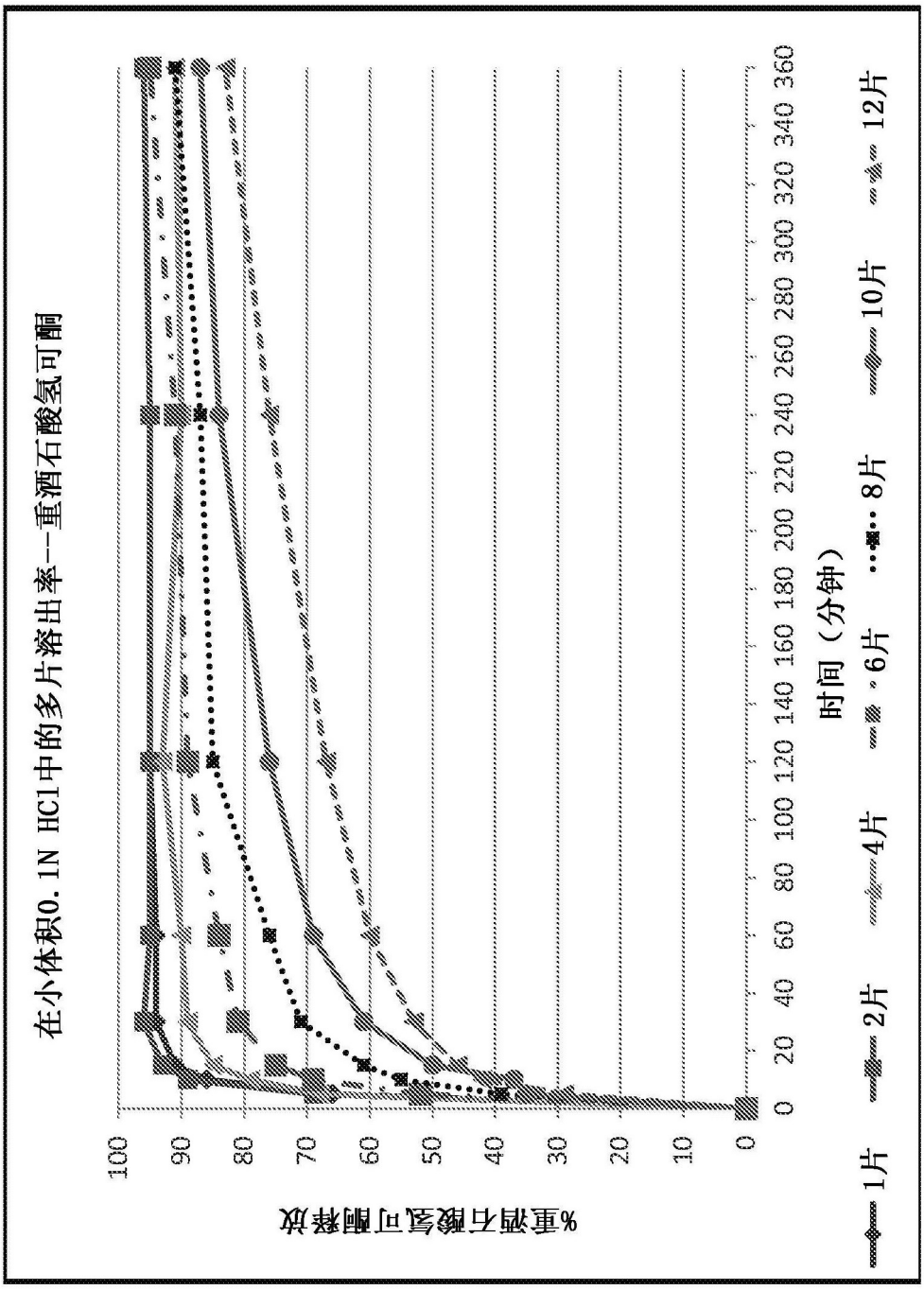

在小体积0.1N HCl中的多片溶出率--重酒石酸氢可酮
%重酒石酸氢可酮释放
100
90
80
70
60
50
40
30
20
10
0
0 20 40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 360
时间（分钟）
1片
2片
4片
6片
8片
10片
12片

图6

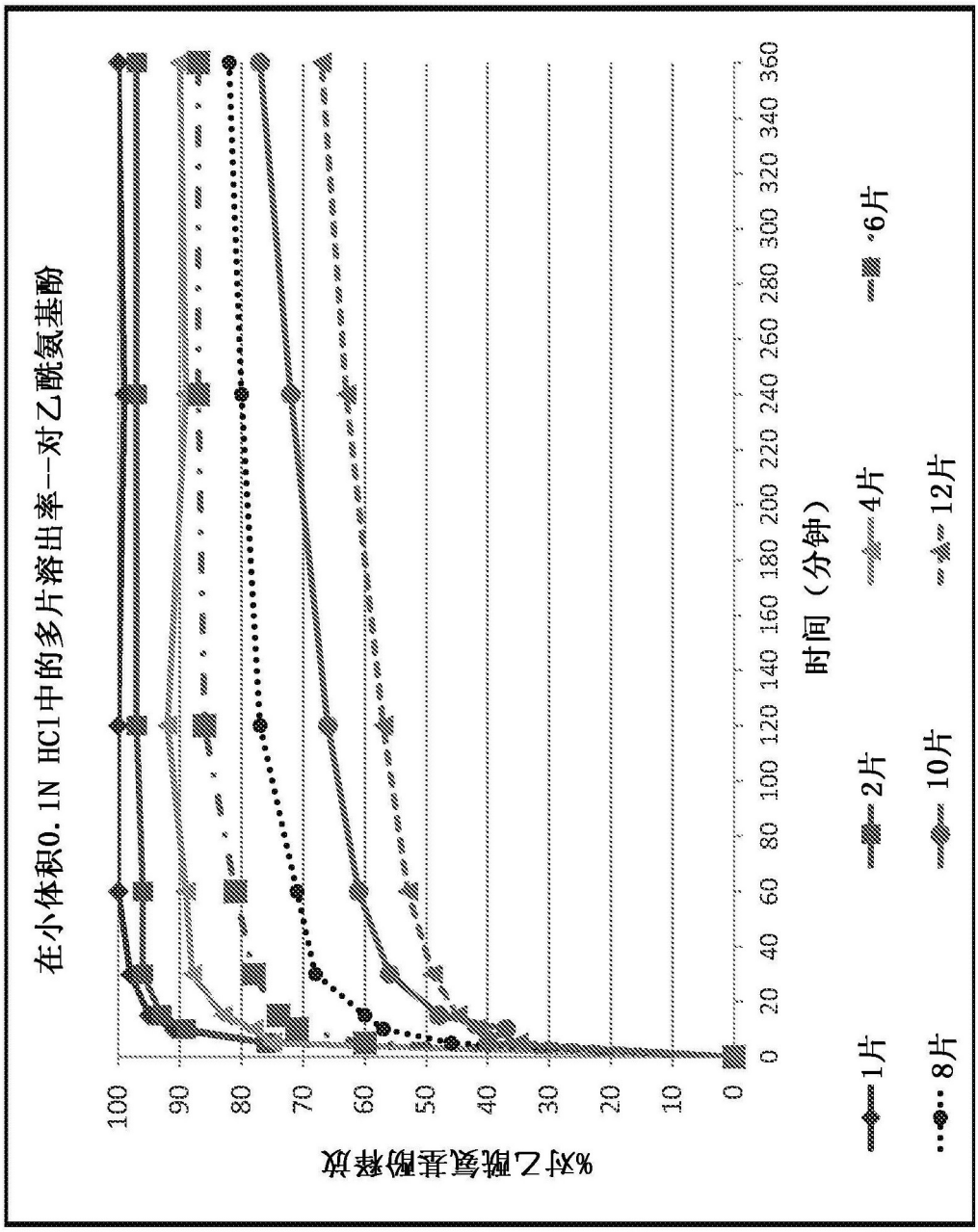

在小体积0.1N HCl中的多片溶出率—对乙酰氨基酚
%对乙酰氨基酚释放
100
90
80
70
60
50
40
30
20
10
0
0 20 40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 360
时间（分钟）
1片
2片
4片
6片
8片
10片
12片

图7

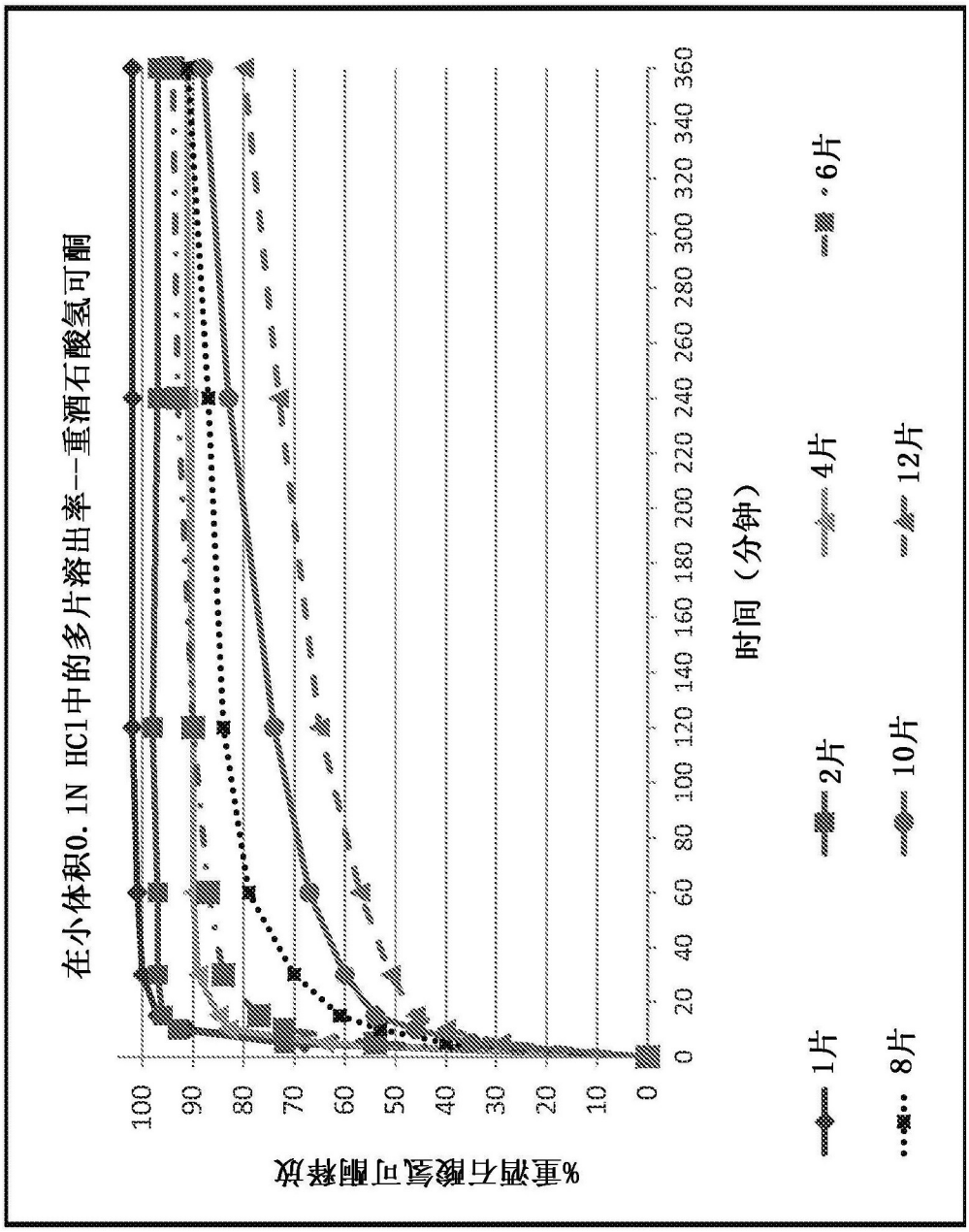

在小体积0.1N HCl中的多片溶出率--重酒石酸氢可酮
%重酒石酸氢可酮释放
100
90
80
70
60
50
40
30
20
10
0
0 20 40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 360
时间（分钟）
1片
2片
4片
6片
8片
10片
12片

图8

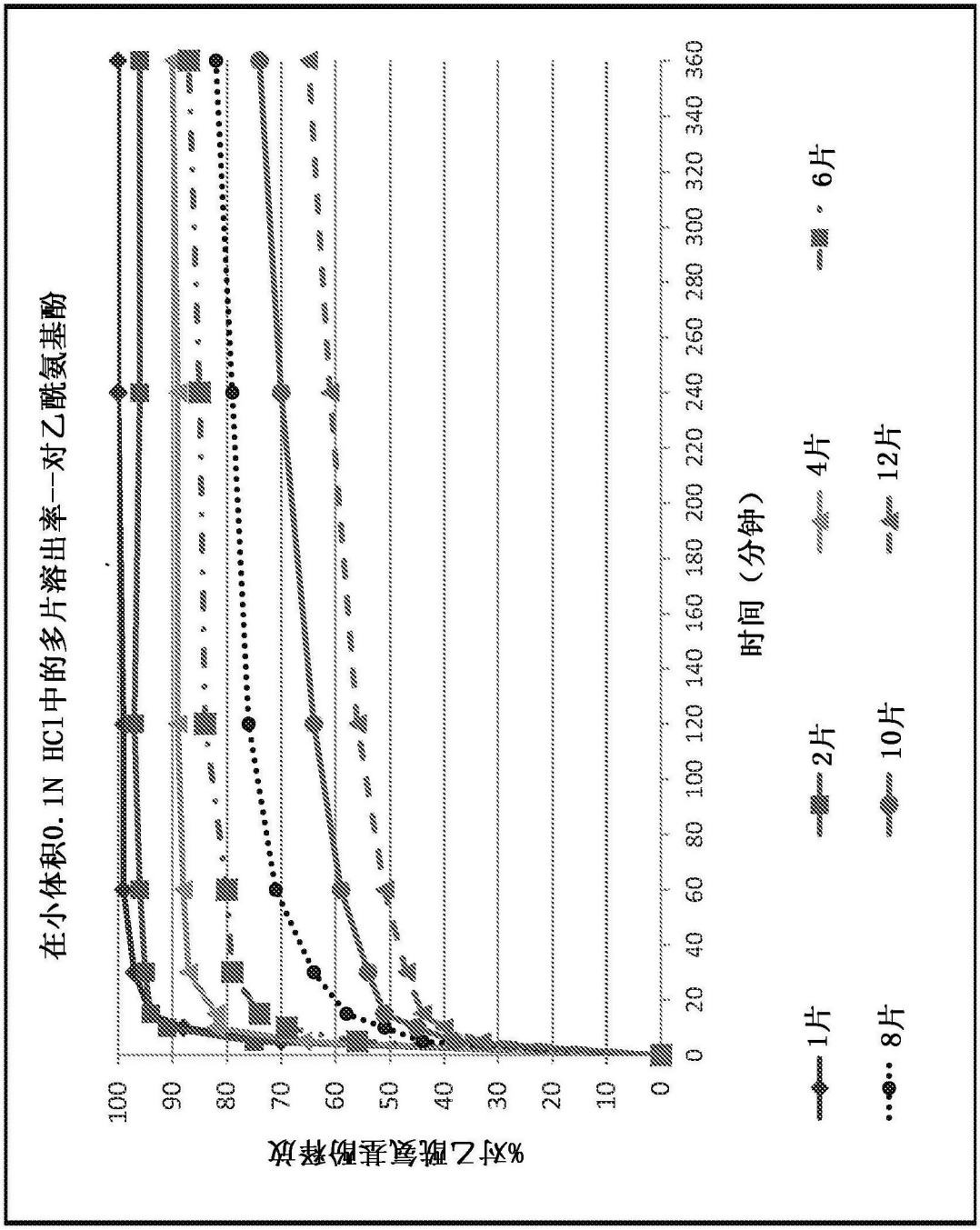

在小体积0.1N HCl中的多片溶出率—对乙酰氨基酚
%对乙酰氨基酚释放
100
90
80
70
60
50
40
30
20
10
0
0 20 40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 360
时间（分钟）
1片
2片
4片
6片
8片
10片
12片

图9

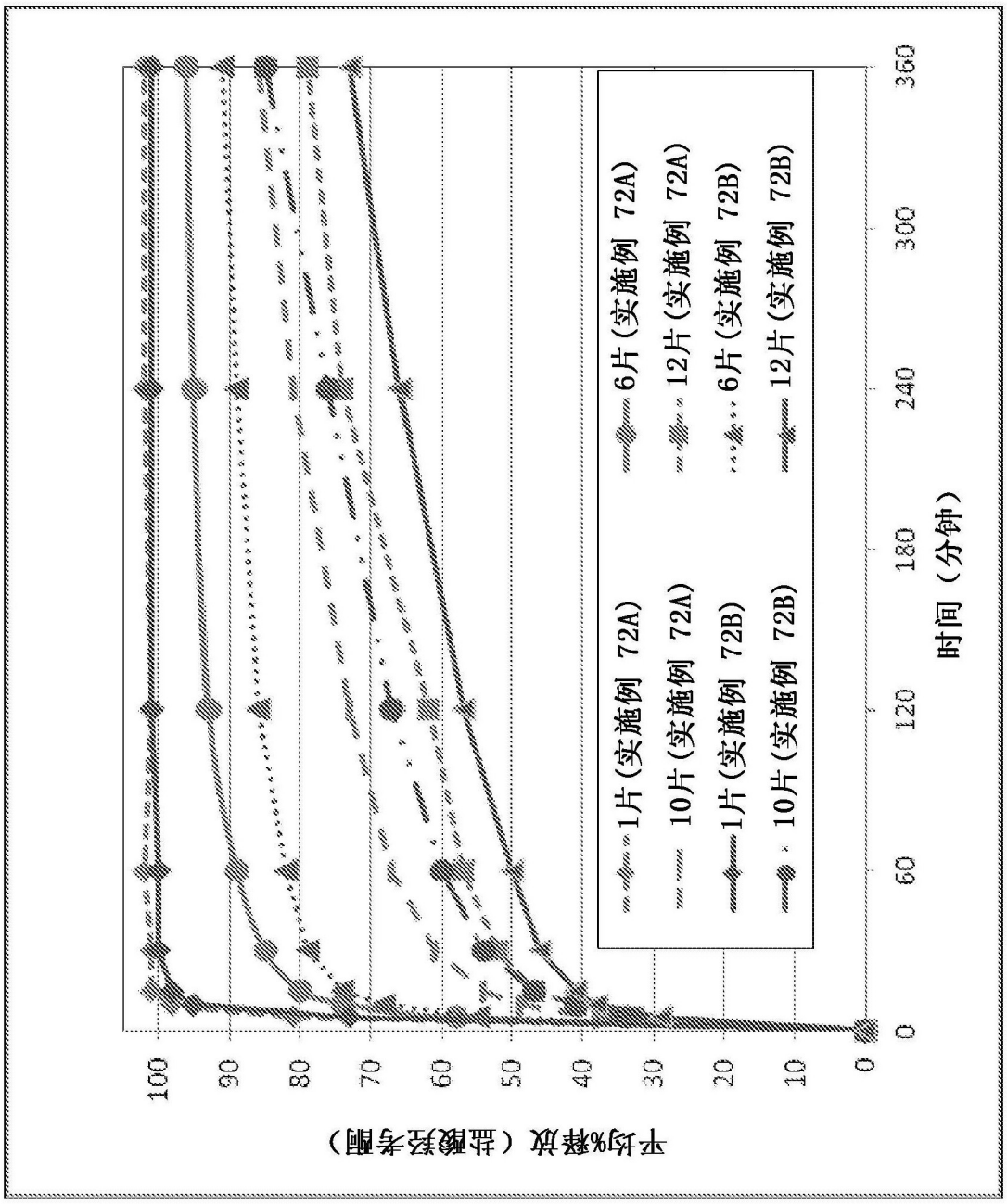

平均%释放（盐酸羟考酮）
100
90
80
70
60
50
40
30
20
10
0
0
60
120
180
240
300
360
时间（分钟）
1片（实施例 72A）
10片（实施例 72A）
1片（实施例 72B）
10片（实施例 72B）
6片（实施例 72A）
12片（实施例 72A）
6片（实施例 72B）
12片（实施例 72B）

图10

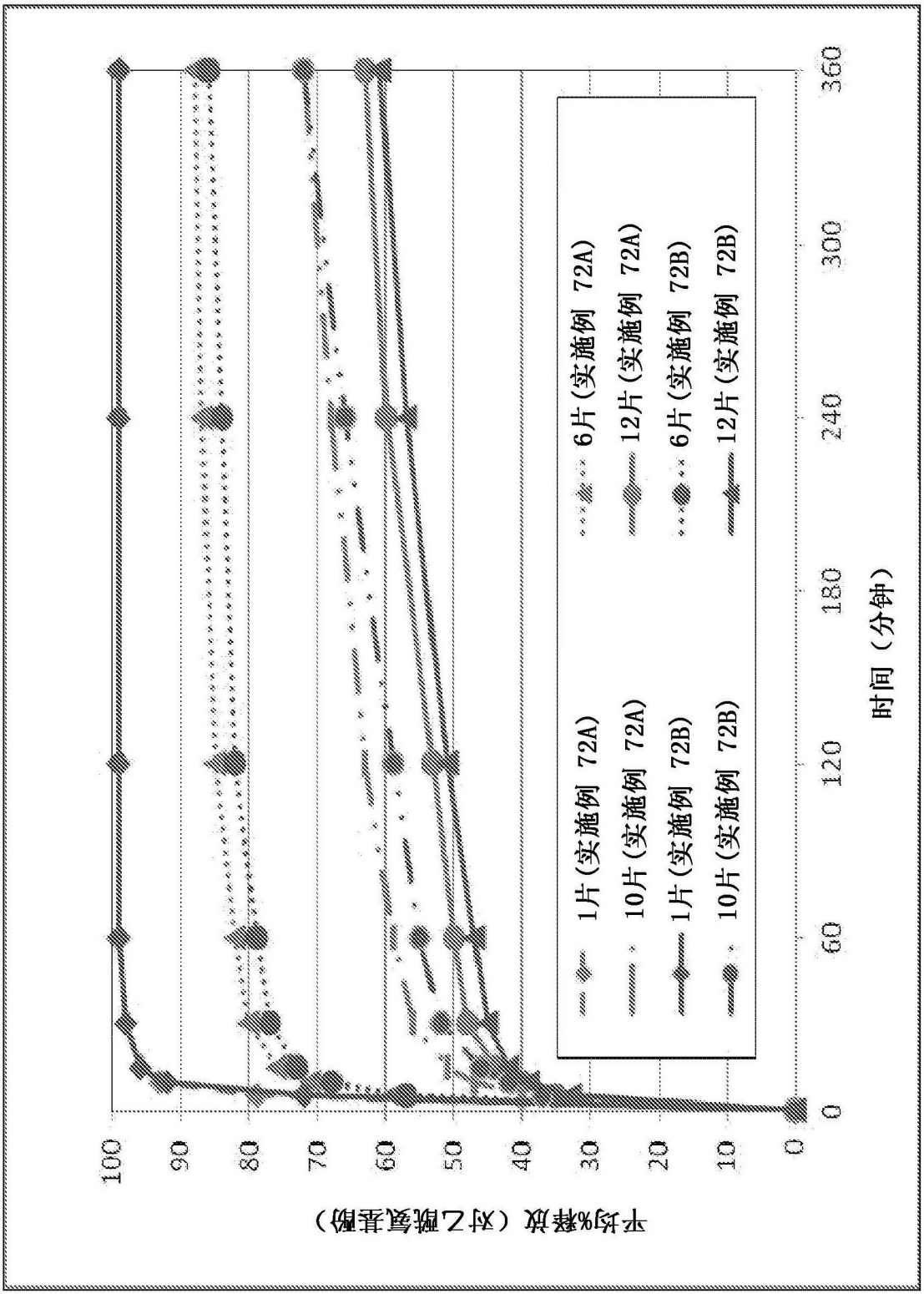

平均%释放（对乙酰氨基酚）
100
90
80
70
60
50
40
30
20
10
0
0
60
120
180
240
300
360
时间（分钟）
1片（实施例 72A）
10片（实施例 72A）
1片（实施例 72B）
10片（实施例 72B）
6片（实施例 72A）
12片（实施例 72A）
6片（实施例 72B）
12片（实施例 72B）

图11

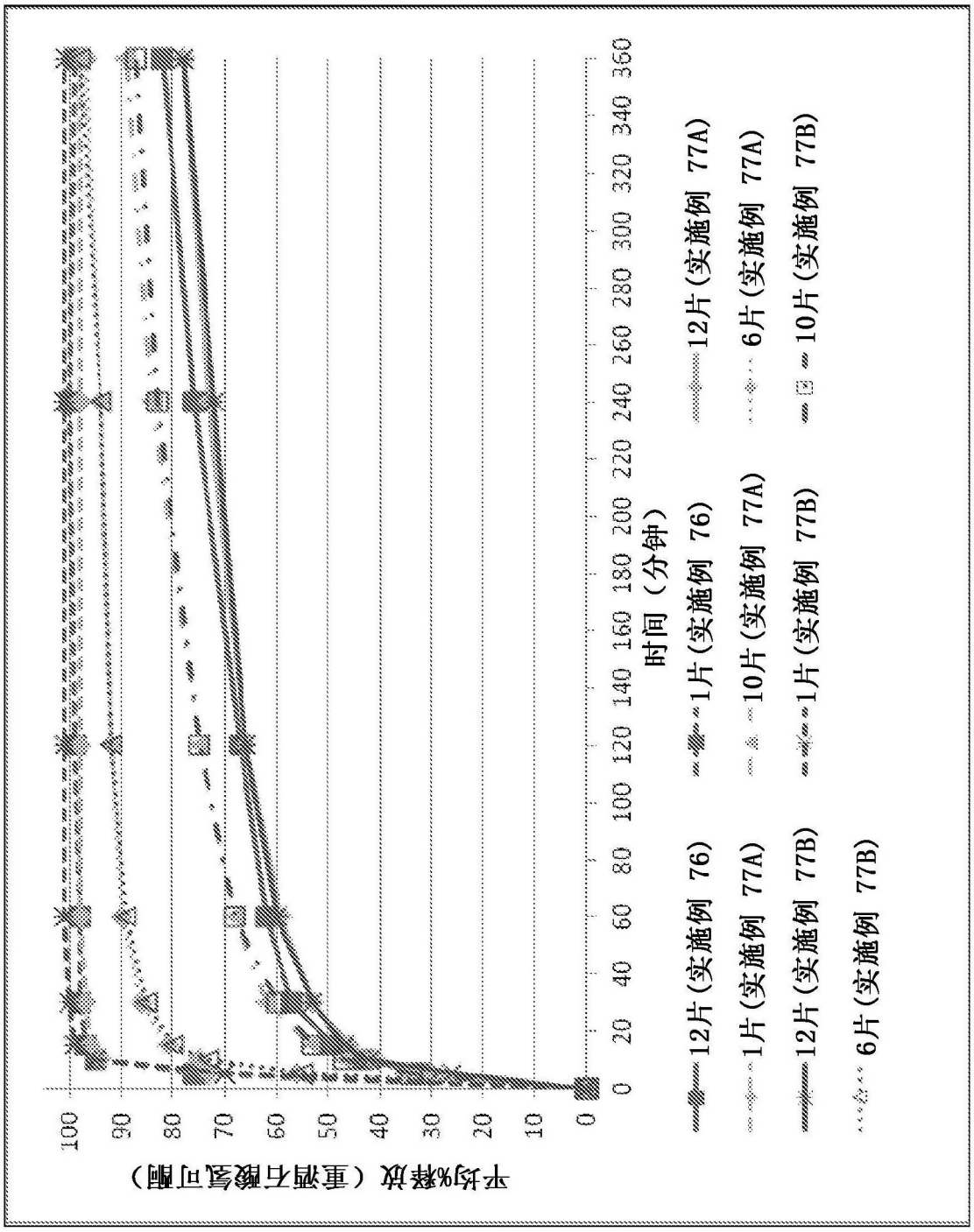

平均%释放（重酒石酸氢可酮）
100
90
80
70
60
50
40
30
20
10
0
0 20 40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 360
时间（分钟）
12片（实施例 76）
1片（实施例 76）
12片（实施例 77A）
1片（实施例 77A）
10片（实施例 77A）
6片（实施例 77A）
12片（实施例 77B）
1片（实施例 77B）
10片（实施例 77B）
6片（实施例 77B）

图12

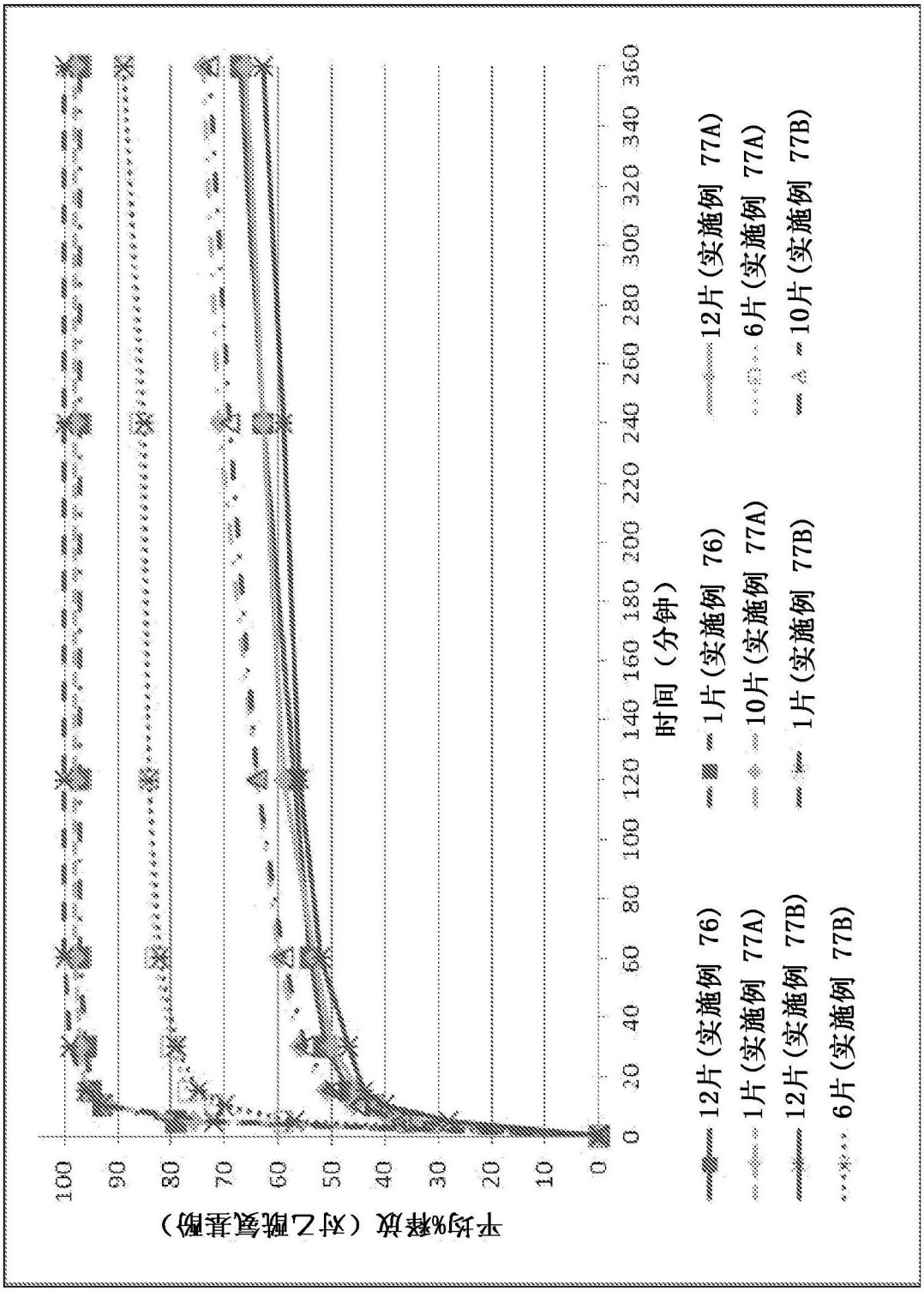

平均%释放（对乙酰氨基酚）
100
90
80
70
60
50
40
30
20
10
0
0 20 40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 360
时间（分钟）
12片（实施例 76）
1片（实施例 76）
12片（实施例 77A）
1片（实施例 77A）
12片（实施例 77B）
10片（实施例 77A）
6片（实施例 77A）
1片（实施例 77B）
6片（实施例 77B）
10片（实施例 77B）

图13

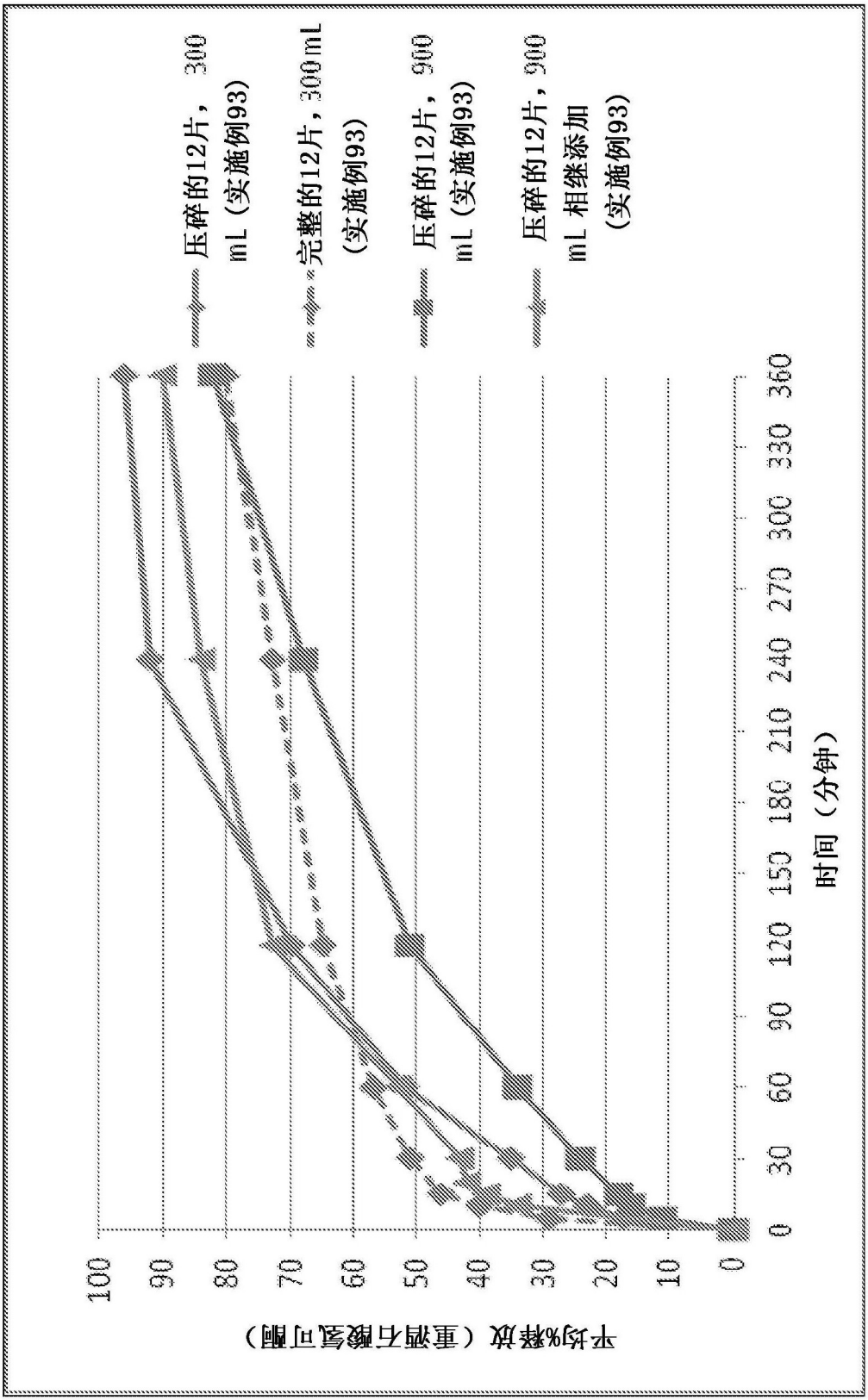

压碎的12片，300 mL（实施例93）
完整的12片，300 mL（实施例93）
压碎的12片，900 mL（实施例93）
压碎的12片，900 mL 相继添加（实施例93）
平均%释放（重酒石酸氢可酮）
时间（分钟）
0
10
20
30
40
50
60
70
80
90
100
0
30
60
90
120
150
180
210
240
270
300
330
360

图14

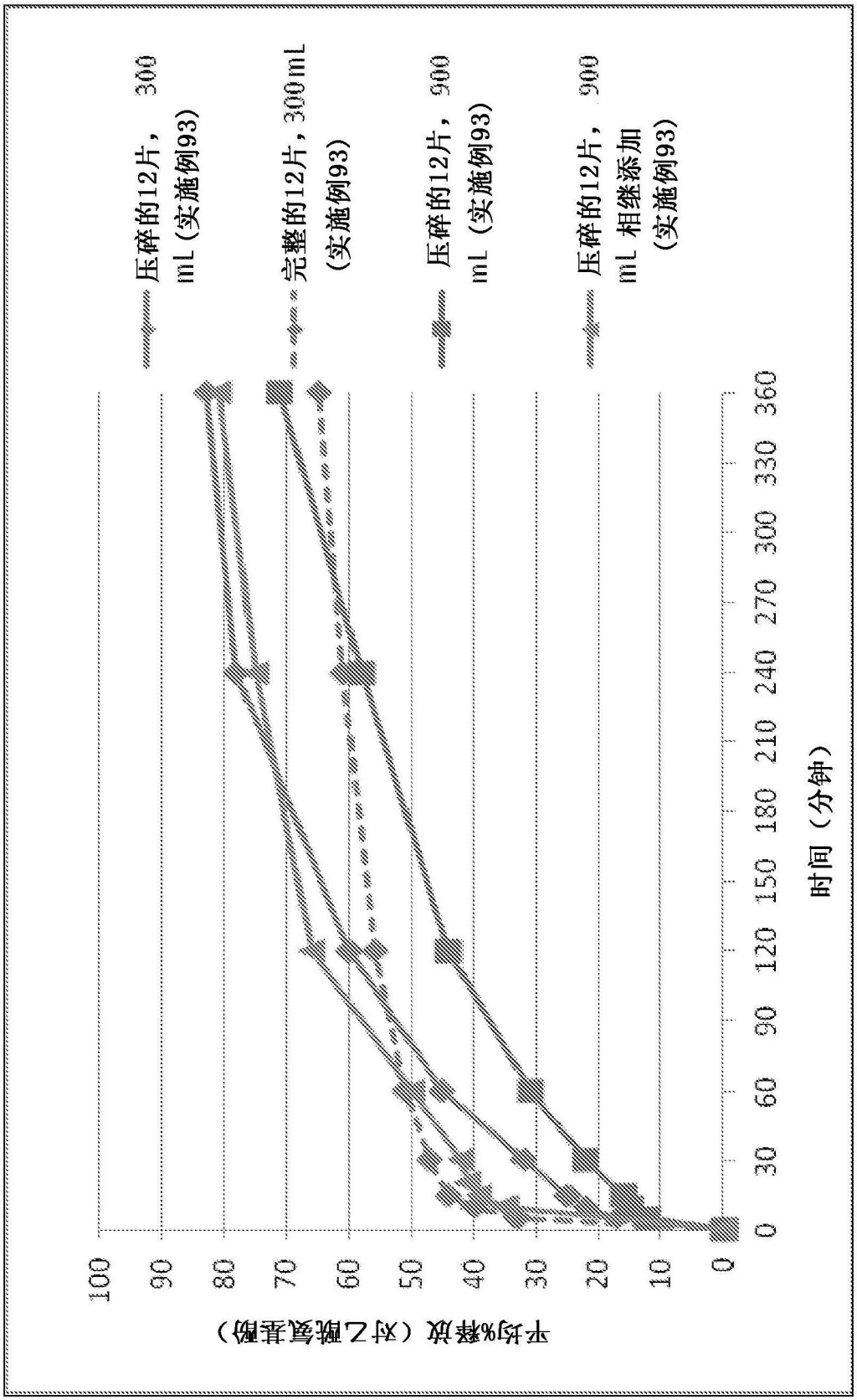

压碎的12片，300 ml（实施例93）
完整的12片，300 ml（实施例93）
压碎的12片，900 ml（实施例93）
压碎的12片，900 ml 相继添加（实施例93）
平均%释放（对乙酰氨基酚）
时间（分钟）
0
10
20
30
40
50
60
70
80
90
100
0
30
60
90
120
150
180
210
240
270
300
330
360

图15