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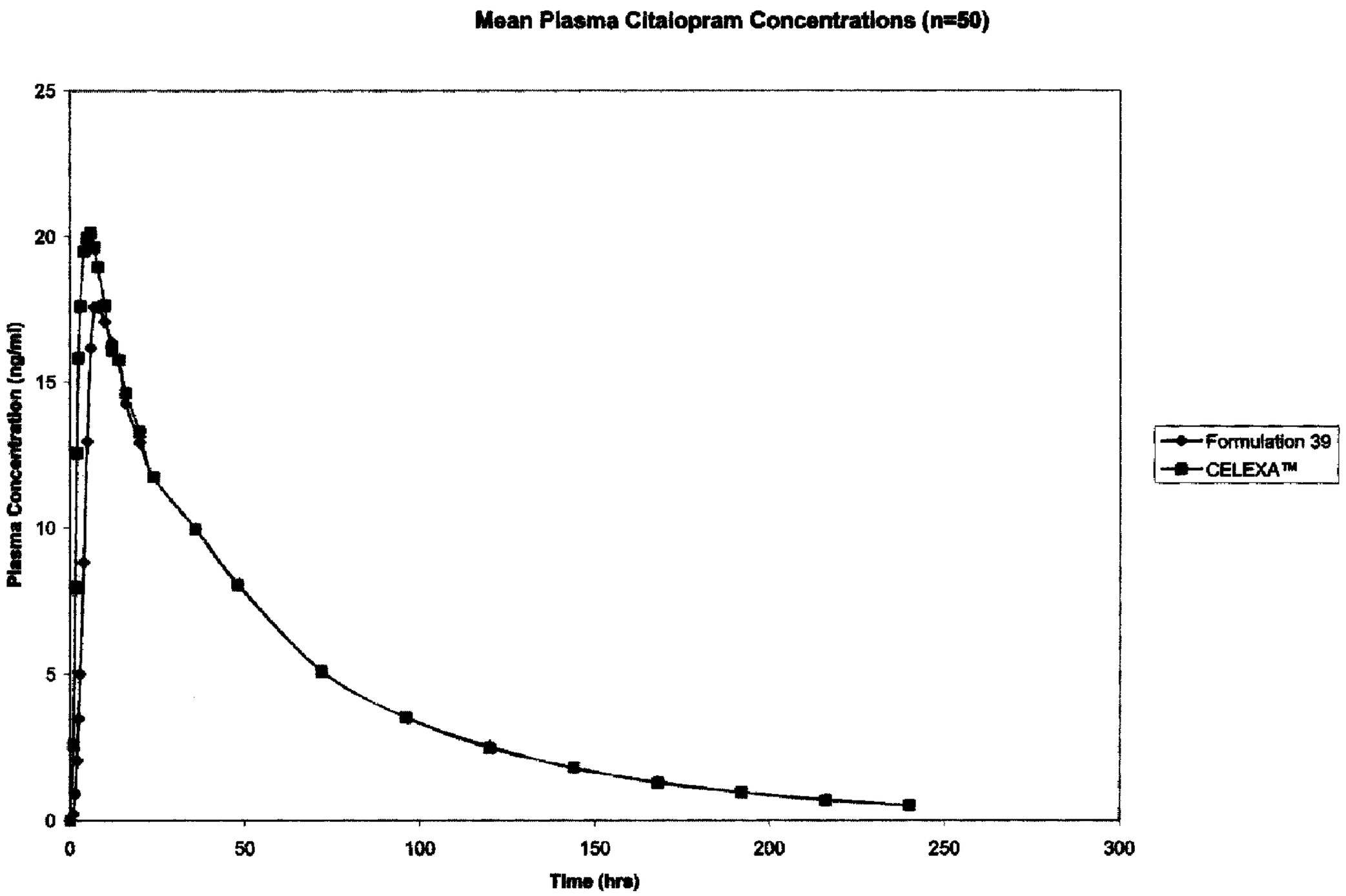
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(54) Titre : PREPARATIONS A LIBERATION MODIFIEE CONTENANT DES INHIBITEURS SELECTIFS DE LA RECAPTURE DE LA SEROTONINE

(54) Title: MODIFIED RELEASE FORMULATIONS OF SELECTIVE SEROTONIN RE-UPTAKE INHIBITORS



(57) Abrégé/Abstract:
A modified release pharmaceutical composition for oral administration, suitable for once daily dosing, comprising a form of at least one selective serotonin re-uptake inhibitor (SSRI) selected from the group consisting of SSRIs, racemic mixtures thereof,

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(57) Abrégé(suite)/Abstract(continued):
enantiomers thereof, pharmaceutically acceptable salts thereof, and combinations thereof in combination with at least one pharmaceutically-acceptable excipient wherein the pharmaceutical composition exhibits the following in vitro dissolution profile when measured using the USP Paddle Method at 100 rpm in 900 mL of a buffered medium having a pH between about 5.5 and about 7.5 at 37.0± 0.5°C: (a) between about 0% and about 50% (by wt) of the form of the at least one SSRI is released after about 1 hour; (b) between about 0% and about 75% (by wt) of the form of the at least one SSRI is released after about 2 hours; (c) between about 3% and about 95% (by wt) of the form of the at least one SSRI is released after about 4 hours; (d) between about 10% and about 100% (by wt) of the form of the at least one SSRI is released after about 8 hours; (e) between about 20% and about 100% (by wt) of the form of the at least one SSRI is released after about 12 hours; (f) between about 30% and about 100% (by wt) of the form of the at least one SSRI is released after about 16 hours; (g) between about 50% and about 100% (by wt) of the form of the at least one SSRI is released after about 24 hours; and (h) in excess of about 80% (by wt) of the form of the at least one SSRI is released after about 36 hours.

ABSTRACT

A modified release pharmaceutical composition for oral administration, suitable for once daily dosing, comprising a form of at least one selective serotonin re-uptake inhibitor (SSRI) selected from the group consisting of SSRIs, racemic mixtures thereof, enantiomers thereof, pharmaceutically acceptable salts thereof, and combinations thereof in combination with at least one pharmaceutically-acceptable excipient wherein the pharmaceutical composition exhibits the following *in vitro* dissolution profile when measured using the USP Paddle Method at 100 rpm in 900 mL of a buffered medium having a pH between about 5.5 and about 7.5 at 37.0± 0.5°C:

(a) between about 0% and about 50% (by wt) of the form of the at least one SSRI is released after about 1 hour;

(b) between about 0% and about 75% (by wt) of the form of the at least one SSRI is released after about 2 hours;

(c) between about 3% and about 95% (by wt) of the form of the at least one SSRI is released after about 4 hours;

(d) between about 10% and about 100% (by wt) of the form of the at least one SSRI is released after about 8 hours;

(e) between about 20% and about 100% (by wt) of the form of the at least one SSRI is released after about 12 hours;

(f) between about 30% and about 100% (by wt) of the form of the at least one SSRI is released after about 16 hours;

(g) between about 50% and about 100% (by wt) of the form of the at least one SSRI is released after about 24 hours; and

(h) in excess of about 80% (by wt) of the form of the at least one SSRI is released after about 36 hours.

TITLE OF INVENTION

MODIFIED RELEASE FORMULATIONS OF SELECTIVE SEROTONIN RE-UPTAKE INHIBITORS

FIELD OF INVENTION

The present invention relates to modified release pharmaceutical compositions for oral administration and more particularly to modified release pharmaceutical compositions of a form of at least one selective serotonin re-uptake inhibitor selected from the group consisting of a selective serotonin reuptake inhibitor, racemic mixtures thereof, enantiomers thereof, pharmaceutically-acceptable salts thereof and combinations thereof.

BACKGROUND OF THE INVENTION

Clinical depression (unipolar depression) is a disturbance of mood that is distinguishable from the usual mood fluctuations of everyday life. There are several approaches to the treatment of depression depending on the severity of the condition and the risks to the patient. Antidepressants are classified into different groups either structurally or depending on which central neurotransmitters they act upon. The older tricyclic and related cyclic antidepressants and the monoamine oxidase inhibitors (MAOIs) have now been joined by the highly selective neuronal serotonin (5HT) reuptake inhibitors (SSRIs) which provide important improvements in adverse effect profile and safety. The mechanism of action of the SSRIs as anti-depressants is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from their inhibition of central nervous system (CNS) neuronal reuptake of serotonin. There are currently seven SSRIs available on the market today, namely Fluoxetine HCl, Fluvoxamine maleate, Paroxetine HCl, Sertraline HCl, Venlafaxine HCl, Citalopram HBr and Escitalopram oxalate.

Fluoxetine HCl, which was first described in United States Patent No. 4,314,081, is designated as (±)-N-methyl-3-phenyl-3-[(α,α,α-trifluoro-*p*-tolyl)oxy)propylamine hydrochloride. Conventional immediate release preparations of Fluoxetine HCl are commercially available in the United States from Eli Lilly and Company under the proprietary name PROZAC® as 10 mg, 20 mg or 40 mg PULVULES®, 10 mg tablets and a 20 mg/5 ml oral solution. Each PULVULE® contains starch, gelatin, silicone, titanium dioxide, iron oxide and other inactive ingredients. The 10 mg and 20 mg PULVULES® also contain FD&C Blue No. 1, and the 40 mg PULVULE® also contains FD&C Blue No. 1 and FD&C Yellow No. 6. Each tablet contains microcrystalline cellulose, magnesium stearate, crospovidone, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, yellow iron oxide, FD&C Blue No. 1 aluminum lake, and polysorbate 80. The oral solution contains alcohol 0.23%, benzoic acid, flavoring agent, glycerin, purified water, and sucrose. The 56th Edition (2002) of the Physician's Desk Reference (PDR), page 1238, states that following a single oral 40 mg dose, peak plasma concentrations of Fluoxetine from 15 to 55 mg/ml are observed after 6 to 8 hours. The PULVULE®, tablet and oral solution dosage forms of Fluoxetine are bioequivalent. Food does not appear to affect the systemic bioavailability of Fluoxetine, although it may delay its absorption by one to two hours, which is probably not clinically significant. Thus, Fluoxetine may be administered with or without food. Such conventional immediate release preparations, however, do not provide a modified release of Fluoxetine HCl.

A delayed release preparation of Fluoxetine HCl is also commercially available in the United States from Ely Lilly and Company under the proprietary name PROZAC® WEEKLY™ as 90 mg delayed release capsules, containing enteric coated pellets of Fluoxetine HCl. The capsules also contain FD&C Yellow #10, FD&C Blue #2, gelatin, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose acetate

succinate, sodium lauryl sulfate, sucrose, sugar spheres, talc, titanium dioxide, triethylcitrate and other inactive ingredients. PROZAC® WEEKLY™ capsules contain enteric coated pellets that resist dissolution until reaching a segment of the gastrointestinal tract where the pH exceeds 5.5. The enteric coating delays the onset of absorption of Fluoxetine one to two hours relative to the immediate release formulations. The PROZAC® WEEKLY™ delayed release capsule dosage form of Fluoxetine is bioequivalent to the PULVULE®, tablet and oral solution dosage forms of Fluoxetine. The PROZAC® WEEKLY™ delayed release capsule formulation is disclosed in United States Patent No. 5,910,319.

Fluvoxamine maleate, which was first described in United States Patent No. 4,085,225, is an SSRI belonging to a new chemical series, the 2-aminoethyl oxime ethers of aralkylketones and is designated as 5-methoxy-4'-(trifluoromethyl)valerophenone-(E)-O-(2-aminoethyl)oxime maleate. A conventional immediate release preparation of Fluvoxamine maleate is commercially available in the United States from Solvay Pharmaceuticals, Inc. under the proprietary name LUVOX® as 25 mg, 50 mg and 100 mg tablets for oral administration. Each tablet contains the following inactive ingredients: carnauba wax, hydroxypropyl methylcellulose, mannitol, polyethylene glycol, polysorbate 80, pregelatinized starch (potato), silicon dioxide, sodium stearyl fumarate, starch (corn), and titanium dioxide. The 50 mg and 100 mg tablets also contain synthetic iron oxides. The 56th Edition of the PDR, page 3257, states that the absolute bioavailability of Fluvoxamine maleate is 53%. Oral bioavailability is not significantly affected by food. In a dose proportionality study involving Fluvoxamine maleate at 100, 200 and 300 mg/day for 10 consecutive days in 30 normal volunteers, steady state was achieved after about a week of dosing. Maximum plasma concentrations at steady state occurred within 3-8 hours of dosing and reached concentrations averaging 88, 283

and 546 ng/ml, respectively. Such a conventional immediate release preparation, however, does not provide a modified release of Fluvoxamine maleate.

Paroxetine HCl, which was first described in United States Patent Nos. 3,912,743, 4,007,196 and 4,721,723, is an orally administered antidepressant in the hemihydrate form with a chemical structure unrelated to other SSRIs or to tricyclic, tetracyclic or other available antidepressant agents. It is the hydrochloride salt of a phenylpiperidine compound identified chemically as (-)-*trans*-4*R*-(4′-fluorophenyl)-3*S*[(3′,4′-methylenedioxyphenoxy)methyl] piperidine hydrochloride (hemihydrate). Conventional immediate release preparations of Paroxetine HCl are commercially available in the United States from GlaxoSmithKline under the proprietary name PAXIL® as 10 mg, 20 mg, 30 mg and 40 mg film coated tablets and as a 10 mg/5 ml suspension for oral administration. Each film coated tablet contains the inactive ingredients dibasic calcium phosphate dihydrate, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycols, polysorbate 80, sodium starch glycolate, titanium dioxide and one or more of the following: D&C Red No. 30, D&C Yellow No. 10, FD&C Blue No. 2 and FD&C Yellow No. 6. The oral suspension contains the inactive ingredients polacrilin potassium, microcrystalline cellulose, propylene glycol, glycerin, sorbitol, methyl paraben, propyl paraben, sodium citrate dihydrate, citric acid anhydrate, sodium saccharin, flavourings, FD&C Yellow No. 6 and simethicone emulsion, USP. The 56th Edition of the PDR, page 1609 states that in a study in which normal male subjects received 30 mg tablets daily for 30 days, steady state Paroxetine concentrations were achieved by approximately 10 days for most subjects. At steady state, mean values of C_{max}, T_{max}, C_{min} and $t_{½}$ were 61.7 ng/ml (CV 45%), 5.2 hours (CV 10%), 30.7 ng/ml (CV 67%) and 21.0 hours (CV 32%), respectively. The steady state C_{max} and C_{min} values were about 6 and 14 times what would be predicted from single

dose studies. Steady state drug exposure based on AUC_{0-24} was about 8 times greater than would have been predicted from single dose data in these subjects. The effects of food on the bioavailability of Paroxetine were studied and subjects were administered a single dose with and without food. AUC was only slightly increased (6%) when drug was administered with food, but the C_{max} 29% greater, while the time to reach peak plasma concentration decreased from 6.4 hours post dosing to 4.9 hours. Such conventional immediate release preparations, however, do not provide a modified release of Paroxetine HCl.

A controlled release preparation of Paroxetine HCl is also commercially available in the United States from GlaxoSmithKline under the proprietary name PAXIL® CR™ as 12.5 mg, 25 mg and 37.5 mg enteric film coated, controlled release tablets. One layer of the tablet consists of a degradable barrier layer and the other contains the active material in a hydrophilic matrix. Inactive ingredients consist of hydroxypropyl methylcellulose, polyvinyl pyrolidone, lactose monohydrate, magnesium stearate, colloidal silicon dioxide, glyceryl behenate, methacrylic acid copolymer type C, sodium lauryl sulfate, polysorbate 80, talc, triethyl citrate, and one or more of the following colorants: yellow ferric oxide, red ferric oxide, D&C Red #30, D&C Yellow #6, D&C Yellow #10, FD&C Blue #2. PAXIL® CR™ tablets contain a degradable polymer matrix (GEOMATRIX™, a trademark of Jago Pharma Muttenz, Switzerland) designed to control the dissolution rate of Paroxetine over a period of approximately 4 to 5 hours. In addition to controlling the rate of drug release *in vivo*, an enteric coat delays the start of drug release until PAXIL® CR™ tablets have left the stomach. In a study in which normal male and female subjects (n=23) received single oral doses of PAXIL® CR™ at 4 dosage strengths (12.5 mg, 25 mg, 37.5 mg and 50 mg), Paroxetine mean C_{max} and AUC_{0-inf} values at these doses were 2.0, 5.5, 9.0 and 12.5 mg/ml and 121, 261, 338 and

540 ng.hr./ml, respectively. T_{max} was observed typically between 6 and 10 hours post dose, reflecting a reduction in absorption rate compared with immediate release formulations. The mean elimination half life of Paroxetine was 15 to 20 hours throughout this range of single PAXIL® CR™ doses. The bioavailability of 25 mg PAXIL® CR™ is not affected by food. During repeated administration of PAXIL® CR™ (25 mg once daily), steady state was reached within two weeks (i.e., comparable to immediate release formulations). In a repeat dose study in which normal male and female subjects (n=23) received PAXIL® CR™ (25 mg daily), mean steady state C_{max}, C_{min} and AUC_{0-24} values were 30 ng/ml, 20 ng/ml and 550 ng.hr./ml, respectively. According to the United States Food and Drug Administration (FDA) Approved Drug Products Publication (the "FDA Orange Book"), United States Patent No. 4,522,123 relates to the PAXIL® CR™ controlled release tablet formulation.

Sertraline HCl, which was first described in United States Patent No. 4,536,518, is chemically unrelated to other SSRIs, tricyclic, tetracyclic, or other available antidepressant agents. Sertraline HCl has the following chemical name: (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine hydrochloride.

Conventional immediate release preparations of Sertraline HCl are commercially available in the United States from Pfizer Inc. under the trade name ZOLOFT® as 25 mg, 50 mg and 100 mg scored tablets and as 20 mg/ml oral concentrate. The tablets contain the following inactive ingredients: dibasic calcium phosphate dihydrate, D&C Yellow #10 aluminum lake (in 25mg tablet), FD&C Blue #1 aluminum lake (in 25 mg tablet), FD&C Red #40 aluminum lake (in 25 mg tablet), FD&C Blue #2 aluminum lake (in 50 mg tablet), hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, synthetic yellow iron oxide (in 100 mg tablet), and titanium dioxide. The

solution contains the following inactive ingredients: glycerine, alcohol (12%), menthol and butylated hydroxytoluene (BHT). The 56th Edition of the PDR, on page 2751, states that in man, following oral once daily dosing over the range of 50-200 mg for 14 days, mean peak plasma concentrations (C_{max}) of Sertraline occurred between 4.5-8.4 hours post dosing. The affects of food on the bioavailability of the Sertraline tablet and oral concentrate were studied in subjects administered a single dose with and without food. For the tablet, area under the plasma concentration time curve (AUC) was slightly increased when drug was administered with food but the C_{max} was 25% greater, while the time to reach peak plasma concentration (T_{max}) decreased from 8 hours post dosing to 5.5 hours. For the oral concentrate, T_{max} was slightly prolonged from 5.9 hours to 7.0 hours with food. Such conventional immediate release preparations, however, do not provide a modified release of Sertraline HCl.

Venlafaxine HCl, which was first described in United States Patent No. 4,535,186, is chemically unrelated to tricyclic, tetracyclic, or other available antidepressant agents. It is designated as (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride or (±)-1-[α-[(dimethylamino)methyl]-p-methoxybenzyl]cyclohexanol hydrochloride. A conventional immediate release preparation of Venlafaxine HCl is commercially available in the United States from Wyeth-Ayerst under the proprietary name EFFEXOR® as 25 mg, 37.5 mg, 50 mg, 75 mg or 100 mg compressed tablets. Inactive ingredients consist of cellulose, iron oxides, lactose, magnesium stearate, and sodium starch glycolate. Such a conventional immediate release preparation does not provide a modified release of Venlafaxine HCl.

An extended release preparation of Venlafaxine HCl is also available from Wyeth-Ayerst under the proprietary name EFFEXOR® XR as 37.5 mg, 75 mg or 150 mg extended release capsules for once a day oral administration. Drug release is controlled

by diffusion through the coating membrane on the spheroids and is not pH dependent. Inactive ingredients consist of cellulose, ethylcellulose, gelatin, hydroxypropyl methylcellulose, iron oxide and titanium dioxide. The 37.5 mg capsule also contains D&C Red #28, D&C Yellow #10, and FD&C Blue #1. The 56th Edition of the PDR, page 3499, states that administration of EFFEXOR® XR (150 mg q24 hours) generally resulted in lower C_{max} (150 ng/ml) and later T_{max} (5.5 hours) than for immediate release Venlafaxine tablets (C_{max} for immediate release 75 mg q12 hours was 225 ng/ml; T_{max} was 2 hours). The FDA Orange Book states that United States Patent Nos. 6,274,171, 6,419,958 and 6,403,120 all relate to the EFFEXOR® XR extended release capsule formulation.

Citalopram HBr, which was first described in United States Patent No. 4,136,193, is a racemic bicyclic phthalane derivative designated as (RS)-1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-5-phthalancarbonitrile hydrobromide. Conventional immediate release preparations of Citalopram HBr are commercially available in the United States from Forest Laboratories, Inc. under the proprietary name CELEXA™ as 20 mg and 40 mg film coated tablets and as 2 mg/ml oral solution. The tablets contain the following inactive ingredients: copolyvidone, corn starch, cross-carmellose sodium, glycerin, lactose monohydrate, magnesium stearate, hydroxypropyl methylcellulose, microcrystalline cellulose, polyethylene glycol and titanium dioxide. Iron oxides are used as colouring agents in the 10 mg and 20 mg tablets. The oral solution contains the following inactive ingredients: sorbitol, purified water, propylene glycol methylparaben, natural peppermint flavour and propylparaben. The 56th Edition of the PDR, page 1365, states that following a single oral dose (40 mg tablet) of Citalopram, peak blood levels occur at about 4 hours. The absolute bioavailability of Citalopram was about 80% relative to an intravenous dose and absorption is not

affected by food. Such conventional immediate release preparations, however, do not provide a modified release of Citalopram HBr.

Escitalopram oxalate, which was first described in United States Patent No. RE 34712, is the pure S-enantiomer (single isomer) of the racemic bicyclic phthalane derivative of Citalopram. Escitalopram oxalate is designated as S-(+)-1-[3-(dimethyl-amino)propyl]-1-(*p*-fluorophenyl)-5-phthalancarbonitrile oxalate. A conventional immediate release preparation of Escitalopram oxalate is commercially available in the United States from Forest Laboratories, Inc. under the proprietary name LEXAPRO™ as 10 mg and 20 mg film coated tablets. The tablets contain the following inactive ingredients: talc, croscarmellose sodium, microcrystalline cellulose/colloidal silicon dioxide and magnesium stearate. The film coating contains hydroxypropyl methylcellulose, titanium dioxide and polyethylene glycol. The single and multiple dose pharmacokinetics of Escitalopram are linear and dose proportional in a dose range of 10 to 30 mg per day. Biotransformation of Escitalopram is mainly hepatic with a mean terminal half life of about 27 to 32 hours. With once daily dosing, steady state plasma concentrations are achieved within approximately one week. At steady state, the extent of accumulation of Escitalopram in plasma in young healthy subjects was 2.2 to 2.5 times the plasma concentrations observed after a single dose. Following a single oral dose (20 mg tablet) of Escitalopram, the mean T_{max} was 5 $\pm$ 1.5 hours. Absorption of Escitalopram is not affected by food. The FDA Orange Book states that United States Patent No. RE 34712 relates to the LEXAPRO™ formulation. Such a conventional immediate release preparation, however, does not provide a modified release of Escitalopram oxalate.

SUMMARY OF THE INVENTION

In accordance with one aspect of the present invention, there is provided a modified release pharmaceutical composition for oral administration, suitable for once daily dosing, comprising a form of at least one selective serotonin re-uptake inhibitor (SSRI) selected from the group consisting of SSRIs, racemic mixtures thereof, enantiomers thereof, pharmaceutically acceptable salts thereof, and combinations thereof in combination with at least one pharmaceutically-acceptable excipient, wherein the pharmaceutical composition, when orally administered to a patient, induces a statistically significant lower mean fluctuation index in the plasma than an immediate release composition of the form of the at least one SSRI while maintaining bioavailability substantially equivalent to that of the immediate release composition.

In accordance with another aspect of the present invention, there is provided a modified release pharmaceutical composition for oral administration, suitable for once daily dosing, comprising a form of at least one selective serotonin re-uptake inhibitor (SSRI) selected from the group consisting of SSRIs, racemic mixtures thereof, enantiomers thereof, pharmaceutically acceptable salts thereof, and combinations thereof in combination with at least one pharmaceutically-acceptable excipient, wherein the pharmaceutical composition, when orally administered to a patient, produces a mean maximum plasma concentration (C_{max}) of the form of the at least one SSRI that is lower than that produced by an immediate release pharmaceutical composition of the form of the at least one SSRI, and the area under the plasma concentration-time curve (AUC) and the mean minimum plasma concentration (C_{min}) are substantially equivalent to that of the immediate release pharmaceutical composition.

In accordance with another aspect of the present invention, there is provided a modified release pharmaceutical composition for oral administration, suitable for once daily dosing, comprising a form of at least one selective serotonin re-uptake inhibitor (SSRI) selected from the group consisting of SSRIs, racemic mixtures thereof, enantiomers thereof, pharmaceutically acceptable salts thereof, and combinations thereof in combination with at least one pharmaceutically-acceptable excipient, wherein the pharmaceutical composition, when orally administered to a patient, produces a mean maximum plasma concentration (C_{max}) of the form of the at least one SSRI and an area under a plasma concentration vs. time curve (AUC) within the range of from about -20% to about +25% of that produced by an immediate release pharmaceutical composition of the form of the at least one SSRI.

In an embodiment of the present invention, the form of the at least one SSRI is Citalopram HBr and the immediate release pharmaceutical composition is the subject of the United States Food and Drug Administration Approved New Drug Application number N20822 or N21046.

In an embodiment of the present invention, the form of the at least one SSRI is Escitalopram oxalate and the immediate release pharmaceutical composition is the subject of the United States Food and Drug Administration Approved New Drug Application number N21323.

In an embodiment of the present invention, the form of the at least one SSRI is Fluoxetine HCl and the immediate release pharmaceutical composition is the subject of the United States Food and Drug Administration Approved New Drug Application number N18936, N20101, N20974, or N75755.

In an embodiment of the present invention, the form of the at least one SSRI is Fluvoxamine maleate and the immediate release pharmaceutical composition is the subject of the United States Food and Drug Administration Approved New Drug Application number N20243 or N75888.

In an embodiment of the present invention, the form of the at least one SSRI is Sertraline HCl and the immediate release pharmaceutical composition is the subject of the United States Food and Drug Administration Approved New Drug Application number N20990 or N19839.

In an embodiment of the present invention, the form of the at least one SSRI is Venlafaxine HCl and the immediate release pharmaceutical composition is the subject of the United States Food and Drug Administration Approved New Drug Application number N20151.

In an embodiment of the present invention, the form of the at least one SSRI is Paroxetine HCl and the immediate release pharmaceutical composition is the subject of the United States Food and Drug Administration Approved New Drug Application number N20710 or N20031.

In accordance with another aspect of the present invention, there is provided a modified release pharmaceutical composition for oral administration, suitable for once daily dosing, comprising a form of at least one selective serotonin re-uptake inhibitor (SSRI) selected from the group consisting of SSRIs, racemic mixtures thereof, enantiomers thereof, pharmaceutically acceptable salts thereof, and combinations thereof in combination with at least one pharmaceutically-acceptable excipient wherein the pharmaceutical composition exhibits the following *in vitro* dissolution profile when measured using the USP Paddle Method at 100 rpm in 900 mL of a buffered medium having a pH between about 5.5 and about 7.5 at 37.0± 0.5°C:

(a) between about 0% and about 50% (by wt) of the form of the at least one SSRI is released after about 1 hour;

(b) between about 0% and about 75% (by wt) of the form of the at least one SSRI is released after about 2 hours;

(c) between about 3% and about 95% (by wt) of the form of the at least one SSRI is released after about 4 hours;

(d) between about 10% and about 100% (by wt) of the form of the at least one SSRI is released after about 8 hours;

(e) between about 20% and about 100% (by wt) of the form of the at least one SSRI is released after about 12 hours;

(f) between about 30% and about 100% (by wt) of the form of the at least one SSRI is released after about 16 hours;

(g) between about 50% and about 100% (by wt) of the form of the at least one SSRI is released after about 24 hours; and

(h) in excess of about 80% (by wt) of the form of the at least one SSRI is released after about 36 hours.

In an embodiment of the present invention, the composition exhibits the following *in vitro* dissolution profile when measured using the USP paddle method at 100 rpm in 900 ml of a buffered medium having a pH from about 5.5 to about 7.5 at 37.0 ± 0.5°C:

(a) from about 20% to about 50% (by weight) of the form of the at least one SSRI is released after about 1 hour;

(b) from about 40% to about 75% (by weight) of the form of the at least one SSRI is released after about 2 hours;

(c) from about 60% to about 95% (by weight) of the form of the at least one SSRI is released after about 4 hours;

(d) from about 80% to about 100% (by weight) of the form of the at least one SSRI is released after about 8 hours; and

(e) from about 90% to about 100% (by weight) of the form of the at least one SSRI is released after about 12 hours.

In an embodiment of the present invention, the composition exhibits the following *in vitro* dissolution profile when measured using the USP paddle method at 100 rpm in 900 ml of a buffered medium having a pH from about 5.5 to about 7.5 at 37.0 ± 0.5° C:

(a) from about 0% to about 50% (by weight) of the form of the at least one SSRI is released after about 1 hour;

(b) from about 0% to about 75% (by weight) of the form of the at least one SSRI is released after about 2 hours;

(c) from about 10% to about 95% (by weight) of the form of the at least one SSRI is released after about 4 hours;

(d) from about 35% to about 100% (by weight) of the form of the at least one SSRI is released after about 8 hours;

(e) from about 55% to about 100% (by weight) of the form of the at least one SSRI is released after about 12 hours;

(f) from about 70% to about 100% (by weight) of the form of the at least one SSRI is released after about 16 hours; and

(g) in excess of about 90% (by weight) of the form of the at least one SSRI is released after about 24 hours.

In an embodiment of the present invention, the composition exhibits the following *in vitro* dissolution profile when measured using the USP paddle method at 100 rpm in 900 ml of a buffered medium having a pH from about 5.5 to about 7.5 at 37.0 ± 0.5°C:

(a) from about 0% to about 30% (by weight) of the form of the at least one SSRI is released after about 1 hour;

(b) from about 0% to about 45% (by weight) of the form of the at least one SSRI is released after about 2 hours;

(c) from about 3% to about 55% (by weight) of the form of the at least one SSRI is released after about 4 hours;

(d) from about 10% to about 65% (by weight) of the form of the at least one SSRI is released after about 8 hours;

(e) from about 20% to about 75% (by weight) of the form of the at least one SSRI is released after about 12 hours;

(f) from about 30% to about 88% (by weight) of the form of the at least one SSRI is released after about 16 hours;

(g) from about 50% to about 100% (by weight) of the form of the at least one SSRI is released after about 24 hours; and

(h) in excess of about 80% (by weight) of the form of the at least one SSRI is released after about 36 hours.

In an embodiment of the present invention, the composition exhibits the following *in vitro* dissolution profile when measured using the USP paddle method at 100 rpm in 900 ml of a buffered medium having a pH from about 5.5 to about 7.5 at 37.0 ± 0.5°C:

(a) from about 5% to about 50% (by weight) of the form of the at least one SSRI is released after about 1 hour;

(b) from about 10% to about 75% (by weight) of the form of the at least one SSRI is released after about 2 hours;

(c) from about 20% to about 95% (by weight) of the form of the at least one SSRI is released after about 4 hours;

(d) from about 40% to about 100% (by weight) of the form of the at least one SSRI is released after about 8 hours;

(e) more than about 50% (by weight) of the form of the at least one SSRI is released after about 12 hours;

(f) more than about 70% (by weight) of the form of the at least one SSRI is released after about 18 hours; and

(g) more than about 80% (by weight) of the form of the at least one SSRI is released after about 24 hours.

In an embodiment of the present invention, the composition exhibits the following *in vitro* dissolution profile when measured using the USP paddle method at 100 rpm in 900 ml of a buffered medium having a pH from about 5.5 to about 7.5 at 37.0 ± 0.5°C:

(a) from about 15% to about 25% (by weight) of the form of the at least one SSRI is released after about 1 hour;

(b) from about 25% to about 35% (by weight) of the form of the at least one SSRI is released after about 2 hours;

(c) from about 30% to about 45% (by weight) of the form of the at least one SSRI is released after about 4 hours;

(d) from about 40% to about 60% (by weight) of the form of the at least one SSRI is released after about 8 hours;

(e) from about 55% to about 70% (by weight) of the form of the at least one SSRI is released after about 12 hours; and

(f) from about 60% to about 75% (by weight) of the form of the at least one SSRI is released after about 16 hours.

In an embodiment of the present invention, the composition exhibits the following *in vitro* dissolution profile when measured using the USP paddle method at 100 rpm in 900 ml of a buffered medium having a pH from about 5.5 to about 7.5 at 37.0 ± 0.5°C:

(a) from about 10% to about 30% (by weight) of the form of the at least one SSRI is released after about 1 hour;

(b) from about 46% to about 66% (by weight) of the form of the at least one SSRI is released after about 4 hours;

(c) from about 70% to about 90% (by weight) of the form of the at least one SSRI is released after about 8 hours; and

(d) in excess of about 80% (by weight) of the form of the at least one SSRI is released after about 12 hours.

In an embodiment of the present invention, the pharmaceutical composition exhibits the following *in vitro* dissolution profile when measured using the USP Paddle Method at 100 rpm in 900 ml of a buffered medium, having a pH between about 5.5 and about 7.5 at 37.0 ± 0.5°C:

(a) from about 3% to about 20% (by weight) of the form of the at least one SSRI is release after about 1 hour;

(b) from about 7% to about 32% (by weight) of the form of the at least one SSRI is released after about 2 hours;

(c) from about 17% to about 50% (by weight) of the form of the at least one SSRI is released after about 4 hours;

(d) from about 30% to about 75% (by weight) of the form of the at least one SSRI is released after about 8 hours;

(e) from about 55% to about 90% (by weight) of the form of the at least one SSRI is released after about 12 hours;

(f) from about 68% to about 98% (by weight) of the form of the at least one SSRI is released after about 16 hours; and

(g) in excess of about 85% (by weight) of the form of the at least one SSRI is released after about 24 hours.

In an embodiment of the present invention, the pharmaceutical composition exhibits the following *in vitro* dissolution profile when measured using the USP Paddle Method at 100 rpm in 900 ml of a buffered medium, having a pH between about 5.5 and about 7.5 at 37.0 ± 0.5°C:

(a) from about 18% to about 30% (by weight) of the form of the at least one SSRI is release after about 1 hour;

(b) from about 28% to about 43% (by weight) of the form of the at least one SSRI is released after about 2 hours;

(c) from about 45% to about 78% (by weight) of the form of the at least one SSRI is released after about 4 hours;

(d) from about 68% to about 98% (by weight) of the form of the at least one SSRI is released after about 8 hours;

(e) from about 82% to about 100% (by weight) of the form of the at least one SSRI is released after about 12 hours;

(f) from about 90% to about 100% (by weight) of the form of the at least one SSRI is released after about 16 hours; and

(g) in excess of about 95% (by weight) of the form of the at least one SSRI is released after about 24 hours.

In an embodiment of the present invention, the pharmaceutical composition exhibits the following *in vitro* dissolution profile when measured using the USP Paddle Method at 100 rpm in 900 ml of a buffered medium, having a pH from about 5.5 and about 7.5 at 37.0 ± 0.5°C:

(a) from about 10% to about 22% (by weight) of the form of the at least one SSRI is release after about 1 hour;

(b) from about 16% to about 35% (by weight) of the form of the at least one SSRI is released after about 2 hours;

(c) from about 28% to about 55% (by weight) of the form of the at least one SSRI is released after about 4 hours;

(d) from about 48% to about 80% (by weight) of the form of the at least one SSRI is released after about 8 hours;

(e) from about 62% to about 100% (by weight) of the form of the at least one SSRI is released after about 12 hours;

(f) from about 73% to about 100% (by weight) of the form of the at least one SSRI is released after about 16 hours; and

(g) in excess of about 80% (by weight) of the form of the at least one SSRI is released after about 24 hours.

In an embodiment of the present invention, the pharmaceutical composition exhibits the following *in vitro* dissolution profile when measured using the USP Paddle Method at 100 rpm in 900 ml of a buffered medium, having a pH from about 5.5 and about 7.5 at 37.0 ± 0.5°C:

(a) from about 20% to about 24% (by weight) of the form of the at least one SSRI is release after about 1 hour;

(b) from about 30% to about 38% (by weight) of the form of the at least one SSRI is released after about 2 hours;

(c) from about 50% to about 58% (by weight) of the form of the at least one SSRI is released after about 4 hours;

(d) from about 75% to about 85% (by weight) of the form of the at least one SSRI is released after about 8 hours;

(e) from about 90% to about 100% (by weight) of the form of the at least one SSRI is released after about 12 hours; and

(f) in excess of about 90% (by weight) of the form of the at least one SSRI is released after about 16 hours.

In an embodiment of the present invention, the pharmaceutical composition exhibits the following *in vitro* dissolution profile when measured using the USP Paddle Method at 100 rpm in 900 ml of a buffered medium, having a pH from about 5.5 and about 7.5 at 37.0 ± 0.5°C:

(a) from about 20% to about 25% (by weight) of the form of the at least one SSRI is release after about 1 hour;

(b) from about 32% to about 38% (by weight) of the form of the at least one SSRI is released after about 2 hours;

(c) from about 50% to about 60% (by weight) of the form of the at least one SSRI is released after about 4 hours;

(d) from about 75% to about 85% (by weight) of the form of the at least one SSRI is released after about 8 hours;

(e) from about 90% to about 100% (by weight) of the form of the at least one SSRI is released after about 12 hours; and

(f) in excess of about 90% (by weight) of the form of the at least one SSRI is released after about 16 hours.

In accordance with another aspect of the present invention, there is provided a modified release pharmaceutical composition for oral administration, suitable for once daily dosing, comprising about 20 mg of a form of at least one selective serotonin re-uptake inhibitor (SSRI) selected from the group consisting of SSRIs, racemic mixtures thereof, enantiomers thereof, pharmaceutically acceptable salts thereof and combinations thereof in combination with at least one pharmaceutically-acceptable excipient, wherein the composition when orally administered to a patient, provides a mean maximum plasma concentration (C_{max}) of the form of the at least one SSRI from about 5.0 ng/ml to about 28.0 ng/ml.

In an embodiment of the present invention, the composition when orally administered to a fasting patient, provides a C_{max} of the form of the at least one SSRI from about 5.0 ng/ml to about 28.0 ng/ml.

In an embodiment of the present invention, the composition when orally administered to a fasting patient, provides a C_{max} of the form of the at least one SSRI from about 7.0 ng/ml to about 14.0 ng/ml.

In an embodiment of the present invention, the composition when orally administered to a fasting patient, provides a C_{max} of the form of the at least one SSRI from about 8.0 ng/ml to about 12.0 ng/ml.

In an embodiment of the present invention, the composition when orally administered to a fasting patient, provides a C_{max} of the form of the at least one SSRI from about 8.0 ng/ml to about 15.0 ng/ml.

In an embodiment of the present invention, the composition when orally administered to a fasting patient, provides a C_{max} of the form of the at least one SSRI from about 10.0 ng/ml to about 14.0 ng/ml.

In an embodiment of the present invention, the composition when orally administered to a fasting patient, provides a C_{max} of the form of the at least one SSRI from about 13.0 ng/ml to about 21.0 ng/ml.

In an embodiment of the present invention, the composition when orally administered to a fasting patient, provides a C_{max} of the form of the at least one SSRI from about 15.0 ng/ml to about 19.0 ng/ml.

In an embodiment of the present invention, the composition when orally administered to a fasting patient, provides a C_{max} of the form of the at least one SSRI from about 5.0 ng/ml to about 14.0 ng/ml.

In an embodiment of the present invention, the composition when orally administered to a fasting patient, provides a C_{max} of the form of the at least one SSRI from about 9.0 ng/ml to about 13.0 ng/ml.

In an embodiment of the present invention, the composition when orally administered to a fasting patient, provides a C_{max} of the form of the at least one SSRI from about 5.0 ng/ml to about 16.0 ng/ml.

In an embodiment of the present invention, the composition when orally administered to a fasting patient, provides a C_{max} of the form of the at least one SSRI from about 12.0 ng/ml to about 19.0 ng/ml.

In an embodiment of the present invention, the composition when orally administered to a fasting patient, provides a C_{max} of the form of the at least one SSRI from about 13.0 ng/ml to about 17.0 ng/ml.

In an embodiment of the present invention, the composition when orally administered to a fasting patient, provides a C_{max} of the form of the at least one SSRI from about 14.0 ng/ml to about 21.0 ng/ml.

In an embodiment of the present invention, the composition when orally administered to a fasting patient, provides a C_{max} of the form of the at least one SSRI from about 14.0 ng/ml to about 18.0 ng/ml.

In an embodiment of the present invention, the composition when orally administered to a fasting patient, provides a C_{max} of the form of the at least one SSRI from about 13.0 ng/ml to about 25.0 ng/ml.

In an embodiment of the present invention, the composition when orally administered to a fasting patient, provides a C_{max} of the form of the at least one SSRI from about 16.0 ng/ml to about 20.0 ng/ml.

In an embodiment of the present invention, the composition when orally administered to a fasting patient, provides a C_{max} of the form of the at least one SSRI from about 6.0 ng/ml to about 28.0 ng/ml.

In an embodiment of the present invention, the composition when orally administered to a fasting patient, provides a C_{max} of the form of the at least one SSRI from about 15.0 ng/ml to about 19.0 ng/ml.

In an embodiment of the present invention, the composition when orally administered to a fed patient, provides a C_{max} of the form of the at least one SSRI from about 9.0 ng/ml to about 18.0 ng/ml.

In an embodiment of the present invention, the composition when orally administered to a fed patient, provides a C_{max} of the form of the at least one SSRI from about 9.0 ng/ml to about 16.0 ng/ml.

In an embodiment of the present invention, the composition when orally administered to a fed patient, provides a C_{max} of the form of the at least one SSRI from about 11.0 ng/ml to about 15.0 ng/ml.

In an embodiment of the present invention, the composition when orally administered to a fed patient, provides a C_{max} of the form of the at least one SSRI from about 11.0 to about 18.0 ng/mL.

In an embodiment of the present invention, the composition when orally administered to a fed patient, provides a C_{max} of the form of the at least one SSRI from about 13.0 ng/ml to about 17.0 ng/ml.

In accordance with another aspect of the present invention, there is provided a modified release pharmaceutical composition for oral administration, suitable for once daily dosing, comprising a form of at least one selective serotonin re-uptake inhibitor (SSRI) selected from the group consisting of SSRIs, racemic mixtures thereof, enantiomers thereof, pharmaceutically acceptable salts thereof and combinations thereof in combination with at least one pharmaceutically-acceptable excipient, wherein the pharmaceutical composition when orally administered to a patient, provides a medicament plasma concentration-time curve wherein the mean maximum plasma concentration (C_{max}) in a fasted patient divided by C_{max} in a fed patient ranges from about 0.20 to about 1.55.

In an embodiment of the present invention, the composition, when orally administered to a patient, provides a medicament plasma concentration time curve wherein the C_{max} in a fasted patient divided by the C_{max} in a fed patient ranges from about 0.30 to about 1.55.

In an embodiment of the present invention, the composition, when orally administered to a patient, provides a medicament plasma concentration time curve wherein the C_{max} in a fasted patient divided by the C_{max} in a fed patient ranges from about 0.50 to about 0.90.

In an embodiment of the present invention, the composition, when orally administered to a patient, provides a plasma concentration-time curve wherein the C_{max} of the form of the at least one SSRI in a fasted patient divided by the C_{max} of the form of the at least one SSRI in a fed patient ranges from about 0.25 to about 1.45.

In an embodiment of the present invention, the composition, when orally administered to a patient, provides a plasma concentration-time curve wherein the C_{max} of the form of the at least one SSRI in a fasted patient divided by the C_{max} of the form of the at least one SSRI in a fed patient ranges from about 0.45 to about 0.90.

In accordance with another aspect of the present invention, there is provided a modified release pharmaceutical composition for oral administration, suitable for once daily dosing, comprising about 20 mg of a form of at least one selective serotonin re-uptake inhibitor (SSRI) selected from the group consisting of SSRIs, racemic mixtures thereof, enantiomers thereof, pharmaceutically acceptable salts thereof and combinations thereof in combination with at least one pharmaceutically-acceptable excipient, wherein the composition when orally administered to a patient, provides a mean maximum plasma concentration (C_{max}) of the form of the at least one SSRI from about 6.0 ng/ml to about 28.0 ng/ml.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a C_{max} of the form of the at least one SSRI ranging from about 6.0 ng/ml to about 28.0 ng/ml.

In an embodiment of the present invention, the composition, when orally administered to a fed patient, provides a C_{max} of the form of the at least one SSRI ranging from about 15.0 ng/ml to about 19.0 ng/ml.

In accordance with another aspect of the present invention, there is provided a modified release pharmaceutical composition for oral administration, suitable for once daily dosing, comprising about 40 mg of a form of at least one selective serotonin re-uptake inhibitor (SSRI) selected from the group consisting of SSRIs, racemic mixtures thereof, enantiomers thereof, pharmaceutically acceptable salts thereof and combinations thereof in combination with at least one pharmaceutically-acceptable excipient, wherein the composition when orally administered to a patient, provides a mean maximum plasma concentration (C_{max}) of the form of the at least one SSRI from about 20.0 ng/ml to about 36.0 ng/ml.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a C_{max} of the form of the at least one SSRI ranging from about 20.0 ng/ml to about 36.0 ng/ml.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a C_{max} of the form of the at least one SSRI ranging from about 26.0 ng/ml to about 30.0 ng/ml.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a C_{max} of the form of the at least one SSRI ranging from about 23.0 ng/ml to about 36.0 ng/ml.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a C_{max} of the form of the at least one SSRI ranging from about 28.0 ng/ml to about 32.0 ng/ml.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a C_{max} of the form of the at least one SSRI ranging from about 22.0 ng/ml to about 36.0 ng/ml.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a C_{max} of the form of the at least one SSRI ranging from about 27.0 ng/ml to about 31.0 ng/ml.

In accordance with another aspect of the present invention, there is provided a modified release pharmaceutical composition for oral administration, suitable for once daily dosing, comprising a form of at least one selective serotonin re-uptake inhibitor (SSRI) selected from the group consisting of SSRIs, racemic mixtures thereof, enantiomers thereof, pharmaceutically acceptable salts thereof and combinations thereof in combination with at least one pharmaceutically-acceptable excipient, wherein the composition when orally administered to a patient, provides a time to mean maximum plasma concentration (T_{max}) ranging from about 4 to about 22 hours.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a T_{max} ranging from about 4 hours to about 22 hours.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a T_{max} ranging from about 17 hours to about 21 hours.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a T_{max} ranging from about 15 hours to about 19 hours.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a T_{max} ranging from about 7 hours to about 11 hours.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a T_{max} ranging from about 12 hours to about 16 hours.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a T_{max} ranging from about 11 hours to about 15 hours.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a T_{max} ranging from about 7 hours to about 13 hours.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a T_{max} ranging from about 8 hours to about 12 hours.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a T_{max} ranging from about 5 hours to about 11 hours.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a T_{max} ranging from about 6 hours to about 10 hours.

In an embodiment of the present invention, the composition, when orally administered to a fed patient, provides a T_{max} ranging from about 14 to about 21 hours.

In an embodiment of the present invention, the composition, when orally administered to a fed patient, provides a T_{max} ranging from about 17 hours to about 21 hours.

In an embodiment of the present invention, the composition, when orally administered to a fed patient, provides a T_{max} ranging from about 14 hours to about 18 hours.

In accordance with another aspect of the present invention, there is provided a modified release pharmaceutical composition for oral administration, suitable for once daily dosing, comprising a form of at least one selective serotonin re-uptake inhibitor (SSRI) selected from the group consisting of SSRIs, racemic mixtures thereof, enantiomers thereof, pharmaceutically acceptable salts thereof and combinations thereof in combination with at least one pharmaceutically-acceptable excipient, wherein the composition, when orally administered to a patient, provides a plasma concentration-time curve wherein the time to mean maximum plasma concentration (T_{max}) of the form of the at least one SSRI in a fasted patient divided by the T_{max} of the form of the at least one SSRI in a fed patient ranges from about 0.50 to about 1.10.

In an embodiment of the present invention, the composition when orally administered to a patient, provides a medicament plasma concentration-time curve wherein the T_{max} in a fasted patient divided by the T_{max} in a fed patient ranges from about 0.50 to about 0.95.

In an embodiment of the present invention, the composition when orally administered to a patient, provides a medicament plasma concentration-time curve

wherein the T_{max} in a fasted patient divided by the T_{max} in a fed patient ranges from about 0.70 to about 0.80.

In an embodiment of the present invention, the composition when orally administered to a patient, provides a medicament plasma concentration-time curve wherein the T_{max} in a fasted patient divided by the T_{max} in a fed patient ranges from about 0.60 to about 1.10.

In an embodiment of the present invention, the composition when orally administered to a patient, provides a medicament plasma concentration-time curve wherein the T_{max} in a fasted patient divided by the T_{max} in a fed patient ranges from about 0.80 to about 0.85.

In accordance with another aspect of the present invention, there is provided a modified release pharmaceutical composition for oral administration, suitable for once daily dosing, comprising a form of at least one selective serotonin re-uptake inhibitor (SSRI) selected from the group consisting of SSRIs, racemic mixtures thereof, enantiomers thereof, pharmaceutically acceptable salts thereof and combinations thereof in combination with at least one pharmaceutically-acceptable excipient, wherein the composition when orally administered to a patient, provides a time to mean maximum plasma concentration (T_{max}) ranging from about 4 to about 9 hours.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a T_{max} ranging from about 4 hours to about 9 hours.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a T_{max} ranging from about 5 hours to about 8 hours.

In accordance with another aspect of the present invention, there is provided a modified release pharmaceutical composition for oral administration, suitable for once daily dosing, comprising a form of at least one selective serotonin re-uptake inhibitor (SSRI) selected from the group consisting of SSRIs, racemic mixtures thereof, enantiomers thereof, pharmaceutically acceptable salts thereof and combinations thereof in combination with at least one pharmaceutically-acceptable excipient, wherein the composition when orally administered to a patient, provides a time to mean maximum plasma concentration (T_{max}) ranging from about 5 to about 14 hours.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a T_{max} ranging from about 5 hours to about 14 hours.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a T_{max} ranging from about 7 hours to about 13 hours.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a T_{max} ranging from about 8 hours to about 12 hours.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a T_{max} ranging from about 6 hours to about 10 hours.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a T_{max} ranging from about 5 hours to about 12 hours.

In accordance with another aspect of the present invention, there is provided a modified release pharmaceutical composition for oral administration, suitable for once

daily dosing, comprising about 20 mg of a form of at least one selective serotonin re-uptake inhibitor (SSRI) selected from the group consisting of SSRIs, racemic mixtures thereof, enantiomers thereof, pharmaceutically acceptable salts thereof and combinations thereof in combination with at least one pharmaceutically-acceptable excipient, wherein the composition when orally administered to a patient provides a plasma concentration time curve with an area under the curve from zero to infinity ($AUC_{(0\text{-}inf)}$) ranging from about 400 ng.hr/ml to about 1500 ng.hr/ml.

In an embodiment of the present invention, wherein the composition, when orally administered to a fasting patient, provides a plasma concentration time curve with an $AUC_{(0\text{-}inf)}$ ranging from about 400 ng.hr/ml to about 1500 ng.hr/ml.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a plasma concentration time curve with an $AUC_{(0\text{-}inf)}$ ranging from about 400 ng.hr/ml to about 800 ng.hr/ml.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a plasma concentration-time curve of the form of the at least one SSRI with an $AUC_{(0\text{-}inf)}$ ranging from about 500 ng.hr/ml to about 900 ng.hr/ml.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a plasma concentration-time curve of the form of the at least one SSRI with an $AUC_{(0\text{-}inf)}$ ranging from about 600 ng.hr/ml to about 1000 ng.hr/ml.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a plasma concentration-time curve of the form of the at least one SSRI with an $AUC_{(0\text{-}inf)}$ ranging from about 700 ng.hr/ml to about 1100 ng.hr/ml.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a plasma concentration-time curve of the form of the at least one SSRI with an $AUC_{(0\text{-}inf)}$ ranging from about 800 ng.hr/ml to about 1200 ng.hr/ml.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a plasma concentration-time curve of the form of the at least one SSRI with an $AUC_{(0\text{-}inf)}$ ranging from about 900 ng.hr/ml to about 1300 ng.hr/ml.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a plasma concentration-time curve of the form of the at least one SSRI with an $AUC_{(0\text{-}inf)}$ ranging from about 1000 ng.hr/ml to about 1400 ng.hr/ml.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a plasma concentration-time curve of the form of the at least one SSRI with an $AUC_{(0\text{-}inf)}$ ranging from about 1100 ng.hr/ml to about 1500 ng.hr/ml.

In an embodiment of the present invention, the composition, when orally administered to a fed patient, provides a plasma concentration-time curve of the form of the at least one SSRI with an $AUC_{(0\text{-}inf)}$ ranging from about 600 ng.hr/ml to about 1000 ng.hr/ml.

In an embodiment of the present invention, the composition, when orally administered to a fed patient, provides a plasma concentration-time curve of the form of the at least one SSRI with an $AUC_{(0\text{-}inf)}$ ranging from about 700 ng.hr/ml to about 1100 ng.hr/ml.

In accordance with another aspect of the present invention, there is provided a modified release pharmaceutical composition for oral administration, suitable for once daily dosing, comprising a form of at least one selective serotonin re-uptake inhibitor (SSRI) selected from the group consisting of SSRIs, racemic mixtures thereof, enantiomers thereof, pharmaceutically acceptable salts thereof and combinations thereof in combination with at least one pharmaceutically acceptable excipient, wherein the pharmaceutical composition, when orally administered to a patient, provides an area under the curve from zero to infinity ($AUC_{(0\text{-}inf)}$) in a fasted patient, divided by $AUC_{(0\text{-}inf)}$ in a fed patient ranges from about 0.60 to about 0.80.

In accordance with another aspect of the present invention, there is provided a modified release pharmaceutical composition for oral administration, suitable for once daily dosing, comprising about 20 mg of a form of at least one selective serotonin re-uptake inhibitor (SSRI) selected from the group consisting of SSRIs, racemic mixtures thereof, enantiomers thereof, pharmaceutically acceptable salts thereof and combinations thereof in combination with at least one pharmaceutically-acceptable excipient, wherein the composition when orally administered to a patient provides a plasma concentration time curve with an area under the curve (AUC) ranging from about 100 ng.hr/ml to about 1000 ng.hr/ml.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a plasma concentration-time curve of the form of the at least one SSRI with an AUC ranging from about 100 ng.hr/ml to about 1000 ng.hr/ml.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a plasma concentration-time curve of the

form of the at least one SSRI with an AUC ranging from about 200 ng.hr/ml to about 600 ng.hr/ml.

In accordance with another aspect of the present invention, there is provided a modified release pharmaceutical composition for oral administration, suitable for once daily dosing, comprising about 40 mg of a form of at least one selective serotonin reuptake inhibitor (SSRI) selected from the group consisting of SSRIs, racemic mixtures thereof, enantiomers thereof, pharmaceutically acceptable salts thereof and combinations thereof in combination with at least one pharmaceutically-acceptable excipient, wherein the composition when orally administered to a patient provides a plasma concentration time curve with an area under the curve from zero to infinity ($AUC_{(0\text{-}inf)}$) ranging from about 600 ng.hr/ml to about 12000 ng.hr/ml.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a plasma concentration-time curve of the form of the at least one SSRI with an $AUC_{(0\text{-}inf)}$ ranging from about 600 ng.hr/ml to about 12000 ng.hr/ml.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a plasma concentration-time curve of the form of the at least one SSRI with an $AUC_{(0\text{-}inf)}$ ranging from about 600 ng.hr/ml to about 2200 ng.hr/ml.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a plasma concentration-time curve of the form of the at least one SSRI with an $AUC_{(0\text{-}inf)}$ ranging from about 1200 ng.hr/ml to about 1600 ng.hr/ml.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a plasma concentration-time curve of the form of the at least one SSRI with an $AUC_{(0\text{-}inf)}$ ranging from about 600 ng.hr/ml to about 1500 ng.hr/ml.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a plasma concentration-time curve of the form of the at least one SSRI with an $AUC_{(0\text{-}inf)}$ ranging from about 800 ng.hr/ml to about 1200 ng.hr/ml.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a plasma concentration-time curve of the form of the at least one SSRI with an $AUC_{(0\text{-}inf)}$ ranging from about 3000 ng.hr/ml to about 12000 ng.hr/ml.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a plasma concentration-time curve of the form of the at least one SSRI with an $AUC_{(0\text{-}inf)}$ ranging from about 5000 ng.hr/ml to about 9000 ng.hr/ml.

In accordance with another aspect of the present invention, there is provided a modified release pharmaceutical composition for oral administration, suitable for once daily dosing, comprising a form of at least one selective serotonin re-uptake inhibitor (SSRI) selected from the group consisting of SSRIs, racemic mixtures thereof, enantiomers thereof, pharmaceutically acceptable salts thereof in combinations thereof in combination with at least one pharmaceutically acceptable excipient, wherein the composition, when orally administered to a patient, provides a plasma concentration time curve with an area under the curve from zero to t hours ($AUC_{(0\text{-}t)}$) ranging from about 400 ng.hr/ml to about 1500 ng.hr/ml.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a plasma concentration time curve with an $AUC_{(0-t)}$ ranging from about 400 ng.hr/ml to about 1500 ng.hr/ml.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a plasma concentration time curve with an $AUC_{(0-t)}$ ranging from about 400 ng.hr/ml to about 800 ng.hr/ml.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a plasma concentration time curve with an $AUC_{(0-t)}$ ranging from about 500 ng.hr/ml to about 900 ng.hr/ml.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a plasma concentration time curve with an $AUC_{(0-t)}$ ranging from about 800 ng.hr/ml to about 1200 ng.hr/ml.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a plasma concentration time curve with an $AUC_{(0-t)}$ ranging from about 600 ng.hr/ml to about 1000 ng.hr/ml.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a plasma concentration time curve with an $AUC_{(0-t)}$ ranging from about 700 ng.hr/ml to about 1100 ng.hr/ml.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a plasma concentration time curve with an $AUC_{(0-t)}$ ranging from about 800 ng.hr/ml to about 1200 ng.hr/ml.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a plasma concentration time curve with an $AUC_{(0-t)}$ ranging from about 900 ng.hr/ml to about 1300 ng.hr/ml.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a plasma concentration time curve with an $AUC_{(0-t)}$ ranging from about 1000 ng.hr/ml to about 1400 ng.hr/ml.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a plasma concentration time curve with an $AUC_{(0-t)}$ ranging from about 1100 ng.hr/ml to about 1500 ng.hr/ml.

In an embodiment of the present invention, the composition, when orally administered to a fed patient, provides a plasma concentration time curve with an $AUC_{(0-t)}$ ranging from about 600 ng.hr/ml to about 1000 ng.hr/ml.

In an embodiment of the present invention, the composition, when orally administered to a fed patient, provides a plasma concentration time curve with an $AUC_{(0-t)}$ ranging from about 700 ng.hr/ml to about 1100 ng.hr/ml.

In accordance with another aspect of the present invention, there is provided a modified release pharmaceutical composition for oral administration, suitable for once daily dosing, comprising a form of at least one selective serotonin re-uptake inhibitor (SSRI) selected from the group consisting of SSRIs, racemic mixtures thereof, enantiomers thereof, pharmaceutically acceptable salts thereof and combinations thereof in combination with at least one pharmaceutically acceptable excipient, wherein the pharmaceutical composition, when orally administered to a patient, provides a medicament plasma concentration time curve wherein the area under the curve from zero to t hours ($AUC_{(0-t)}$) in a fasted patient divided by the $AUC_{(0-t)}$ in a fed patient ranges from about 0.60 to about 0.80.

In accordance with another aspect of the present invention, there is provided a modified release pharmaceutical composition for oral administration, suitable for once daily dosing, comprising about 40 mg of a form of at least one selective serotonin re-

uptake inhibitor (SSRI) selected from the group consisting of SSRIs, racemic mixtures thereof, enantiomers thereof, pharmaceutically acceptable salts thereof in combinations thereof in combination with at least one pharmaceutically acceptable excipient, wherein the composition, when orally administered to a patient, provides a plasma concentration time curve with an area under the curve from zero to t hours ($AUC_{(0-t)}$) ranging from about 500 ng.hr/ml to about 6500 ng.hr/ml.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a plasma concentration time curve with an $AUC_{(0-t)}$ ranging from about 500 ng.hr/ml to about 6500 ng.hr/ml.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a plasma concentration time curve with an $AUC_{(0-t)}$ ranging from about 500 ng.hr/ml to about 2200 ng.hr/ml.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a plasma concentration time curve with an $AUC_{(0-t)}$ ranging from about 1000 ng.hr/ml to about 1500 ng.hr/ml.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a plasma concentration time curve with an $AUC_{(0-t)}$ ranging from about 500 ng.hr/ml to about 1500 ng.hr/ml.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a plasma concentration time curve with an $AUC_{(0-t)}$ ranging from about 800 ng.hr/ml to about 1200 ng.hr/ml.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a plasma concentration time curve with an $AUC_{(0-t)}$ ranging from about 3000 ng.hr/ml to about 6200 ng.hr/ml.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a plasma concentration time curve with an $AUC_{(0-t)}$ ranging from about 4400 ng.hr/ml to about 4800 ng.hr/ml.

In accordance with another aspect of the present invention, there is provided a modified release pharmaceutical composition for oral administration, suitable for once daily dosing, comprising about 20 mg of a form of at least one selective serotonin re-uptake inhibitor (SSRI) selected from the group consisting of SSRIs, racemic mixtures thereof, enantiomers thereof, pharmaceutically acceptable salts thereof and combinations thereof in combination with at least one pharmaceutically-acceptable excipient, wherein the composition when orally administered to a patient provides a plasma concentration time curve with an area under the curve from zero to 24 hours ($AUC_{(0-24)}$) ranging from about 100 ng.hr/ml to about 500 ng.hr/ml.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a plasma concentration-time curve of the form of the at least one SSRI with an $AUC_{(0-24)}$ ranging from about 100 to about 500 ng.hr/ml.

In an embodiment of the present invention, the composition, when orally administered to a fasting patient, provides a plasma concentration-time curve of the form of the at least one SSRI with an $AUC_{(0-24)}$ ranging from about 200 to about 400 ng.hr/ml.

In accordance with another aspect of the present invention, there is provided a modified release pharmaceutical composition for oral administration, suitable for once daily dosing, comprising a form of at least one selective serotonin re-uptake inhibitor (SSRI) selected from the group consisting of SSRIs, racemic mixtures thereof, enantiomers thereof, pharmaceutically acceptable salts thereof and combinations

thereof in combination with at least one pharmaceutically-acceptable excipient, wherein the pharmaceutical composition when orally administered to a patient as a single dose, releases the form of the at least one SSRI *in vivo* such that the duration over which the plasma level of the form of the at least one SSRI is equal to or greater than 50% of the mean maximum plasma concentration (C_{max}) is about 20 hours or greater.

In an embodiment of the present invention, the composition, when orally administered to a patient as a single dose, releases the form of the at least one SSRI *in vivo* such that the duration over which the plasma level of the form of the at least one SSRI is equal to or greater than 50% of the C_{max} is about 24 hours or greater.

In an embodiment of the present invention, the composition, when orally administered to a patient as a single dose, releases the form of the at least one SSRI *in vivo* such that the duration over which the plasma level of the form of the at least one SSRI is equal to or greater than 50% of the C_{max} is about 30 hours or greater.

In an embodiment of the present invention, the composition, when orally administered to a patient as a single dose, releases the form of the at least one SSRI *in vivo* such that the duration over which the plasma level of the form of the at least one SSRI is equal to or greater than 50% of the C_{max} is about 40 hours or greater.

In accordance with another aspect of the present invention, there is provided a modified release pharmaceutical composition for oral administration, suitable for once daily dosing, comprising a form of at least one selective serotonin re-uptake inhibitor (SSRI) selected from the group consisting of SSRIs, racemic mixtures thereof, enantiomers thereof, pharmaceutically acceptable salts thereof and combinations thereof in combination with at least one pharmaceutically-acceptable excipient, wherein the pharmaceutical composition, when orally administered to a patient as a single dose, releases the form of the at least one SSRI *in vivo* such that the duration over which the

plasma level of the form of the at least one SSRI is equal to or greater than 75% of the mean maximum plasma concentration (C_{max}) is about 6 hours or greater.

In an embodiment of the present invention, the pharmaceutical composition, when orally administered to a patient as a single dose, releases the form of the at least one SSRI *in vivo* such that the duration over which the plasma level of the form of the at least one SSRI is equal to or greater than 75% of the C_{max} is about 12 hours or greater.

In an embodiment of the present invention, the pharmaceutical composition, when orally administered to a patient as a single dose, releases the form of the at least one SSRI *in vivo* such that the duration over which the plasma level of the form of the at least one SSRI is equal to or greater than 75% of the C_{max} is about 18 hours or greater.

In an embodiment of the present invention, the pharmaceutical composition, when orally administered to a patient as a single dose, releases the form of the at least one SSRI *in vivo* such that the duration over which the plasma level of the form of the at least one SSRI is equal to or greater than 75% of the C_{max} is about 30 hours or greater.

In accordance with another aspect of the present invention, there is provided a modified release pharmaceutical composition for oral administration, suitable for once daily dosing, comprising a form of at least one selective serotonin re-uptake inhibitor (SSRI) selected from the group consisting of SSRIs, racemic mixtures thereof, enantiomers thereof, pharmaceutically acceptable salts thereof and combinations thereof in combination with at least one pharmaceutically-acceptable excipient, wherein the pharmaceutical composition, when orally administered to a patient releases the form of the at least one SSRI *in vivo* at steady state such that the plasma level of the form of the at least one SSRI over the 24 hour dosing period is equal to or greater than 50% of the mean maximum plasma concentration (C_{max}).

In an embodiment of the present invention, the pharmaceutical composition, when orally administered to a patient releases the form of the at least one SSRI *in vivo* at steady state such that the duration over which the plasma level of the form of the at least one SSRI over the 24 hour dosing period is equal to or greater than 75% of the C_{max} is about 12 hours or greater.

In accordance with another aspect of the present invention, there is provided a modified release pharmaceutical composition for oral administration, suitable for once daily dosing, comprising a form of at least one selective serotonin reuptake inhibitor selected from the group consisting of SSRIs, racemic mixtures thereof, enantiomers thereof, pharmaceutically acceptable salts thereof and combinations thereof in combination with at least one pharmaceutically acceptable excipient, wherein the pharmaceutical composition, when orally administered to a patient, provides a mean maximum plasma concentration (C_{max}) which is more than twice the plasma level of said form of said at least one SSRI at about 16 hours after administration of the pharmaceutical composition.

In an embodiment of the present invention, the composition, when orally administered to a patient, provides a C_{max} which is more than twice the plasma level of said form of said at least one SSRI at about 20 hours after administration of the pharmaceutical composition.

In an embodiment of the present invention, the composition, when orally administered to a patient, provides a C_{max} which is more than twice the plasma level of said form of said at least one SSRI at about 24 hours after administration of the pharmaceutical composition.

In an embodiment of the present invention, the composition, when orally administered to a patient, provides a C_{max} which is more than twice the plasma level of said form of said at least one SSRI at about 36 hours after administration of the pharmaceutical composition.

In an embodiment of the present invention, the composition, when orally administered to a patient, provides a C_{max} which is more than twice the plasma level of said form of said at least one SSRI at about 48 hours after administration of the pharmaceutical composition.

In accordance with another aspect of the present invention, there is provided a method of effectively treating depression in humans, comprising orally administering to a human patient on a once a day basis an oral sustained release dosage form containing a form of at least one selective serotonin re-uptake inhibitor (SSRI) selected from the group consisting of SSRIs, racemic mixtures thereof, enantiomers thereof, pharmaceutically acceptable salts thereof and combinations thereof in combination with at least one pharmaceutically acceptable excipient which upon administration provides a time to maximum plasma concentration (T_{max}) of said form of said at least one SSRI in about 6 to about 20 hours and a maximum plasma concentration (C_{max}) which is more than twice the plasma level of said form of said at least one SSRI at about 48 hours after administration of the dosage form, and which dosage form provides effective treatment of depression for about 24 hours or more after administration to the patient.

In accordance with another aspect of the present invention there is provided a method of effectively treating depression in a human patient, comprising orally administering to a human patient on a once a day basis an oral sustained release dosage form containing a form of at least one selective serotonin reuptake inhibitor selected from the group consisting of SSRIs, racemic mixtures thereof, enantiomers thereof,

pharmaceutically acceptable salts thereof and combinations thereof in combination with at least one pharmaceutically acceptable excipient, which provides a maximum plasma concentration (C_{max}) which is more than twice the plasma level of said form of said at least one SSRI at about 48 hours after administration of the dosage form, and which provides effective treatment of depression for about 24 hours or more after administration to the patient.

In an embodiment of the present invention, the form of the at least one SSRI is selected from the group consisting of Fluoxetine, Fluvoxamine, Paroxetine, Sertraline, Venlafaxine, Citalopram, racemic mixtures thereof, enantiomers thereof, pharmaceutically acceptable salts thereof and combinations thereof.

In an embodiment of the present invention, the form of the at least SSRI is Citalopram HBr.

In an embodiment of the present invention, the form of the at least SSRI is Escitalopram oxalate.

In an embodiment of the present invention, the form of the at least SSRI is Fluvoxamine maleate.

In an embodiment of the present invention, the form of the at least SSRI is Paroxetine HCl.

In an embodiment of the present invention, the form of the at least SSRI is Sertraline HCl.

In an embodiment of the present invention, the form of the at least SSRI is Venlafaxine HCl.

In an embodiment of the present invention, the form of the at least one SSRI is present in the pharmaceutical composition in an amount effective to treat at least one condition selected from the group consisting of depression, major depressive disorder,

obsessive compulsive disorder, panic disorder, social anxiety disorder, generalized anxiety disorder, posttraumatic stress disorder and combinations thereof.

In an embodiment of the present invention, the form of the at least one SSRI is present in the pharmaceutical composition in the range of from about 5 mg to about 1000 mg (calculated as the pharmaceutically-acceptable salt) per dosage unit.

In an embodiment of the present invention the form of the least one SSRI is present in the pharmaceutical composition in an amount in the range of from about 10 mg to about 200 mg (calculated as the pharmaceutically acceptable salt) per dosage unit.

In an embodiment of the present invention, the form of the at least one SSRI is present in the pharmaceutical composition in an amount in the range of from about 10 mg to about 100 mg (calculated as the pharmaceutically acceptable salt) per dosage unit.

In an embodiment of the present invention, the at least one pharmaceutically acceptable excipient is selected from the group comprising at least one release rate controlling pharmaceutically acceptable carrier, at least one diluent, at least one binder, at least one filler, at least one solubility enhancer, at least one bioavailability enhancer, at least one lubricant, at least one solubilizing agent, at least one surface active agent, at least one surfactant, at least one acidifying agent and combinations thereof.

In an embodiment of the present invention, the at least one release rate controlling pharmaceutically acceptable carrier is at least one sustained release pharmaceutically acceptable carrier.

In an embodiment of the present invention, the at least one sustained release pharmaceutically acceptable carrier is at least one solid sustained release pharmaceutically acceptable carrier.

In an embodiment of the present invention, the at least one solid sustained release pharmaceutically acceptable carrier is at least one solid sustained release pharmaceutically-acceptable polymer.

In an embodiment of the present invention, the at least one solid sustained release pharmaceutically-acceptable polymer is selected from the group consisting of at least one hydrophilic water-soluble polymer, at least one hydrophobic water-insoluble polymer and combinations thereof.

Any suitable hydrophilic water-soluble polymer conventional in the pharmaceutical art may be used. Examples of hydrophilic polymers suitable for use in the present invention include, but are not limited to, cellulose derivatives, dextrans, starches, carbohydrates, base polymers, natural or hydrophilic gums, xanthans, alginates, gelatins, polyacrylic acids, polyvinyl alcohol (PVA), polyvinyl pyrrolidone (PVP), carbomers or the like. The hydrophilic polymers can be used individually, as well as in mixtures of two or several hydrophilic polymers. In the case of the cellulose derivatives, the alkyl or hydroxyalkyl cellulose derivatives, the alkyl or hydroxyalkyl cellulose derivatives preferably come into consideration such as example, methyl cellulose, ethylcellulose (EC), hydroxy methylcellulose, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC), methylhydroxy ethylcellulose, methylhydroxy ethylcellulose, methylhydroxy propylcellulose or sodium carboxymethyl cellulose.

Suitable cellulose based hydrophilic polymers may have various degrees of substitution and/or different molecular weights corresponding to a different degree of viscosity of the aqueous solution.

In an embodiment of the present invention, the release rate controlling polymer may be selected from the group consisting of hydroxypropylmethyl cellulose, hydroxyethyl cellulose, ethylcellulose, carbomer and combinations thereof.

The hydroxypropyl methylcellulose (HPMC) used as the release rate controlling polymer in the present invention may suitably be any HPMC conventional in the pharmaceutical art. The HPMC used may suitably be, for example, HPMC substitution types 1828, 2208, 2906 and 2910 as described on page 843 of the 24th Edition (2000) of the United States Pharmacopeia (USP XXIV). The hydroxypropyl methylcellulose used may suitably be, for example, METHOCEL® as supplied by Dow Chemical Company. Similar HPMCs are also available from other suppliers. Preferably, the HPMC used is HPMC 2208, more preferably METHOCEL® K4M Premium CR.

The ethylcellulose (EC) used as the release rate controlling polymer in the present invention may suitably be any EC conventional in the pharmaceutical art. The EC used may suitably be, for example, ETHOCEL® as supplied by Dow Chemical Company. Similar ECs are also available from other suppliers. Preferably, the EC used is ETHOCEL® FP, more preferably ETHOCEL® FP 100.

The carbomer used as the release rate controlling polymer in the present invention may suitably be any carbomer conventional in the pharmaceutical art. The carbomer used may suitably be, for example, carbomer 910, carbomer 934 and 934P, carbomer 941 and carbomer 1342 as described on pages 2426 to 2428 of the 19th Edition (2000) of the United States National Formulary (USNFXIX). The carbomer used may suitably be, for example, CARBOPOL® as supplied by B.F. Goodrich. Similar carbomers are also available from other suppliers. Preferably, the carbomer used is carbomer 941, more preferably CARBOPOL® 971P.

In an embodiment of the present invention, the modified release pharmaceutical composition may also comprise other pharmaceutically acceptable ingredients which are conventional in the pharmaceutical arts, such as at least one diluent, at least one lubricant, at least one binder, at least one granulating aid, at least one colourant, at least one flavourant, at least one surfactant, at least one pH adjuster, at least one anti-adherent, at least one glidant, at least one disintegrant, at least one solubility enhancer, at least one bioavailability enhancer, at least one solubilizing agent, at least one surface active agent, at least one surfactant and the like and combinations thereof.

In an embodiment of the present invention, the pharmaceutical composition may further comprise at least one diluent. Any suitable diluent conventional in the pharmaceutical art may be used. Examples of diluents suitable for use in the present invention include, but are not limited to, lactose, microcrystalline cellulose, mannitol and combinations thereof. The lactose used may suitably be lactose anhydrous (direct tabletting) as supplied by Quest International. The microcrystalline cellulose used may suitably be, for example, AVICEL® as supplied by FMC Corporation, preferably AVICEL® PH 101 or AVICEL® PH 102.

In an embodiment of the present invention, the pharmaceutical composition may further comprise at least one binder. Any suitable binder conventional in the pharmaceutical art may be used. An example of a suitable binder for use in the present invention is polyvinyl pyrrolidone, for example KOLLIDON® as supplied by BASF AG, preferably KOLLIDON® 29/32 and/or KOLLIDON® 90F.

In an embodiment of the present invention, the pharmaceutical composition may further comprise at least one lubricant. Any suitable lubricant conventional in the pharmaceutical art may be used. Examples of suitable lubricants for use in the present

invention include, but are not limited to, magnesium stearate, stearic acid and combinations thereof.

In an embodiment of the present invention, the pharmaceutical composition may further comprise at least one surfactant. Any surfactant conventional in the pharmaceutical art may be used. Examples of suitable surfactants for use in the present invention include, but are not limited to, a bile salt, sodium lauryl sulphate (SLS), polyoxyethylene/polyoxypropylene block copolymers, polyethylene glycol hydrogenated castor oils, polyethylene glycols, saturated polyglycolized glycerides from hydrogenated vegetable oils, saturated polyglycolized glycerides, water soluble derivatives of natural source vitamins, sucrose stearate, mannitol, mono- and diglycerides. The polyoxyethylene/polyoxypropylene block polymers used as the surfactant in the present invention may suitably be, for example, poloxamers, preferably poloxamer 407 or poloxamer 188 such as LUTROL® F127 or LUTROL® F68, respectively as supplied by BASF AG. The polyethylene ethylene glycol hydrogenated castor oils used as the surfactant in the present invention may suitably be, for example, PEG-40 hydrogenated castor oil, such as CREMOPHOR® RH40 as supplied by BASF AG. The polyethylene glycols used as the surfactant in the present invention may suitably be, for example, PEG-3350, PEG-600, PEG-8000 such as CARBOWAX® as supplied by Union Carbide and PEG-32 such as LUTROL® E1500 as supplied by BASF AG. The saturated polyglycolized glycerides from hydrogenated vegetable oils used as the surfactant in the present invention may suitably be, for example, lauroyl macrogol-32 glycerides such as GELUCIRE® 44/14 as supplied by Gattefosse SA. The saturated polyglycolized glycerides used as the surfactant in the present invention may suitably be, for example, stearoyl macrogol-32 glycerides such as GELUCIRE® 50/13 as supplied by Gattefosse SA. The water soluble derivatives of natural source vitamins used as the

surfactant in the present invention may suitably be, for example, Vitamin E d-∝-tocopheryl polyethylene glycol 1000 succinate (TPGS) as supplied by Eastman. The sucrose stearate used as the surfactant in the present invention may suitably be, for example, CRODESTA® F160 as supplied by Croda Inc. The mono- and diglycerides used as the surfactant in the present invention may suitably be, for example, a propylene glycol monoester of medium chain fatty acids such as CAPMUL® PG8 as supplied by Abitec Corporation.

In an embodiment of the present invention, the pharmaceutical composition may further comprise at least one acidifying agent. Any acidifying agent conventional in the pharmaceutical art may be used. An example of a suitable acidifying agent for use in the present invention includes, but is not limited to, L-tartaric acid.

In an embodiment of the present invention, the form of the at least one SSRI may be incorporated into a matrix. The matrix may be any matrix conventional in the pharmaceutical art.

In an embodiment of the present invention the matrix is a modified release matrix that affords modified release of the form of the at least one SSRI over at least a 12 hour period and preferably that affords *in vitro* dissolution rates and *in vivo* absorption rates of the form of the at least one SSRI within the ranges specified above.

In an embodiment of the present invention, the matrix is selected from the group consisting of a sustained release matrix and a controlled release matrix.

In an embodiment of the present invention wherein the matrix is a sustained release matrix or a controlled release matrix, the pharmaceutical composition further comprises a modified release coating.

In an embodiment of the present invention, the matrix is a normal release matrix having a coating which provides for modified release of the form of the at least one SSRI.

In an embodiment of the present invention, the pharmaceutical composition further comprises a film coating. Any film coating material conventional in the pharmaceutical art may be used. Preferably, an aqueous film coating is used. The film coating functions to seal all surface pores and to provide a smooth and uniform surface. The film coat is obtained by preferably spray coating film coating dispersions onto the surface of uncoated cores using appropriate coating equipment. Usually these dispersions contain low viscosity hydrophilic polymers such as hydroxypropyl methylcellulose and hydroxypropyl cellulose, and plasticizers such as polyethylene glycol 400. These dispersions are commercially available as OPADRY® from Colorcon, West Point, PA. Similar film coating dispersions are also available from other suppliers. Preferably the optional seal coating membrane is present in a concentration of about 0-5% W/W of the core. An example of a suitable film coating for use in the present invention is OPADRY® II White, preferably OPADRY® II White Y-22-7719. OPADRY® II White Y-22-7719 consists of hydroxypropylmethyl cellulose, titanium dioxide, polydextrose, triacetin and polyethylene glycol. Similar film coating materials are also available from other suppliers.

In an embodiment of the present invention the pharmaceutical composition further comprises a modified-release film coating. Any modified-release film coating material conventional in the pharmaceutical art may be used. The modified release film coating is applied to pharmaceutical products in order to modify drug release. There are two types of modified-release dosage forms, namely those that are delayed release and those that are extended release. Delayed-release products often are designed to

prevent drug release in the upper part of the gastrointestinal (GI) tract. Modified release film coatings used to prepare this type of dosage form are commonly called enteric coatings. Extended-release products are designed to extend drug release over a period of time, a result which can be achieved by the application of a sustained- or controlled-release film coating. Modified release film coating is obtained by preferably spraying modified release film coating dispersions onto the surface of seal coated cores. However, these modified release film coating dispersions can also be coated straight onto the surface of the uncoated cores. In an embodiment of the present invention, the modified release film coating comprises as an aqueous dispersion, preferably with appropriate coating ingredients dispersed therein.

In an embodiment of the present invention, the modified release film coating further comprises plasticizers, film extenders, diffusion enhancers and other excipients such as detackifiers or opacifiers, etc. The hydrophobic polymer is mixed with a film extender/diffusion enhancer to give the hydrophobic polymer some degree of hyrophilicity. The plasticizer is added to reduce the glass transition temperature (T_g) of the polymer so that it can be coalesced at a lower temperature (such as 60°C). The plasticizer also makes the functional coating membrane flexible so that it can stretch to some degree without breaking. Preferably, the ratio of the polymer to film extender in the aqueous polymeric dispersion of the functional coating membrane is from about 0.25-0.75 to 0.99-0.01.

The aqueous dispersions of hydrophobic polymers used as modified release film coatings in the present invention may be used in conjunction with tablets, spheroids (or beads), microspheres, seeds, pellets, ion-exchange resin beads, and other multi-particulate systems in order to obtain a desired controlled-release of the therapeutically active agent. Granules, spheroids, or pellets, etc., prepared in accordance with the

present invention can be presented in a tablet, a capsule or in any other suitable dosage form. The tablets of the present invention may be any suitable shape, such as round, oval, biconcave, hemispherical, any polygonal shape such as square, rectangular, and pentagonal, and the like.

In order to obtain a modified-release formulation, it is usually necessary to overcoat the pharmaceutical composition with a sufficient amount of the aqueous dispersion of the hydrophobic polymer, to obtain a weight gain level from about 2 to about 25%, although the overcoat may be lesser or greater depending upon the physical properties of the form of the at least one SSRI and the desired release rate, the inclusion of plasticizer in the aqueous dispersion and the manner of incorporation of the same, for example.

In an embodiment of the present invention, the hydrophobic polymer is selected from the group consisting of ethylcellulose, an acrylic polymer and combinations thereof.

Although ethylcellulose is one preferred hydrophobic polymer which may be used for coating the pharmaceutical composition of the present invention, those skilled in the art will appreciate that other cellulosic polymers, including other alkyl cellulosic polymers, may be substituted for part or all of the ethylcellulose included in the hydrophobic polymer coatings of the present invention.

One commercially-available aqueous dispersion of ethylcellulose is AQUACOAT® (FMC Corp., Philadelphia, Pa., U.S.A.). AQUACOAT® is prepared by dissolving the ethylcellulose in a water-immiscible organic solvent and then emulsifying the same in water in the presence of a surfactant and a stabilizer. After homogenization to generate submicron droplets, the organic solvent is evaporated under vacuum to form a pseudolatex. The plasticizer is not incorporated in the

pseudolatex during the manufacturing phase. Thus, prior to using the same as a coating, it is necessary to intimately mix the AQUACOAT® with a suitable plasticizer prior to use.

Another aqueous dispersion of ethylcellulose is commercially available as SURELEASE® (Colorcon, Inc., West Point, Pa., U.S.A.). This product is prepared by incorporating plasticizer into the dispersion during the manufacturing process. A hot melt of a polymer, plasticizer (dibutyl sebacate), and stabilizer (oleic acid) is prepared as a homogeneous mixture, which is then diluted with an alkaline solution to obtain an aqueous dispersion which can be applied directly into substrates.

Examples of pharmaceutically-acceptable acrylic polymers suitable for use in the present invention, include but are not limited to acrylic acid and methacrylic acid copolymers, methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyan oethyl methacrylate, methyl methacrylate, copolymers, methacrylic acid copolymers, methyl methacrylate copolymers, methyl methacrylate copolymers, methyl methacrylate copolymers, methacrylic acid copolymer, aminoalkyl methacrylate copolymer, methacrylic acid copolymers, methyl methacrylate copolymers, poly(acrylic acid), poly(methacrylic acid, methacrylic acid alkylamide copolymer, poly(methyl methacrylate), poly(methacrylic acid) (anhydride), methyl methacrylate, polymethacrylate, methyl methacrylate copolymer, poly(methyl methacrylate), poly(methyl methacrylate) copolymer, polyacrylamide, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers.

In order to obtain a desirable dissolution profile, it may be necessary to incorporate two or more pharmaceutically-acceptable acrylic polymers having differing physical properties.

In an embodiment of the present invention, the modified-release coating is an enteric coating. An example of a suitable enteric coating material for use in the present invention is a methacrylic acid copolymer. The methacrylic acid copolymers used may suitably be any methacrylic acid copolymer conventional in the pharmaceutical art such as methacrylic acid copolymer Types A, B and C as described on page 2477 to page 2479 of USNFXIX.

In an embodiment of the present invention, the hydrophobic acrylic polymer is a polymer whose permeability is pH dependent, such as anionic polymers synthesized from methacrylic acid and methacrylic acid methyl ester. Such polymers are commercially available, e.g., from Rohm Pharma GmbH under the tradename EUDRAGIT® L and EUDRAGIT® S. The ratio of free carboxyl groups to the esters is said to be 1:1 in EUDRAGIT® L and 1:2 in EUDRAGIT® S. EUDRAGIT® L is insoluble in acids a pure water, but becomes increasingly permeable above pH 5.0 EUDRAGIT® S is similar, except that it becomes increasingly permeable above pH 7. Preferably, the methacrylic acid copolymer is methacrylic acid copolymer Type A and/or Type B, more preferably EUDRAGIT® L100 and/or EUDRAGIT®S100.

In one preferred embodiment, the acrylic coating is an acrylic resin lacquer used in the form of an aqueous dispersion, such as that which is commercially available from Rohm Pharma under the Tradename EUDRAGIT®. In further preferred embodiments, the acrylic coating comprises a mixture of two acrylic resin lacquers commercially available from Rohm Pharma under the Tradenames EUDRAGIT® L100 and EUDRAGIT® S100, respectively.

EUDRAGIT® L100 and EUDRAGIT® S100 are anionic copolymers based on methacrylic acid and methyl methacrylate. The ratio of free carboxyl groups to the ester groups is about 1:1 in EUDRAGIT® L100 and about 1:2 in EUDRAGIT® S100. The

average molecular weight is about 135,000. The films are insoluble below pH5 and thus resistant to gastric fluid. By salt formation in the neutral to weakly alkaline medium of intestinal fluid, the films dissolve step-wise at pH values above 5.5.

The EUDRAGIT® L/S dispersions of the present invention may be mixed together in any desired ratio in order to ultimately obtain a controlled-release formulation having a desirable dissolution profile. Desirable controlled-release formulations may be obtained, for instance, from an enteric coating derived from 100% EUDRAGIT® L100, 100% EUDRAGIT® S100, 50% EUDRAGIT® L100 and 50% EUDRAGIT® S100, and 90% EUDRAGIT® L100 and 10% EUDRAGIT® S100. Of course, one skilled in the art will recognize that other acrylic polymers may also be used.

In an embodiment of the present invention wherein the modified release film coating comprises an aqueous dispersion of a hydrophobic polymer, the inclusion of an effective amount of a plasticizer in the aqueous dispersion of hydrophobic polymer will further improve the physical properties of the film. For example, because ethylcellulose has a relatively high glass transition temperature and does not form flexible films under normal coating conditions, it is necessary to plasticize the ethylcellulose before using the same as a coating material. Generally, the amount of plasticizer included in a coating solution is based on the concentration of the film-former, e.g., most often from about 1 to about 50 percent by weight of the film-former. Concentration of the plasticizer, however, can only be properly determined after careful experimentation with the particular coating solution and method of application.

Examples of suitable plasticizers for ethylcellulose include water insoluble plasticizers such as dibutyl sebacate, diethyl phthalate, triethyl citrate, tributyl citrate, and triacetin, although it is possible that other water-insoluble plasticizers (such as acetylated monoglycerides, phthalate esters, castor oil, etc.) may be used. Triethyl

citrate is an especially preferred plasticizer for the aqueous dispersions of ethyl cellulose of the present invention.

Examples of suitable plasticizers for the acrylic polymers of the present invention include, but are not limited to citric acid esters such as triethyl citrate, tributyl citrate, dibutyl phthalate, and possibly 1,2-propylene glycol. Other plasticizers which have proved to be suitable for enhancing the elasticity of the films formed from acrylic films such as EUDRAGIT® L/S lacquer solutions include polyethylene glycols, propylene glycol, diethyl phthalate, castor oil, and triacetin. Triethyl citrate is an especially preferred plasticizer for the aqueous dispersions of ethyl cellulose of the present invention.

It has further been found that the addition of a small amount of talc reduces the tendency of the aqueous dispersion to stick during processing, and acts as a polishing agent.

In addition to modifying the dissolution profile by altering the relative amounts of different acrylic resin lacquers, the dissolution profile of the ultimate product may also be modified, for example, by increasing or decreasing the thickness of the retardant coating.

In an embodiment of the present invention, the at least one selective SSRI is selected from the group consisting of Fluoxetine HCl, Fluvoxamine maleate, Paroxetine HCl, Sertraline HCl, Venlafaxine HCl, Citalopram HBr, Escitalopram oxalate and combinations thereof.

In accordance with another aspect of the present invention, there is provided a modified release pharmaceutical composition comprising:

(a) from about 4.0% (w/w) to about 8.0% (w/w) of the form of the at least one SSRI;

(b) from about 10% (w/w) to about 42% (w/w) of at least one release rate controlling polymer;

(c) from about 46% (w/w) to about 70% (w/w) of at least one diluent;

(d) from about 0% (w/w) to about 5% (w/w) of at least one binder;

(e) from about 0% (w/w) to about 5.0% (w/w) of at least one lubricant;

(f) from about 0% (w/w) to about 6.0% (w/w) of at least one surfactant;

(g) from about 0% (w/w) to about 6.0% (w/w) of at least one solubilizing agent;

(h) from about 0% (w/w) to about 6.0% (w/w) of at least one bioavailability enhancer; and

(i) from about 0% (w/w) to about 6.0% (w/w) of at least one acidifying agent.

In accordance with another aspect of the present invention, there is provided a modified release pharmaceutical composition comprising:

	Ingredients	**% w/w**
(a)	SSRI	4.0-8.0
(b)	Hydroxypropylmethylcellulose 2208 (METHOCEL® K4M Premium CR)	10.0-40.0
(c)	Lactose Anhydrous (DT)	40.0-60.0
(d)	Microcrystalline Cellulose (AVICEL® PH 101)	6.0-10.0
(e)	Polyvinylpyrrolidone (KOLLIDON® 29/32)	0.0-4.0
(f)	Polyvinylpyrrolidone (KOLLIDON® K90F)	0.0-4.0
(g)	Magnesium Stearate	0.0-2.0
(h)	Stearic Acid	0.0-2.0
(i)	Carbomer 941 (CARBOPOL® 971P)	0.0-2.0
(j)	Bile Salt	0.0-3.0
(k)	Sodium Lauryl Sulphate	0.0-3.0
(l)	Poloxamer 407 (LUTROL® F127)	0.0-6.0
(m)	Poloxamer 188 (LUTROL® F68)	0.0-6.0
(n)	PEG-40 hydrogenated castor oil (CREMOPHOR® RH40)	0.0-6.0
(o)	PEG-3350	0.0-6.0
(p)	PEG-600	0.0-6.0
(q)	PEG-8000	0.0-6.0
(r)	Saturated Polyglycolized Glycerides from hydrogenated vegetable oils (GELUCIRE® 44/14)	0.0-6.0
(s)	Saturated Polyglycolized Glycerides (GELUCIRE® 50/13)	0.0-6.0
(t)	Vitamin E TPGS	0.0-6.0
(u)	PEG-32 (LUTROL® E1500)	0.0-6.0
(v)	Sucrose stearate (CRODESTA® F160)	0.0-6.0
(w)	Mannitol	0.0-6.0
(x)	Propylene glycol monoester of medium chain fatty acids (CAPMUL® PG8)	0.0-6.0
(y)	L-Tartaric Acid	0.0-6.0

In accordance with another aspect of the present invention there is provided a modified release pharmaceutical composition comprising:

	Ingredients	**% w/w**
(a)	SSRI	4.0-8.0
(b)	Hydroxypropylmethyl cellulose (METHOCEL® K4M Premium CR)	10.0-40.0
(c)	Lactose Anhydrous (DT)	40.0-60.0
(d)	Microcrystalline Cellulose (AVICEL® PH 101)	6.0-10.0
(e)	Polyvinylpyrrolidone (KOLLIDON® K90F)	0.5-3.50
(f)	Magnesium Stearate	0.5-2.0

In accordance with another aspect of the present invention there is provided a modified release pharmaceutical composition comprising:

	Ingredients	**% w/w**
(a)	Citalopram HBr	4.0-8.0
(b)	Hydroxypropylmethylcellulose 2208 (METHOCEL® K4M Premium CR)	10.0-40.0
(c)	Lactose Anhydrous (DT)	40.0-60.0
(d)	Microcrystalline Cellulose (AVICEL® PH 101)	6.0-10.0
(e)	Polyvinylpyrrolidone (KOLLIDON® 29/32)	0.0-4.0
(f)	Polyvinylpyrrolidone (KOLLIDON® K90F)	0.0-4.0
(g)	Magnesium Stearate	0.0-2.0
(h)	Stearic Acid	0.0-2.0
(i)	Carbomer 941 (CARBOPOL® 971P)	0.0-2.0
(j)	Bile Salt	0.0-3.0
(k)	Sodium Lauryl Sulphate	0.0-3.0
(l)	Poloxamer 407 (LUTROL® F127)	0.0-6.0
(m)	Poloxamer 188 (LUTROL® F68)	0.0-6.0
(n)	PEG-40 hydrogenated castor oil (CREMOPHOR® RH40)	0.0-6.0
(o)	PEG-3350	0.0-6.0
(p)	PEG-600	0.0-6.0
(q)	PEG-8000	0.0-6.0
(r)	Saturated Polyglycolized Glycerides from hydrogenated vegetable oils (GELUCIRE® 44/14)	0.0-6.0
(s)	Saturated Polyglycolized Glycerides (GELUCIRE® 50/13)	0.0-6.0
(t)	Vitamin E TPGS	0.0-6.0
(u)	PEG-32 (LUTROL® E1500)	0.0-6.0
(v)	Sucrose stearate (CRODESTA® F160)	0.0-6.0
(w)	Mannitol	0.0-6.0
(x)	Propylene glycol monoester of medium chain fatty acids (CAPMUL® PG8)	0.0-6.0
(y)	L-Tartaric Acid	0.0-6.0

In accordance with another aspect of the present invention there is provided a modified release pharmaceutical composition comprising:

	Ingredients	**% w/w**
(a)	Citalopram HBr	4.0-8.0
(b)	Hydroxypropylmethyl cellulose (METHOCEL® K4M Premium CR)	10.0-40.0
(c)	Lactose Anhydrous (DT)	40.0-60.0
(d)	Microcrystalline Cellulose (AVICEL® PH 101)	6.0-10.0
(e)	Polyvinylpyrrolidone (KOLLIDON® K90F)	0.5-3.50
(f)	Magnesium Stearate	0.5-2.0

In accordance with another aspect of the present invention there is provided a modified release pharmaceutical composition comprising:

	Ingredients	**% w/w**
(a)	Paroxetine HCl	4.0-8.0
(b)	Hydroxypropylmethyl cellulose (METHOCEL® K4M Premium CR)	10.0-40.0
(c)	Lactose Anhydrous (DT)	40.0-60.0
(d)	Microcrystalline Cellulose (AVICEL® PH 101)	6.0-10.0
(e)	Polyvinylpyrrolidone (KOLLIDON® K90F)	0.5-3.50
(f)	Magnesium Stearate	0.5-2.0

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In accordance with another aspect of the present invention there is provided a modified release pharmaceutical composition comprising:

	Ingredients	**% w/w**
(a)	Fluoxetine HCl	4.0-8.0
(b)	Hydroxypropylmethyl cellulose (METHOCEL® K4M Premium CR)	10.0-40.0
(c)	Lactose Anhydrous (DT)	40.0-60.0
(d)	Microcrystalline Cellulose (AVICEL® PH 101)	6.0-10.0
(e)	Polyvinylpyrrolidone (KOLLIDON® K90F)	0.5-3.50
(f)	Magnesium Stearate	0.5-2.0

In an embodiment of the present invention, the pharmaceutical composition is a matrix tablet.

In an embodiment of the present invention, a wet granulation method issued in the manufacture of the pharmaceutical composition, followed by drying, milling and blending of lubricants before tabletting.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention will be further understood from the following detailed description with reference to the drawings in which:

Figure 1 is a graph illustrating the *in vitro* dissolution profiles of 20 mg Citalopram HBr CR Tablets formulated according to three different embodiments of the present invention.

Figure 2 is a graph illustrating the comparison of the mean plasma Citalopram concentrations (ng/ml) over time after a single dose of one of the three 20 mg Citalopram HBr CR Tablets of Figure 1 or after a single dose of one 20 mg CELEXA™ tablet under fasting conditions.

Figure 3 is a graph illustrating the *in vitro* dissolution profiles of 20 mg Citalopram HBr CR Tablets formulated according to two different embodiments of the present invention.

Figure 4 is a graph illustrating the mean plasma Citalopram concentrations (ng/ml) over time after a single dose of one of two 20 mg Citalopram HBr CR Tablets of Figure 3 under fasting or fed conditions.

Figure 5 is a graph illustrating the *in vitro* dissolution profiles of 20 mg Citalopram HBr CR Tablets formulated according to three different embodiments of the present invention.

Figure 6 is a graph illustrating the *in vitro* dissolution profiles of 20 mg Citalopram HBr CR Tablets formulated according to ten different embodiments of the present invention.

Figure 7 is a graph illustrating the *in vitro* dissolution profiles of 20 mg Citalopram HBr 20 mg CR Tablets formulated according to sixteen different embodiments of the present invention.

Figure 8 is a graph illustrating the *in vitro* dissolution profiles of 20 mg Citalopram HBr CR Tablets formulated according to two different embodiments of the present invention.

Figure 9 is a graph illustrating the *in vitro* dissolution profiles of 20 mg Citalopram HBr CR Tablets formulated according to two different embodiments of the present invention.

Figure 10 is a graph illustrating the *in vitro* dissolution profiles of 20 mg Citalopram HBr CR Tablets formulated according to two different embodiments of the present invention.

Figure 11 is a graph illustrating the mean plasma Citalopram concentrations (ng/ml) over time after a single dose of one of the two 20 mg Citalopram HBr CR Tablets of Figure 10 or after a single dose of one 20 mg CELEXA™ tablet under fasting conditions.

Figure 12 is a graph illustrating the *in vitro* dissolution profile of 20 mg Citalopram HBr CR Tablets formulated according to one embodiment of the present invention.

Figure 13 is a graph illustrating the mean plasma Citalopram concentrations (ng/ml) over time after a single dose of the 20 mg Citalopram HBr CR Tablet of Figure 12 or after a single dose of one 20 mg CELEXA™ tablet under fasting conditions.

Figure 14 is a graph illustrating the mean plasma Desmethylcitalopram concentrations (ng/ml) over time after a single dose of the 20 mg Citalopram HBr CR Tablet of Figure 12 or after a single dose of one 20 mg CELEXA™ tablet under fasting conditions.

Figure 15 is a graph illustrating the mean plasma Didesmethylcitalopram concentrations (ng/ml) over time after a single dose of the 20 mg Citalopram HBr CR Tablet of Figure 12 or after a single dose of one 20 mg CELEXA™ tablet under fasting conditions.

Figure 16 is a graph illustrating the *in vitro* dissolution profiles of 20 mg Citalopram HBr CR Tablets formulated according to an embodiment of the present invention wherein the Citalopram HBr is provided by two different suppliers.

Figure 17 is a graph illustrating the *in vitro* dissolution profile of 20 mg Paroxetine HCl CR Tablets formulated according to an embodiment of the present invention.

Figure 18 is a graph illustrating the mean plasma Paroxetine concentrations (ng/ml) over time after a single dose of the 20 mg Paroxetine HCl CR Tablet of Figure 17 or after a single dose of one 20 mg CELEXA™ tablet under fasting conditions.

Figure 19 is a graph illustrating the *in vitro* dissolution profiles of 40 mg Fluoxetine HCl CR Tablets formulated according to an embodiment of the present invention wherein the Fluoxetine HCl is provided by two different suppliers.

Figure 20 is a graph illustrating the mean plasma Fluoxetine concentrations (ng/ml) over time after a single dose of one of the 40 mg Fluoxetine HCl CR Tablets of Figure 19 or after a single dose of one 40 mg PROZAC® PULVULE® under fasting conditions.

Figure 21 is a graph illustrating the mean plasma Norfluoxetine concentrations (ng/ml) over time after a single dose of one of the 40 mg Fluoxetine HCl CR Tablet of Figure 19 or after a single dose of one 40 mg PROZAC® PULVULE® under fasting conditions.

Figure 22 is a graph illustrating the mean plasma Fluoxetine concentrations (ng/ml) over time after a single dose of one of the 40 mg Fluoxetine HCl CR Tablet of Figure 19 or after a single dose of one 40 mg PROZAC® PULVULE® under fasting conditions.

Figure 23 is a graph illustrating the mean plasma Norfluoxetine concentrations (ng/ml) over time after a single dose of one of the 40 mg Fluoxetine HCl CR Tablet of Figure 19 or after a single dose of one 40 mg PROZAC® PULVULE® under fasting conditions.

Figure 24 is a graph illustrating the mean plasma Fluoxetine concentrations (ng/ml) over time after a single dose of one of the 40 mg Fluoxetine HCl CR Tablet of Figure 19 or after a singe dose of one 40 mg PROZAC® PULVULE® under fasting conditions.

Figure 25 is a graph illustrating the mean plasma Norfluoxetine concentrations (ng/ml) over time after a singe dose of one of the 40 mg Fluoxetine HCl CR Tablet of Figure 19 or after a single dose of one 40 mg PROZAC® PULVULE® under fasting conditions.

Figure 26 is a schematic diagram illustrating the manufacture of SSRI CR Tablets according to one embodiment of the present invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Further details of the preferred embodiments of the present invention are illustrated in the following examples which are understood to be non-limiting.

EXAMPLE 1:

Table 1 provides the composition of four Citalopram HBr Controlled Release (CR) Tablet formulations (Formulations 1, 2, 3 and 4).

Table 1: Citalopram HBr CR Tablet Formulations

CORE INGREDIENTS	Formulation 1 (g)	Formulation 2 (g)	Formulation 3 (g)	Formulation 4 (g)
Citalopram HBr	187.6	187.5	187.5	187.5
HPMC2208 (METHOCEL® K4M Premium CR)	1380.1	1350.1	1050.0	1350.0
HEC (NATROSOL® 250 HHX)	780.2	600.0	NA	600.0
Lactose Anhydrous (DT)	240.1	360.0	1440.1	360.0
MCC (AVICEL® PH 101)	210.2	240.0	240.0	240.0
Carbomer 941 (CARBOPOL® 971P)	112.6	NA	NA	NA
EC (ETHOCEL® 100 FP Premium)	NA	1800.0	NA	180.0
PVP (KOLLIDON® 29/32)	60.1	120.5	52.5	120.5
Magnesium stearate	30.1	30.0	30.0	30.0
Isopropyl Alcohol*	-	-	-	-
COATING INGREDIENTS				
Film Coating OPADRY® II White Y-22-7719	30.0	30.0	30.0	NA
Enteric Coating				
Methacrylic Acid Copolymer, Type A (EUDRAGIT® L 100)	NA	NA	NA	35.75
Methacrylic Acid Copolymer, Type B (EUDRAGIT® S 100)	NA	NA	NA	3.9
Ethanol	NA	NA	NA	650.0
PEG 600	NA	NA	NA	7.8
Talc	NA	NA	NA	6.5
Titanium dioxide	NA	NA	NA	1.6
Iron Oxide	NA	NA	NA	2.6

*Isopropyl Alcohol is not considered as part of the theoretical batch size since it is evaporated during drying of the wet granulation

As can be seen from Table 1, Formulations 1, 2 and 3 comprise an OPADRY® film coating, whereas Formulation 4 comprises an EUDRAGIT® enteric coating.

In vitro dissolution studies were conducted on 20 mg Citalopram HBr CR Tablets formulated according to Formulations 1, 2 and 3. The following dissolution conditions were used for all of the *in vitro* dissolution studies conducted herein for determining the *in vitro* dissolution profiles of SSRI CR Tablets:

Apparatus

USP Dissolution Apparatus #2 (Paddle)

Sinker

Three-prong Sinker

UV/VIS detector wavelength

240 nm

Flow cell

10 mm

Dissolution Medium

Degassed Phosphate Buffer pH 6.5 ±0.05 with 5M HCl or 5M NaOH solution as required

Dissolution Medium volume

900 ml

Paddle Speed

100 rpm

Bath Temperature

37.0 ± 0.5°

Sample Time

Every Hour for 24 h

Table 2 provides the *in vitro* dissolution data of 20 mg Citalopram HBr CR Tablets formulated according to Formulations 1, 2 and 3.

Table 2: *In vitro* Dissolution Data of 20 mg Citalopram HBr CR Tablets Formulated According to Formulations 1, 2 and 3

Time (hrs)	Formulation 1 (% dissolved)	Formulation 2 (% dissolved)	Formulation 3 (% dissolved)
0	0	0	0
1	7.04	12.77	19.03
2	11.42	20.6	30.5
3	15.2	27.06	39.94
4	18.68	32.73	48.14
5	21.98	37.97	55.83
6	25.14	42.86	62.67
7	28.24	47.54	68.84
8	31.21	52.02	74.21
9	34.11	56.27	78.84
10	36.95	60.35	82.73
11	39.8	64.3	86.11
12	42.58	67.94	89.1
13	45.45	71.41	91.71
14	48.35	74.54	93.82
15	51.21	77.24	95.69
16	54.1	79.64	97.02
17	56.73	81.74	98.06
18	59.15	83.62	98.95
19	61.54	85.54	99.78
20	63.84	87.06	100.32
21	66.06	88.94	100.93
22	68.22	90.07	101.41
23	70.27	91.53	102.55
24	72.26	92.73	103.37

Figure 1 compares the *in vitro* dissolution profiles of 20 mg Citalopram HBr CR Tablets formulated according to Formulations 1, 2 and 3. Based on the results of this study, Formulations 1, 2 and 3 were designated as "slow", "medium" and "fast" formulations, respectively, in comparison to each other.

A pilot, single-dose, open-label, four-way, cross-over study was conducted to evaluate the relative bioavailability of 20 mg Citalopram HBr CR Tablets formulated according to Formulations 1, 2 and 3 versus the reference product, 20 mg CELEXA™

tablets (Lot Number: A304; Expiry Date 04/MR; Lundbeck Canada Inc.), under fasting conditions in normal healthy, non-smoking male volunteers. After a fast of at least 10 hours, each subject received a single dose of one (1) 20 mg Citalopram HBr CR Tablet formulated according to Formulation 1, 2 or 3 with 180 ml of water (Regimens A, B, or C, respectively) or a single dose of one (1) 20 mg CELEXA™ tablet with 180 ml of water (Regimen D). The study periods were separated by a washout period of one (1) week. Blood samples were taken at 0.0 (pre-drug), 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0, 72.0, 96.0, 120.0, and 144.0 hours post-drug. Upon completion of the clinical portion of the study, the plasma samples were delivered under frozen conditions to the analytical facility for the analysis of the Citalopram concentrations. Twelve (12) qualified subjects and four (4) alternates were enrolled in the study in two groups. Group I consisted of Subjects #01 through #10, and Group II, consisted of Subjects #11 through #16. Plasma drug concentration, pharmacokinetic and statistical analyses were conducted on eleven (11) subjects.

Table 3 provides the mean plasma Citalopram concentrations (ng/ml) over time after a single dose of one 20 mg Citalopram HBr CR Tablet formulated according to Formulation 1, 2 or 3 or after a single dose of one 20 mg CELEXA™ tablet under fasting conditions.

Table 3: Mean Plasma Citalopram Concentrations (n=11)

Sample Time (Hours)	Formulation 1 1 x 20 mg (ng/ml)	Formulation 2 1 x 20 mg (ng/ml)	Formulation 3 1 x 20 mg (ng/ml)	CELEXA™ 1 x 20 mg (ng/ml)
0.00	0.99 ± 0.97	0.86 ± 0.82	0.75 ± 0.61	0.84 ± 0.78
1.00	1.09 ± 0.95	0.93 ± 0.86	0.93 ± 0.56	4.00 ± 2.86
1.50	1.39 ± 0.95	1.20 ± 0.71	1.55 ± 0.65	10.01 ± 5.01
2.00	1.81 ± 1.13	1.80 ± .0.82	2.39 ± 0.95	14.86 ± 5.18
2.50	2.56 ± 1.55	2.44 ± 0.74	4.22 ± 1.47	18.00 ± 5.98
3.00	3.04 ± 1.52	3.17 ± 0.63	5.49 ± 1.87	20.23 ± 5.22
3.50	3.67 ± 1.68	4.28 ± 1.00	6.95 ± 2.71	20.76 ± 4.13
4.00	4.21 ± 1.60	4.99 ± 1.21	8.09 ± 2.65	21.99 ± 4.10
4.50	4.76 ± 1.78	5.55 ± 1.41	9.12 ± 2.85	21.50 ± 3.39
5.00	5.80 ± 2.24	7.17 ± 2.21	11.92 ± 3.84	21.70 ± 4.50
5.50	6.40 ± 2.37	8.50 ± 2.47	13.30 ± 2.89	22.11 ± 4.12
6.00	7.23 ± 2.88	9.10 ± 2.76	13.35 ± 2.54	20.93 ± 4.57
8.00	8.13 ± 3.00	10.16 ± 3.70	14.94 ± 3.43	21.38 ± 4.74
10.00	9.13 ± 3.11	10.56 ± 3.54	16.29 ± 3.87	19.87 ± 5.37
12.00	9.07 ± 2.79	10.52 ± 4.23	15.16 ± 3.77	18.43 ± 4.17
16.00	8.97 ± 3.51	9.78 ± 3.15	14.83 ± 4.26	15.34 ± 3.04
24.00	8.23 ± 3.35	9.40 ± 3.77	11.73 ± 3.35	12.90 ± 3.36
36.00	7.54 ± 3.92	8.39 ± 3.47	10.16 ± 3.07	10.54 ± 2.29
48.00	6.06 ± 3.08	6.00 ± 2.60	7.43 ± 1.99	8.05 ± 1.73
72.00	4.08 ± 2.23	3.63 ± 1.48	5.27 ± 2.04	5.36 ± 1.82
96.00	2.95 ± 1.60	2.86 ± 1.49	3.42 ± 1.22	3.73 ± 1.57
120.00	1.96 ± 0.93	2.09 ± 1.16	2.43 ± 1.00	2.81 ± 1.30
144.00	1.56 ± 1.09	1.34 ± 0.72	1.76 ± 0.73	2.03 ± 0.92

Figure 2 illustrates the mean plasma Citalopram concentrations (ng/ml) over time after a single dose of one 20 mg Citalopram HBr CR Tablet formulated according to Formulation 1, 2 or 3 or after a single dose of one 20 mg CELEXA™ tablet under fasting conditions.

Table 4 provides the mean pharmacokinetic parameters for plasma Citalopram after a single dose of one 20 mg Citalopram HBr CR Tablet formulated according to Formulation 1, 2 or 3 or after a single dose of one 20 mg CELEXA™ tablet under fasting conditions.

Table 4: Mean Pharmacokinetic Parameters for Plasma Citalopram (n=11)				
Parameter	**Formulation 1 1 x 20 mg Mean (%C.V.)**	**Formulation 2 1 x 20 mg Mean (%C.V.)**	**Formulation 3 1 x 20 mg Mean (%C.V.)**	**CELEXA™ (Lot #: A304) 1 x 20 mg Mean (%C.V.)**
$AUC_{(0-t)}$(ng.hr/ml)	659.01 (44.39)	698.17 (40.18)	907.89 (28.02)	1059.27 (23.61)
$AUC_{(0-inf)}$(ng.hr/ml)	688.21 (37.66)	790.02 (42.31)	1026.34 (29.61)	1150.03 (24.69)
C_{max} (ng/ml)	10.36 (31.23)	11.82 (30.41)	17.21 (18.89)	24.02 (17.48)
T_{max}(hours)	19.27 (66.65)	16.55 (55.92)	9.14 (33.39)	5.87 (40.34)
$t_{1/2}$ (hours)	48.71 (19.19)	45.54 (13.92)	45.37 (14.07)	46.01 (9.44)
K_{el} ($hour^{-1}$)	0.015 (19.930)	0.015 (14.097)	0.016 (14.627)	0.015 (9.741)

In vitro dissolution studies were conducted on 20 mg Citalopram HBr CR Tablets formulated according to Formulations 2 and 4. Table 5 provides the *in vitro* dissolution data of 20 mg Citalopram HBr CR Tablets formulated according to Formulations 2 and 4.

Table 5: *In vitro* Dissolution Data of 20 mg Citalopram HBr CR Tablets Formulated According to Formulations 2 and 4

Time (hrs)	Formulation 2 (% dissolved)	Formulation 4 (% dissolved)
0	0	0
1	12.77	3.36
2	20.6	7.98
3	27.06	12.75
4	32.73	17.65
5	37.97	22.73
6	42.86	27.92
7	47.54	32.95
8	52.02	37.89
9	56.27	42.61
10	60.35	47.14
11	64.3	51.4
12	67.94	55.53
13	71.41	59.39
14	74.54	63.08
15	77.24	66.53
16	79.64	69.8
17	81.74	72.79
18	83.62	75.61
19	85.54	78.22
20	87.06	80.67
21	88.94	82.98
22	90.07	85.05
23	91.53	86.96
24	92.73	88.78

Figure 3 compares the *in vitro* dissolution profiles of 20 mg Citalopram HBr CR Tablets formulated according to Formulations 2 and 4.

A pilot, randomized, single-dose, open-label, four-way, cross-over study was conducted to evaluate the relative bioavailability of 20 mg Citalopram HBr 20 mg CR Tablets formulated according to Formulations 2 and 4 under fasted and fed conditions in normal healthy, non-smoking male volunteers. After a fast of at least 10 hours (for Regimens A and C), or five (5) minutes after complete ingestion of a high-fat content breakfast (for Regimens B and D), each subject received a single dose of one (1) 20 mg

Citalopram CR Tablet formulated according to Formulation 4 (fasted or fed) with 180 ml of water or a single dose of one (1) 20 mg Citalopram CR Tablet formulated according to Formulation 2 (fasted or fed) with 180 ml of water. There was a washout period of one (1) week between study periods. Following each drug administration, blood samples were collected at 0.0 (pre-drug), 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0, 72.0, 96.0, 100.0, and 144.0 hours post-drug. Upon completion of the clinical portion of the study, plasma samples were delivered under frozen conditions to the analytical facility for the analysis of Citalopram concentrations. Twelve (12) subjects and three (3) alternates were entered into the study. Plasma drug concentration, pharmacokinetic and statistical analyses were conducted on the twelve (12) subjects.

Table 6 provides the mean plasma Citalopram concentrations (ng/ml) over time after a single dose of one 20 mg Citalopram HBr CR Tablet formulated according to Formulation 4 or 2 under fasting or fed conditions.

Table 6: Mean Plasma Citalopram Concentrations (n=12)

Sample Time (Hours)	Formulation 4 (Fasted) 1 x 20 mg (ng/ml)	Formulation 4 (Fed) 1 x 20 mg (ng/ml)	Formulation 2 (Fasted) 1 x 20 mg (ng/ml)	Formulation 2 (Fed) 1 x 20 mg (ng/ml)
0.00	0.57 ± 0.58	0.49 ± 0.53	0.68 ± 0.64	0.70 ± 0.66
1.00	0.58 ± 0.57	0.54 ± 0.48	0.81 ± 0.65	0.95 ± 0.84
1.50	0.68 ± 0.61	0.58 ± 0.50	1.05 ± 0.72	1.51 ± 1.17
2.00	0.90 ± 0.55	0.75 ± 0.44	1.40 ± 0.84	2.53 ± 1.65
2.50	1.15 ± 0.67	0.97 ± 0.42	1.99 ± 0.99	3.83 ± 2.74
3.00	1.49 ± 0.74	1.29 ± 0.48	2.56 ± 1.21	4.19 ± 2.69
3.50	1.91 ± 0.79	1.57 ± 0.47	3.13 ± 1.42	5.12 ± 2.97
4.00	2.57 ± 0.86	2.03 ± 0.53	3.78 ± 1.59	6.04 ± 3.45
4.50	3.11 ± 1.12	2.39 ± 0.71	4.43 ± 1.96	6.51 ± 2.83
5.00	4.18 ± 1.42	3.61 ± 1.31	5.17 ± 2.28	8.56 ± 4.41
5.50	5.30 ± 1.76	4.65 ± 1.65	6.26 ± 3.01	9.43 ± 5.67
6.00	5.98 ± 1.72	5.42 ± 1.77	7.47 ± 3.19	10.51 ± 4.95
8.00	7.28 ± 2.08	7.54 ± 2.24	8.16 ± 3.08	11.01 ± 3.37
10.00	8.09 ± 2.50	9.15 ± 2.47	9.25 ± 3.77	12.34 ± 3.54
12.00	8.20 ± 2.85	9.95 ± 2.30	9.39 ± 4.18	12.23 ± 3.30
16.00	8.74 ± 4.03	11.58 ± 2.80	9.68 ± 4.58	13.29 ± 2.86
24.00	7.24 ± 3.22	10.68 ± 3.23	7.59 ± 3.49	11.38 ± 2.91
36.00	6.32 ± 3.22	9.30 ± 2.93	6.48 ± 3.15	9.27 ± 1.85
48.00	4.81 ± 2.68	7.14 ± 2.14	5.04 ± 2.62	7.00 ± 2.16
72.00	2.83 ± 1.61	4.43 ± 1.41	3.19 ± 1.80	4.45 ± 1.19
96.00	1.96 ± 1.15	2.95 ± 1.13	2.27 ± 1.47	2.96 ± 0.92
120.00	1.34 ± 0.93	2.10 ± 0.84	1.48 ± 1.07	2.02 ± 0.69
144.00	0.96 ± 0.71	1.42 ± 0.64	1.07 ± 0.79	1.38 ± 0.62

Figure 4 illustrates the mean plasma Citalopram concentrations (ng/ml) over time after a single dose of one 20 mg Citalopram HBr CR Tablet formulated according to Formulation 4 or 2 under fasting or fed conditions.

Table 7 provides the mean pharmacokinetic parameters for plasma Citalopram after a single dose of one 20 mg Citalopram HBr CR Tablet formulated according to Formulation 4 or 2 under fasting or fed conditions.

Table 7: Mean Pharmacokinetic Parameters for Plasma Citalopram (n=12)				
Parameter	**Formulation 4 (Fasted) 1 x 20 mg Mean (%C.V.)**	**Formulation 4 (Fed) 1 x 20 mg Mean (%C.V.)**	**Formulation 2 (Fasted) 1 x 20 mg Mean (%C.V.)**	**Formulation 2 (Fed) 1 x 20 mg Mean (%C.V.)**
$AUC_{(0-t)}$ (ng.hr/ml)	522.63 (49.28)	740.52 (26.33)	569.46 (49.87)	795.15 (24.02)
$AUC_{(0-inf)}$ (ng.hr/ml)	591.05 (53.90)	834.52 (28.88)	643.50 (53.64)	891.41 (27.09)
C_{max} (ng/ml)	9.46 (37.17)	12.83 (21.82)	10.49 (43.06)	14.61 (29.78)
T_{max} (hours)	13.67 (33.51)	18.83 (37.47)	12.84 (30.08)	15.96 (31.28)
$t_{1/2}$ (hours)	43.66 (22.30)	44.28 (19.61)	42.74 (20.77)	43.93 (28.35)
K_{el}(hour^{-1})	0.017 (19.294)	0.016 (19.9 2)	0.017 (21.014)	0.017(27.221)

EXAMPLE 2

Table 8 provides the composition of three Citalopram HBr CR Tablet formulations (Formulations 5, 6 and 7).

Table 8: Citalopram HBr CR Tablet Formulations			
Ingredients	**Formulation 5 (% w/w)**	**Formulation 6 (% w/w)**	**Formulation 7 (% w/w)**
Citalopram HBr	6.25	6.25	6.18
HPMC (METHOCEL® K4MPrem CR)	35.00	35.00	34.59
Lactose Anhydrous (DT)	48.00	48.00	47.43
MCC (AVICEL® PH 101)	8.00	8.00	7.90
PVP (KOLLIDON® 29/32)	1.75	1.75	1.93
Magnesium Stearate	1.00	NA	0.99
Stearic Acid	NA	1.00	NA
Carbomer 941 (CARBOPOL® 971P)	NA	NA	0.99

As can be seen from Table 8, Formulation 5 comprises magnesium stearate, Formulation 6 comprises stearic acid, and Formulation 7 comprises Carbomer 941.

In vitro dissolution studies were conducted on 20 mg Citalopram HBr CR Tablets formulated according to Formulations 5, 6 and 7. Table 9 provides the *in vitro*

dissolution data of 20 mg Citalopram HBr CR Tablets formulated according to Formulations 5, 6 and 7.

Table 9: *In vitro* Dissolution Data of 20 mg Citalopram HBr CR Tablets Formulated According to Formulations 5, 6 and 7

Time (hrs)	Formulation 5 (% dissolved)	Formulation 6 (% dissolved)	Formulation 7 (% dissolved)
0	0	0	0
1	19.07	18.11	14.71
2	30.51	29.38	23.75
3	39.96	38.1	31.5
4	48.29	45.97	38.49
5	55.8	53.04	44.87
6	62.52	59.42	50.8
7	68.46	65.04	56.1
8	73.74	70.3	61.04
9	78.54	74.89	65.43
10	82.9	78.92	69.49
11	86.64	82.41	73.13
12	89.63	85.54	76.53
13	92.04	88.13	79.61
14	94.05	90.34	82.33
15	95.65	92.23	84.83
16	97.1	93.62	87.06
17	97.86	94.75	89.11
18	98.7	96	90.97
19	99.46	96.85	92.71
20	99.73	97.42	94.45
21	99.87	97.68	95.84
22	100.06	98.42	97.23
23	100.3	99.01	98.57
24	100.35	100.15	99.66

Figure 5 compares the *in vitro* dissolution profiles of 20 mg Citalopram HBr CR Tablets formulated according to Formulations 5, 6 and 7.

EXAMPLES 3 TO 5:

Various further Citalopram HBr CR Tablet formulations were made to test the influence of polymer concentration; the use of surfactant; the use of L-Tartaric acid to improve solubility and absorption; and the use of polyvinyl pyrrolidone (PVP) to

improve solubility. Each of these tests is outlined below, with accompanying dissolution data.

EXAMPLE 3:

Tables 10A and 10B provide the composition of ten Citalopram HBr CR Tablet formulations comprising different concentrations of the polymer hydroxypropyl methylcellulose (METHOCEL® K4M Premium CR) formulated to test the use of polymer and to ascertain the influence of polymer concentration on the *in vitro* dissolution profiles of the formulations.

Table 10A: Citalopram HBr CR Tablet Formulations To Test The Influence Of Polymer Concentration

	Formulation No.				
Ingredient	**5 (% w/w)**	**8 (% w/w)**	**9 (% w/w)**	**10 (% w/w)**	**11 (% w/w)**
Citalopram HBr	6.25	6.25	6.25	6.25	6.25
HPMC (METHOCEL® K4MPrem CR)	35.00	30.00	20.00	15.00	10.00
Lactose Anhydrous (DT)	48.00	53.00	63.00	68.00	73.00
MCC (AVICEL® PH 101)	8.00	8.00	8.00	8.00	8.00
PVP (KOLLIDON® 29/32)	1.75	1.75	1.75	1.75	1.75
Magnesium Stearate	1.00	1.00	1.00	1.00	1.00

Table 10B: Citalopram HBr CR Tablet Formulations To Test The Influence Of Polymer Concentration

	Formulation No.				
Ingredient	**12 (% w/w)**	**13 (% w/w)**	**14 (% w/w)**	**15 (% w/w)**	**16 (% w/w)**
Citalopram HBr	6.25	6.25	6.25	6.25	6.25
HPMC (METHOCEL® K4MPrem CR)	20.00	22.00	30.00	26.00	28.00
Lactose Anhydrous (DT)	63.00	61.00	53.00	57.00	55.00
MCC (AVICEL® PH 101)	8.00	8.00	8.00	8.00	8.00
PVP (KOLLIDON® 29/32)	1.75	1.75	1.75	1.75	1.75
Magnesium Stearate	1.00	1.00	1.00	1.00	1.00

In vitro dissolution studies were conducted on 20 mg Citalopram HBr CR Tablets formulated according to Formulations 5 and 8 to 16. Tables 11A and 11B provide the *in vitro* dissolution data of 20 mg Citalopram HBr CR Tablets formulated according to Formulations 8 to 16.

Table 11A: *In vitro* Dissolution Data of 20 mg Citalopram HBr CR Tablets Formulated According to Formulations 8 to 11

Time (hrs)	Formulation 8 (% dissolved)	Formulation 9 (% dissolved)	Formulation 10 (% dissolved)	Formulation 11 (% dissolved)
0	0	0	0	0
1	19	20	25	29
2	30	32	38	42
3	40	42	50	58
4	47	50	59	76
5	54	58	68	94
6	60	65	76	95
7	66	71	82	95
8	71	77	87	96
9	75	81	93	96
10	78	85	96	96
11	82	88	98	96
12	84	91	99	97
13	87	93	100	97
14	88	95	100	97
15	90	96	100	
16	91	96	100	
17	92	97	100	
18	93	97	100	
19	94	98		
20	94	99		
21	95	99		
22	95	98		
23	96	98		
24	96	99		

Table 11B: *In vitro* Dissolution Data of 20 mg Citalopram HBr CR Tablets Formulated According to Formulations 12 to 16

Time (hrs)	Formulation 12 (% dissolved)	Formulation 13 (% dissolved)	Formulation 14 (% dissolved)	Formulation 15 (% dissolved)	Formulation 16 (% dissolved)
0	0	0	0	0	0
1	23	23	20	22	21
2	36	36	32	35	33
3	47	47	42	45	43
4	56	56	51	55	51
5	64	64	59	63	59
6	72	71	65	69	66
7	83	78	71	75	72
8	87	83	76	80	77
9	91	87	80	86	81
10		91	84	88	84
11		94	87	91	87
12		97	90	93	90
13		99	92	95	92
14		100	94	98	94
15		101	96	99	96
16		102	97	100	97
17		103	98	101	98
18			99	102	98
19			100	102	98

Figure 6 compares the *in vitro* dissolution profiles of 20 mg Citalopram HBr CR Tablets formulated according to Formulations 5 and 8 to 16.

EXAMPLE 4:

Tables 12A, 12B and 12C provide the composition of sixteen Citalopram HBr CR Tablet formulations comprising different surfactants formulated to test the use of surfactant and to ascertain its effect on the *in vitro* dissolution profiles of the formulations.

Table 12A: Citalopram HBr CR Tablet Formulations To Test The Use of Surfactant

	Formulation No.					
Ingredient	**17** (% w/w)	**18** (% w/w)	**19** (% w/w)	**20** (% w/w)	**21** (% w/w)	**22** (% w/w)
Citalopram HBr	6.25	6.25	6.25	6.25	7.14	7.14
HPMC (METHOCEL® K4MPrem CR)	35.00	35.00	30.00	30.00	30.00	30.00
Lactose Anhydrous (DT)	46.00	46.00	48.00	48.00	47.00	47.00
MCC (AVICEL® PH 101)	8.00	8.00	8.00	8.00	8.00	8.00
PVP (KOLLIDON® 29/32)	1.75	1.75	1.75	NA	2.00	2.00
PVP (KOLLIDON® 90F)	NA	NA	NA	1.75	NA	NA
Magnesium Stearate	1.00	1.00	1.00	1.00	1.00	1.00
Bile Salt	2.00	NA	NA	NA	NA	NA
SLS	NA	2.00	NA	NA	NA	NA
Poloxamer 407 (LUTROL®-F 127)	NA	NA	5.00	NA	5.00	NA
Poloxamer 188 (LUTROL®-F 68)	NA	NA	NA	5.00	NA	NA
PEG-40 hydrogenated castor oil (CREMOPHOR® RH 40)	NA	NA	NA	NA	NA	5.00

Table 12B: Citalopram HBr CR Tablet Formulations To Test The Use of Surfactant

	Formulation No.					
Ingredient	**23** (% w/w)	**24** (% w/w)	**25** (% w/w)	**26** (% w/w)	**27** (% w/w)	**28** (% w/w)
Citalopram HBr	7.14	7.14	7.14	7.14	7.14	7.14
HPMC (METHOCEL® K4MPrem CR)	30.00	30.00	30.00	30.00	30.00	30.00
Lactose Anhydrous (DT)	47.00	47.00	47.00	47.00	47.00	47.00
MCC (AVICEL® PH 101)	8.00	8.00	8.00	8.00	8.00	8.00
PVP (KOLLIDON® 90F)	2.00	2.00	2.00	2.00	2.00	2.00
Magnesium Stearate	1.00	1.00	1.00	1.00	1.00	1.00
PEG-3350	5.00	NA	NA	NA	NA	NA
PEG-600	NA	5.00	NA	NA	NA	NA
PEG-8000	NA	NA	5.00	NA	NA	NA
Saturated polyglycolized glycerides from hydrogenated vegetable oils (GELUCIRE® 44/14)	NA	NA	NA	5.00	NA	NA
Saturated polyglycolized glycerides (GELUCIRE® 50/13)	NA	NA	NA	NA	5.00	NA
Vitamin E TPGS	NA	NA	NA	NA	NA	5.00

Table 12C: Citalopram HBr CR Tablet Formulations To Test The Use of Surfactant

	Formulation No.			
Ingredient	**29 (% w/w)**	**30 (% w/w)**	**31 (% w/w)**	**32 (% w/w)**
Citalopram HBr	7.14	7.14	7.14	7.14
HPMC (METHOCEL® K4MPrem CR)	30.00	30.00	30.00	30.00
Lactose Anhydrous (DT)	47.00	47.00	47.00	47.00
MCC (AVICEL® PH 101)	8.00	8.00	8.00	8.00
PVP (KOLLIDON® 90F)	2.00	2.00	2.00	2.00
Magnesium Stearate	1.00	1.00	1.00	1.00
LUTROL® E 1500	5.00	NA	NA	NA
Sucrose stearate (CRODESTA®-F 160)	NA	5.00	NA	NA
Mannitol	NA	NA	5.00	NA
CAPMUL® PG8	NA	NA	NA	5.00

In vitro dissolution studies were conducted on 20 mg Citalopram HBr CR Tablets formulated according to Formulations 17 to 32. Tables 13A, 13B and 13C provide the *in vitro* dissolution data of 20 mg Citalopram HBr CR Tablets formulated according to Formulations 17 to 32.

Table 13A: *In vitro* Dissolution Data of 20 mg Citalopram HBr CR Tablets Formulated According to Formulations 17 to 22

Time (hrs)	Formulation 17 (% dissolved)	Formulation 18 (% dissolved)	Formulation 19 (% dissolved)	Formulation 20 (% dissolved)	Formulation 21 (% dissolved)	Formulation 22 (% dissolved)
0	0	0	0	0	0	0
1	15	11	20	18	21	19
2	24	18	32	28	33	31
3	31	24	42	36	43	40
4	38	30	51	43	52	48
5	44	35	58	49	59	55
6	50	40	65	55	65	62
7	55	45	71	61	71	67
8	59	50	76	66	76	73
9	64	54	81	71	80	82
10	68	58	85	75	84	
11	71	61	89	79	87	
12	75	64	92	82	90	
13	78	67	94	86	92	
14	80	70	96	88	94	
15	83	73	98	91	96	
16	85	75	99	92	97	
17	86	78	100	94	98	
18	88	80	101	95	99	
19	89	82	102	97	100	
20	91	83	102	98	100	
21	92	85	102	98	101	
22	93	87	102	99	101	
23	94	88	103	99	101	
24	95	89		100	102	

Table 13B: *In vitro* Dissolution Data of 20 mg Citalopram HBr CR Tablets Formulated According to Formulations 23 to 28

Time (hrs)	Formulation 23 (% dissolved)	Formulation 24 (% dissolved)	Formulation 25 (% dissolved)	Formulation 26 (% dissolved)	Formulation 27 (% dissolved)	Formulation 28 (% dissolved)
0	0	0	0	0	0	0
1	21	21	20	21	19	19
2	32	33	31	32	30	29
3	42	44	41	41	40	38
4	51	53	50	50	48	46
5	59	60	57		55	53
6	66	67	64		62	59
7	72	73	71		68	63
8	78	79	76		74	69
9	83	83	81		78	73
10	87	87	85		83	77
11	90	90	88		86	81
12	93	92	91		89	84
13	95	94	93		92	87
14	97	96	95		94	90
15	99	97	97		96	92
16	100	98	98		98	94
17	101	99	99		100	96
18	102	100	100		102	98
19	102	100	100		104	99
20	103		100			

Table 13C: *In vitro* Dissolution Data of 20 mg Citalopram HBr CR Tablets Formulated According to Formulations 29 to 32

Time (hrs)	Formulation 29 (% dissolved)	Formulation 30 (% dissolved)	Formulation 31 (% dissolved)	Formulation 32 (% dissolved)
0	0	0	0	0
1	21	17	21	21
2	33	27	33	32
3	43	36	43	42
4	52	43	52	51
5	60	50	60	59
6	68	56	66	66
7	74	61	72	72
8	80	66	77	77
9	84	70	82	82
10	88		85	86
11	91		89	89
12	94		91	91
13	96		94	93
14	97		95	95
15	98		97	96
16	99		98	98
17	100		98	99
18	101		99	100
19	101		99	101
20	101		100	102

Figure 7 compares the *in vitro* dissolution profiles of 20 mg Citalopram HBr CR Tablets formulated according to Formulations 17 to 32.

EXAMPLE 5:

Table 14 provides the composition of a Citalopram HBr CR Tablet formulation comprising L-Tartaric acid formulated to test the use of L-Tartaric acid and to ascertain its effect on the *in vitro* dissolution profile of the formulation.

Table 14: Citalopram HBr CR Tablet Formulation to Test the Use of L-Tartaric Acid	
Ingredient	**Formulation 33 (% w/w)**
Citalopram HBr	6.25
HPMC (METHOCEL® K4MPrem CR)	35.00
Lactose Anhydrous (DT)	43.00
MCC (AVICEL® PH 101)	8.00
PVP (KOLLIDON® 29/32)	1.75
Magnesium Stearate	1.00
L-Tartaric Acid	5

In vitro dissolution studies were conducted on 20 mg Citalopram HBr CR Tablets formulated according to Formulations 33. Table 15 provides the *in vitro* dissolution data of 20 mg Citalopram HBr CR Tablets formulated according to Formulation 33.

Table 15: *In vitro* Dissolution Data of 20 mg Citalopram HBr CR Tablets Formulated According to Formulation 33	
Time (hrs)	**Formulation 33 (% dissolved)**
0	0
1	21
2	33
3	43
4	52
5	59
6	66
7	72
8	78
9	82
10	87
11	90
12	93
13	95
14	97
15	99
16	100
17	100
18	101
19	101
20	102

Figure 8 compares the *in vitro* dissolution profiles of 20 mg Citalopram HBr Tablets formulated according to Formulations 5 and 33.

EXAMPLE 6:

Table 16 provides the composition of two Citalopram HBr CR Tablet formulations comprising different concentrations of polyvinyl pyrrolidone (KOLLIDON® 90F) formulated to test an increase in the amount of polyvinyl pyrrolidone concentration and to determine its effect on solubility.

Table 16: Citalopram HBr CR Tablet Formulations to Test the Increase in the Amount of PVP

	Formulation No.	
Ingredient	**34 (% w/w)**	**35 (% w/w)**
Citalopram HBr	6.25	6.25
HPMC (METHOCEL® K4MPrem CR)	30.00	30.00
Lactose Anhydrous (DT)	53.00	53.00
MCC (AVICEL® PH 101)	7.25	10.25
PVP (KOLLIDON® 90F)	2.5	3.5
Magnesium Stearate	1.00	1.00

In vitro dissolution studies were conducted on 20 mg Citalopram HBr CR Tablets formulated according to Formulations 34 and 35. Table 17 provides the *in vitro* dissolution data of 20 mg Citalopram HBr CR Tablets formulated according to Formulations 34 and 35.

Table 17: *In vitro* Dissolution Data of 20 mg Citalopram HBr CR Tablets Formulated According to Formulations 34 and 35

Time (hrs)	Formulation 34 (2.5% PVP) (% dissolved)	Formulation 35 (3.5% PVP) (% dissolved)
0	0	0
1	21	21
2	33	33
3	43	42
4	52	51
5	60	59
6	66	65
7	72	71
8	77	76
9	82	80
10	85	84
11	89	87
12	91	90
13	94	92
14	96	94
15	97	96
16	98	97
17	99	98
18	100	99
19	100	99
20	101	99
21		100

Figure 9 compares the *in vitro* dissolution profiles of 20 mg Citalopram HBr CR Tablets formulated according to Formulations 34 and 35.

EXAMPLE 7:

Table 18 provides the composition of two Citalopram HBr CR Tablet formulations; one formulated with Poloxamer 407 (PLURONIC® F127) (Formulation 36) and one formulated with PEG-8000 (Formulation 37).

Table 18: Citalopram HBr CR Tablet Formulations to Compare the Effect of Poloxamer 407 vs. PEG-8000

Core Ingredients	**Formulation 36 (g)**	**Formulation 37 (g)**
Citalopram HBr	187.5	187.5
HPMC (METHOCEL® PremK4M CR)	900.0	780.0
Lactose Anhydrous (DT)	1440.0	1560.0
MCC (AVICEL® PH 101)	217.5	217.5
Poloxamer 407 (PLURONIC® F127)	45.0	NA
PEG 8000	NA	150.0
PVP (KOLLIDON® 90F)	75.0	75.0
Magnesium stearate	30.0	30.0
Water*	-	-
ISP*	-	-
Coating Ingredients		
OPADRY® II White Y-22-7719	60	60

* Alcohol and Water are not considered as part of the theoretical batch size since they are evaporated during drying of the wet granulation.

In vitro dissolution studies were conducted on 20 mg Citalopram HBr CR Tablets formulated according to Formulations 36 and 37. Table 19 provides the *in vitro* dissolution data of 20 mg Citalopram HBr CR Tablets formulated according to Formulations 36 and 37.

Table 19: *In vitro* Dissolution Data of 20 mg Citalopram HBr CR Tablets Formulated According to Formulations 36 and 37

Time (Hrs)	Formulation 36 (Poloxamer 407)	Formulation 37 (PEG-8000)
0	0	0
1	18	20
2	28	31
3	36	41
4	43	50
5	49	57
6	55	64
7	61	71
8	66	76
9	71	81
10	75	85
11	79	88
12	82	91
13	86	93
14	88	95
15	91	97
16	92	98
17	94	99
18	95	100
19	97	100
20	98	100
21	98	
22	99	
23	99	
24	100	

Figure 10 compares the *in vitro* dissolution profiles of 20 mg Citalopram HBr CR Tablets formulated according to Formulations 36 and 37.

A randomized, three-way, single-dose, fasting, cross-over study was conducted to evaluate the bioavailability of 20 mg Citalopram HBr CR Tablets formulated according to Formulations 36 and 37 versus the reference product, 20 mg CELEXA™ tablets (Lundbeck Canada Inc. - Lot #: A304; Expiry Date: 04/MR) under fasting conditions in normal, healthy, non-smoking male volunteers. There was a one-(1) week washout period between the three study periods. Following each drug administration,

blood samples were taken at 0.0 (pre-drug), 1.0, 9.0,3.0,3.5,4.0,4.5,5.0,5.5,6.0, 8.0,10.0,12.0,16.0,24.0,36.0,48.0,72.0, 96.0,120.0 and 144.0 hours post-drug administration. Upon completion of the clinical portion of the study, all plasma samples were transferred to the analytical facility for analysis. Fifteen (15) qualified subjects and three (3) alternates were entered into the study. Laboratory analysis, and pharmacokinetic and statistical analyses were conducted on the first fifteen (15) evaluable subjects in a balanced group who completed the study.

Table 20 provides the mean plasma Citalopram concentrations (ng/ml) over time after a single dose of one 20 mg Citalopram HBr Tablet formulated according to Formulation 36 or 37 or after a single dose of one 20 mg CELEXA™ tablet under fasting conditions.

Table 20: Mean Plasma Citalopram Concentrations (n=15)

Sample Time (Hours)	Formulation 36 1 x 20 mg (ng/ml)	Formulation 37 1 x 20 mg (ng/ml)	CELEXA™ 1 x 20 mg (ng/ml)
0.00	0.74 ± 0.69	0.77 ± 0.92	0.51 ± 0.41
1.00	0.87 ± 0.76	0.91 ± 0.96	3.16 ± 2.36
2.00	2.18 ± 0.97	2.30 ± 1.10	11.77 ± 3.69
3.00	4.66 ± 1.78	4.78 ± 1.95	16.94 ± 3.43
3.50	5.85 ± 1.69	6.38 ± 2.40	16.89 ± 2.98
4.00	7.67 ± 2.80	7.78 ± 3.03	17.81 ± 3.30
4.50	8.75 ± 2.65	8.99 ± 3.20	18.29 ± 2.81
5.00	10.93 ± 2.99	11.44 ± 4.65	18.82 ± 3.30
5.50	12.45 ± 4.23	13.76 ± 5.18	18.87 ± 2.78
6.00	13.45 ± 3.94	14.56 ± 4.47	19.22 ± 2.70
8.00	14.72 ± 3.36	15.47 ± 3.42	17.88 ± 2.76
10.00	14.20 ± 3.07	15.30 ± 3.25	16.59 ± 2.88
12.00	14.41 ± 3.26	15.32 ± 3.56	15.69 ± 2.62
16.00	12.79 ± 2.81	13.60 ± 3.20	13.51 ± 1.66
24.00	10.14 ± 2.80	10.62 ± 2.97	11.04 ± 1.78
36.00	8.76 ± 2.95	9.29 ± 3.02	9.14 ± 1.77
48.00	6.69 ± 2.38	7.26 ± 2.61	7.15 ± 1.67
72.00	4.19 ± 1.74	4.35 ± 1.55	4.49 ± 1.19
96.00	2.82 ± 1.42	2.98 ± 1.33	3.05 ± 0.98
120.00	1.99 ± 1.13	1.92 ± 0.99	2.11 ± 0.81
144.00	1.43 ± 0.94	1.47 ± 0.94	1.52 ± 0.67

Figure 11 illustrates the mean plasma Citalopram concentrations (ng/ml) over time after a single dose of one 20 mg Citalopram HBr CR Tablet formulated according to Formulation 36 or 37 or after a single dose of one product 20 mg CELEXA™ tablet under fasting conditions.

Table 21 provides the mean pharmacokinetic parameters for plasma Citalopram after a single dose of one 20 mg Citalopram HBr CR Tablet formulated according to Formulation 36 or 37 or after a single dose of one 20 mg CELEXA™ tablet under fasting conditions.

Table 21: Mean Pharmacokinetic Parameters for Plasma Citalopram (n=15)			
	Geometric Mean Arithmetic Mean (%C.V.)		
Parameter	**Formulation 36 1 x 20 mg**	**Formulation 37 1 x 20 mg**	**CELEXA™ 1 x 20 mg**
$AUC_{(0 - t\ hours)}$ (ng.hr/ml)	748.98 785.59 (32.94)	799.78 830.67 (31.78)	883.21 896.80 (18.48)
$AUC_{(0 - infinity)}$ (ng.hr/ml)	832.37 886.63 (39.08)	890.39 942.57 (40.05)	984.00 1007.02 (22.89)
C_{max} (ng/ml)	15.12 15.42 (20.08)	16.22 16.62 (24.62)	19.93 20.13 (14.28)
T_{max} (hours)**	10.00 (2.26)	8.00 (2.26)	5.50 (1.98)
$t_{1/2}$ (hours)*	43.71 (20.63)	45.68 (28.77)	46.11 (28.60)
K_{el} ($hour^{-1}$)*	0.016 (18.240)	0.016 (21.295)	0.016 (21.932)

*These are arithmetic means (%.C.V.)
**This is median (±SD)

EXAMPLE 8:

Table 22 provides the composition of a Citalopram HBr CR Tablet formulation (Formulation 38) based on the ingredients in Formulation 5 with adjustments to the amounts of the rate controlling polymer, HPMC and Lactose Anhydrous (DT).

Table 22: Citalopram HBr CR Tablet Formulation	
Ingredients	**Formulation 38 (% w/w)**
Citalopram HBr	6.31
HPMC (METHOCEL® K4MPrem CR)	27.31
Lactose Anhydrous (DT)	56.56
MCC (AVICEL® PH 101)	8.08
PVP (KOLLIDON® 29/32)	NA
PVP (KOLLIDON® K90F)	1.77
Magnesium Stearate	0.99
Isopropyl Alcohol*	--

*Evaporated

EXAMPLE 9:

Table 23 provides the composition of a Citalopram HBr CR Tablet formulation (Formulation 39) based on the ingredients in Formulation 38 with only minor adjustment in the amounts of HPMC and Lactose Anhydrous (DT).

Table 23: Citalopram HBr CR Tablet Formulation

Ingredients	Formulation 39 (% w/w)
Citalopram HBr	6.31
HPMC (METHOCEL® K4MPrem CR)	26.51
Lactose Anhydrous (DT)	57.31
MCC (AVICEL® PH 101)	8.00
PVP (KOLLIDON® K90F)	1.77
Magnesium Stearate	0.99
Isopropyl Alcohol	*

In vitro dissolution studies were conducted on 20 mg Citalopram HBr CR Tablets formulated according to Formulation 39. Table 24 provides the *in vitro* dissolution data of 20 mg Citalopram HBr CR Tablets formulated according to Formulation 39.

Table 24: Citalopram HBr CR Tablet Formulation

Time (Hrs)	Formulation 39 (% dissolved)
0	0
1	23.17
2	35.81
3	46.01
4	54.94
5	62.74
6	69.62
7	75.53
8	80.66
9	85.04
10	88.75
11	92.03
12	94.76
13	97.07
14	98.82
15	100.22
16	101.46
17	102.55
18	103.44
19	104.36
20	105.23

Figure 12 illustrates the *in vitro* dissolution profile of 20 mg Citalopram HBr CR Tablets formulated according to Formulation 39.

A randomized, two-way, single-dose, blinded, cross-over design study was conducted to evaluate the bioavailability of 20 mg Citalopram HBr CR Tablets formulated according to Formulation 39 relative to 20 mg CELEXA™ tablets under fasting conditions in normal, healthy, non-smoking male volunteers. The study periods were separated by a four- (4) week washout period. Blood sampling for drug content analysis was carried out at 0.0 (pre-drug), 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 10.0, 12.0, 14.0, 16.0, 20.0. 24.0, 36.0, 48.0, 72.0, 96.0, 120.0, 144.0. 168.0, 192.0, 216.0, 240.0 hours post-drug administration. Upon completion of the clinical portion of the study, all plasma samples were delivered to the analytical facility for the determination of the

concentrations of Citalopram and its metabolites, Desmethylcitalopram (DCT) and Didesmethylcitalopram (DDCT) in the samples. Sixty-two (62) qualified subjects were entered into the study. Pharmacokinetic and statistical analyses were conducted on fifty (50) evaluable subjects that completed the study.

Table 25 provides the mean plasma Citalopram concentrations (ng/ml) over time after a single dose of one 20 mg Citalopram HBr CR Tablet formulated according to Formulation 39 or after a single dose of one 20 mg CELEXA™ tablet under fasting conditions.

Table 25: Mean Plasma Citalopram Concentrations (n=50)

Time (hrs)	Formulation 39 1 x 20 mg (ng/ml)	CELEXA™ 1 x 20 mg (ng/ml)
0	0.00 ± 0.00	0.00 ± 0.00
1	0.21 ± 0.24	2.59 ± 2.13
1.5	0.91 ± 0.56	7.98 ± 5.00
2	2.04 ± 1.10	12.55 ± 5.37
2.5	3.46 ± 1.47	15.83 ± 5.32
3	5.00 ± 1.79	17.62 ± 5.08
4	8.82 ± 3.35	19.50 ± 4.54
5	12.98 ± 3.96	19.98 ± 4.01
6	16.17 ± 4.86	20.15 ± 4.06
7	17.57 ± 4.83	19.63 ± 3.92
8	17.60 ± 4.73	18.96 ± 3.74
10	17.07 ± 4.41	17.62 ± 3.66
12	16.35 ± 4.13	16.09 ± 3.43
14	15.73 ± 4.02	15.76 ± 3.28
16	14.27 ± 3.86	14.62 ± 3.39
20	12.94 ± 3.34	13.29 ± 3.01
24	11.73 ± 3.11	11.74 ± 2.81
36	9.98 ± 3.07	9.95 ± 2.64
48	8.09 ± 2.59	8.05 ± 2.29
72	5.11 ± 1.97	5.08 ± 2.08
96	3.53 ± 1.66	3.51 ± 1.65
120	2.53 ± 1.34	2.46 ± 1.46
144	1.78 ± 1.01	1.80 ± 1.23
168	1.31 ± 0.85	1.27 ± 0.86
192	0.95 ± 0.67	0.94 ± 0.70
216	0.71 ± 0.58	0.67 ± 0.57
240	0.50 ± 0.46	0.51 ± 0.48

Figure 13 illustrates the mean plasma Citalopram concentrations (ng/ml) over time after a single dose of one 20 mg Citalopram HBr CR Tablet formulated according to Formulation 39 or after a single dose of one 20 mg CELEXA™ tablet under fasting conditions.

Table 26 provides the mean pharmacokinetic parameters for plasma Citalopram after a single dose of one 20 mg Citalopram HBr CR Tablet formulated according to Formulation 39 or after a single dose of one 20 mg CELEXA™ tablet.

Table 26: Mean Pharmacokinetic Parameters for Plasma Citalopram (n=50)			
	Geometric Mean Arithmetic Mean (±SD)		Ratio of Geometric Means (%) Test/Reference
Parameter	**Formulation 39 1 x 20 mg**	**CELEXA™ 1 x 20 mg**	
$AUC_{(0-t\ hours)}$ (ng.hr/ml)	953.60 1016.14±353.93	1015.36 1066.22± 341.50	94%
$AUC_{(0-24\ hours)}$ (ng.hr/ml)	295.89 305.41±76.53	354.25 360.43±73.33	84%
$AUC_{(0-infinity)}$ (ng.hr/ml)	1002.55 1073.17±388.23	1056.69 1115.12±381.10	94%
C_{max} (ng/ml)	17.96 18.56±4.64	21.22 21.64±4.19	85%
T_{max} (hours)**	8.00±1.81	6.00±2.46	N/A
t½ (hours)*	52.63±11.25	53.23±11.21	N/A
K_{el} ($hour^{-1}$)*	0.014±0.003	0.014±0.003	N/A

*These are arithmetic means (±SD)
**This is median (±SD)

Table 27 provides the comparison of plasma Citalopram data after a single dose of one 20 mg Citalopram HBr CR Tablet formulated according to Formulation 39 versus after a single dose of one 20 mg CELEXA™ tablet under fasting conditions (Uncorrected).

Table 27: Comparison of Plasma Citalopram Data (Formulation 39 vs. CELEXA™ - Uncorrected)			
	$AUC_{(0-t\ hours)}$	**$AUC_{(0-infinity)}$**	**C_{max}**
90% Geometric C.I.[1]	90%-97%	91%-98%	81%-88%
Ratio of Means[2]	94%	94%	85%
95% Geometric C.I.[3]	90% - 98%	90%- 98%	80% -89%
Westlake's C.L.[4]	7%	7%	17%

1. 90% Geometric Confidence interval using log-transformed data and CELEXA™ (Lundbeck Canada Inc.) as the reference.
2. Calculated using geometric means according to the formula: $e^{(Formulation\ 39)*(CELEXA™)}$ x 100%.
3. 95% Geometric Confidence interval using log-transformed data and CELEXA™ (Lundbeck Canada Inc.) as the reference.
4. Confidence Limit using Westlake's method and CELEXA™ (Lundbeck Canada Inc.) as the reference.

Table 28 provides the comparison of plasma Citalopram data after a single dose of one 20 mg Citalopram HBr CR Tablet formulated according to Formulation 39 versus

after a single dose of one 20 mg CELEXA™ tablet under fasting conditions (Potency Corrected).

Table 28: Comparison of Plasma Citalopram Data (Formulation 39 vs. CELEXA™ - Potency Corrected)

	$AUC_{(0-t\ hours)}$	C_{max}
90% Geometric C.I.[1]	86% - 92%	77% - 84%
Ratio of Means[2]	89%	80%

1. 90% Geometric Confidence interval using log-transformed data and CELEXA™ (Lundbeck Canada Inc.) as the reference.
2. Calculated using geometric means according to the formula: $e^{(Formulation\ 39)*(CELEXA™)} \times 100\%$.

Table 29 provides the mean plasma Desmethylcitalopram concentrations (ng/ml) over time after a single dose of one 20 mg Citalopram HBr CR Tablet formulated according to Formulation 39 or after a single dose of one 20 mg CELEXA™ tablet under fasting conditions.

Table 29: Mean Plasma Desmethylcitalopram Concentrations (n=50)

Time (hrs)	Formulation 39 1 x 20 mg (ng/ml)	CELEXA™ 1 x 20 mg (ng/ml)
0	0	0
1	0.02	0.34
1.5	0.09	0.8
2	0.2	1.19
2.5	0.32	1.39
3	0.45	1.51
4	0.76	1.75
5	1.13	1.92
6	1.36	2.07
7	1.62	2.22
8	1.74	2.32
10	2.01	2.52
12	2.1	2.47
14	2.17	2.55
16	2.15	2.5
20	2.16	2.56
24	2.08	2.37
36	2.37	2.57
48	2.34	2.48
72	1.98	1.98
96	1.61	1.64
120	1.28	1.27
144	1.01	0.99
168	0.77	0.76
192	0.61	0.61
216	0.49	0.48
240	0.39	0.38

Figure 14 illustrates the mean plasma Desmethylcitalopram concentrations (ng/ml) over time after a single dose of one 20 mg Citalopram HBr CR Tablet formulated according to Formulation 39 or after a single dose of one 20 mg CELEXA™ tablet under fasting conditions.

Table 30 provides the mean pharmacokinetic parameters for plasma Desmethylcitalopram after a single dose of one 20 mg Citalopram HBr CR Tablet

formulated according to Formulation 39 or after a single dose of one 20 mg CELEXA™ tablet under fasting conditions.

Table 30: Mean Pharmacokinetic Parameters for Plasma Desmethylcitalopram (n=50)

	Geometric Mean Arithmetic Mean (±SD)		Ratio of Geometric Means (%) Test/Reference
Parameter	**Formulation 39 1 x 20 mg**	**CELEXA™ 1 x 20 mg**	
$AUC_{(0-t\ hours)}$ (ng hr/ml)	299.08 310.24±82.79	319.39 328.90±78.49	94%
$AUC_{(0-24\ hours)}$ (ng.hr/ml)	298.87 310.24±82.79	320.54 328.90±78.49	77%
$AUC_{(0-infinity)}$ (ng.hr/ml	339.75 356.61±110.33	359.42 373.26±104.14	94%
C_{max} (ng/ml)	2.46 2.55±0.65	2.76 2.86±0.75	89%
T_{max} (hours)**	36.00±14.72	20.00±19.03	N/A
$t_{1/2}$ (hours)*	70.20±24.99	69.01±28.32	N/A
K_{el} ($hour^{-1}$)*	0.011±0.003	0.011±0.003	N/A

*These are arithmetic means (±SD)
**This is median (±SD)

Table 31 provides the comparison of plasma Desmethylcitalopram data after a single dose of one 20 mg Citalopram HBr CR Tablet formulated according to Formulation 39 versus after a single dose of one 20 mg CELEXA™ tablet under fasting conditions (Uncorrected).

Table 31: Comparison of Plasma Desmethylcitalopram Data (Formulation 39 vs. CELEXA™ - Uncorrected)			
	AUC (0 - t hours)	**AUC** (O - infinity)	C_{max}
90% Geometric C.I.[1]	90%-97%	91%-98%	85%–93%
Ratio of Means[2]	94%	94%	89%
95% Geometric C.I.[3]	90% - 98%	90%- 99%	85% -93%
Westlake's C.L.[4]	8%	7%	14%

1. 90% Geometric Confidence interval using log-transformed data and CELEXA™ (Lundbeck Canada Inc.) as the reference.
2. Calculated using geometric means according to the formula: $e^{(Formulation\ 39)*(CELEXA™)} \times 100\%$.
3. 95% Geometric Confidence interval using log-transformed data and CELEXA™ (Lundbeck Canada Inc.) as the reference.
4. Confidence Limit using Westlake's method and CELEXA™ (Lundbeck Canada Inc.) as the reference.

Table 32 provides the comparison of plasma Desmethylcitalopram data after a single dose of one 20 mg Citalopram HBr CR Tablet formulated according to Formulation 39 versus after a single dose of one 20 mg CELEXA™ tablet under fasting conditions (Potency Corrected).

Table 32: Comparison of Plasma Desmethylcitalopram Data (Formulation 39 vs. CELEXA™ - Potency Corrected)		
	AUC (0 - t hours)	C_{max}
90% Geometric C.I.[1]	86% - 92%	81% - 88%
Ratio of Means[2]	89%	84%

1. 90% Geometric Confidence interval using log-transformed data and CELEXA™ (Lundbeck Canada Inc.) as the reference.
2. Calculated using geometric means according to the formula: $e^{(Formulation\ 39)*(CELEXA™)} \times 100\%$.

Table 33 provides the mean plasma Didesmethylcitalopram concentrations (ng/ml) over time after a single dose of one 20 mg Citalopram HBr CR Tablet formulated according to Formulation 39 or after a single dose of one 20 mg CELEXA™ tablet under fasting conditions.

Table 33: Mean Plasma Didesmethylcitalopram Concentrations (n=50)

Time (hrs)	Formulation 39 1 x 20 mg (ng/ml)	CELEXA™ 1 x 20 mg (ng/ml)
0	0	0
1	0	0.01
1.5	0	0.03
2	0	0.05
2.5	0	0.07
3	0.04	0.09
4	0.03	0.11
5	0.06	0.12
6	0.09	0.14
7	0.11	0.16
8	0.13	0.19
10	0.18	0.24
12	0.21	0.24
14	0.23	0.32
16	0.25	0.31
20	0.27	0.35
24	0.29	0.35
36	0.39	0.46
48	0.46	0.51
72	0.49	0.5
96	0.48	0.48
120	0.43	0.44
144	0.38	0.37
168	0.31	0.3
192	0.27	0.25
216	0.22	0.21
240	0.18	0.17

Figure 15 illustrates the mean plasma Didesmethylcitalopram concentrations (ng/ml) over time after a single dose of one 20 mg Citalopram HBr CR Tablet formulated according to Formulation 39 or after a single dose of one 20 mg CELEXA™ tablet under fasting conditions.

Table 34 provides the mean pharmacokinetic parameters for plasma Didesmethylcitalopram after a single dose of one 20 mg Citalopram HBr CR Tablet

formulated according to Formulation 39 or after a single dose of one 20 mg CELEXA™ tablet under fasting conditions.

Table 34: Mean Pharmacokinetic Parameters for Plasma Didesmethylcitalopram (n=50)

	Geometric Mean Arithmetic Mean (±SD)		Ratio of Geometric Means (%) Test/Reference
Parameter	**Formulation 39 1 x 20 mg**	**CELEXA™ 1 x 20 mg**	
$AUC_{(0 - t\ hours)}$ (ng hr/ml)	74.43 82.96±45.63	64.67 85.22±49.10	99%
$AUC_{(0-24\ hours)}$ (ng.hr/ml)	3.49 4.17±2.66	3.63 5.48±3.83	80%
$AUC_{(0 - infinity)}$ (ng.hr/ml)	111.92 356.61±110.33	103.74 373.26±104.14	98%
C_{max} (ng/ml)	0.50 0.57±0.32	0.49 0.60±0.37	99%
T_{max} (hours)**	84.00±37.03	72.00±35.04	N/A
$t_{1/2}$ (hours)*	84.90±29.41	97.78±60.73	N/A
K_{el} ($hour^{-1}$)	0.009±0.003	0.009±0.003	N/A

*These are arithmetic means (±SD)

**This is median (±SD)

Table 35 provides the comparison of plasma Didesmethylcitalopram data after a single dose of one 20 mg Citalopram HBr CR Tablet formulated according to Formulation 39 versus after a single dose of one 20 mg CELEXA™ tablet under fasting conditions (Uncorrected).

Table 35: Comparison of Plasma Didesmethylcitalopram Data (Formulation 39 vs. CELEXA™ - Uncorrected)			
	AUC (0 - t hours)	AUC (0 - infinity)	C_{max}
90% Geometric C.I.[1]	94%-103%	89%-108%	93%–105%
Ratio of Means[2]	99%	98%	99%
95% Geometric C.I.[3]	93% 104%	87%-110%	91%-107%
Westlake's C.L.[4]	7%	10%	10%

1. 90% Geometric Confidence interval using log-transformed data and CELEXA™ (Lundbeck Canada Inc.) as the reference.
2. Calculated using geometric means according to the formula: $e^{(Formulation\ 39)'(CELEXA™)} \times 100\%$.
3. 95% Geometric Confidence interval using log-transformed data and CELEXA™ (Lundbeck Canada Inc.) as the reference.
4. Confidence Limit using Westlake's method and CELEXA™ (Lundbeck Canada Inc.) as the reference.

Table 36 provides the comparison of plasma Didesmethylcitalopram data after a single dose of one 20 mg Citalopram HBr CR Tablet formulated according to Formulation 39 versus after a single dose of one 20 mg CELEXA™ tablet under fasting conditions (Potency Corrected).

Table 36: Comparison of Plasma Didesmethylcitalopram Data (Formulation 39 vs. CELEXA™ - Potency Corrected)		
	$AUC_{(0 - t\ hours)}$	C_{max}
90% Geometric C.I.[1]	89% - 98%	88%-100%
Ratio of Means[2]	94%	94%

1. 90% Geometric Confidence interval using log-transformed data and CELEXA™ (Lundbeck Canada Inc.) as the reference.
2. Calculated using geometric means according to the formula: $e^{(Formulation\ 39)'(CELEXA™)} \times 100\%$.

Based on the 20 mg Citalopram HBr CR Tablet formulated according to Formulation 39 to the 20 mg CELEXA™ tablet comparison of Citalopram and its metabolites, Desmethylcitalopram (DCT) and Didesmethylcitalopram (DDCT) plasma data, the 90% geometric confidence intervals for $AUC_{(0-t)}$, $AUC_{(0-infinity)}$ and C_{max} were found to be within the 80% - 125% range and, therefore, the 20 mg Citalopram HBr CR Tablets formulated according to Formulation 39 are bioequivalent to the 20 mg CELEXA™ tablets. Also, based on the general linear model for T_{max}, there is a significant difference between the 20 mg Citalopram HBr CR Tablets formulated

according to Formulation 39 and the 20 mg CELEXA™ tablets (Lundbeck Canada Inc., Lot Number: A 304; Expiry Dam: 04/MR) under fasting conditions.

The potency correction for the actual drug strengths had the effect of shifting the uncorrected data to lower values, without affecting the conclusions for bioequivalence, in the measured data. That is, for the $AUC_{(0-t)}$, the 90% geometric confidence intervals (C.I.),were shifted from 90%-97% to 86%-92%, and the relative ratio of the means was shifted from 94% to 89%. Similarly, for the C_{max} parameter, the relative ratio of the means was reduced from 85% to 80%. Thus, the potency corrected data still meets the standards for bioequivalence for both the measured and potency corrected data.

EXAMPLE 10:

Citalopram HBr was provided by two different suppliers (Supplier 1 and Supplier 2). Particle size measurements were conducted on Citalopram HBr provided by Supplier 1 and Supplier 2. Tables 37A and 37B provide the particle size measurement data of Citalopram HBr provided by Supplier 1 and Supplier 2, respectively.

Table 37A: Particle Size Measurement Data of Citalopram HBr Provided by Supplier 1					
Condition					
T% (He-Ne):	97.7%	Dist. Form:	Std.	Sampling times:	10
Trigger:	NO	R.R. Index:	1.64-0.00i		
Shaker:	80	Air P.:	HIGH	Vacuum:	ON
Format					
Dist. Base:	Volume	Scalling:	Auto	Axis:	LogX – Linear Y
Data					
Median:	7.781µm	SP. Area:	10290cm²/cm²	S.D.:	4.704µm
Mode:	8,253µm	Mean:	8.569µm		
C.V.:	54.90%				
Span:	(D 20.0-D 10.0)/D50=0.172				
Dia.on %	(90.0%):	14.874µm	% on Dia.	(1.000µm):	0.7%
Dia.on %	(70.0%):	10.295µm	% on Dia.	(5.000µm):	23.4%
Dia.on %	(35.0%):	6.212µm	% on Dia.	(10.000µm):	68.1%
Dia.on %	(20.0%):	4.606µm	% on Dia.	(15.000µm):	90.4%
Dia.on %	(10.0%):	3.267µm	% on Dia.	(20.000µm):	97.6%

Table 37B: Particle Size Measurement Data of Citalopram HBr Provided by Supplier 2			
System Details			
Dispersed in air			
1% - 12% Obscuration, 1000 sweeps (100, 1 000 mm lenses)			
Range Lens: 100 mm	Beam Length: 10.00 mm	Sampler: MS64	Obscuration: 6.1%
Presentation: 2RHA	[Particle R.I = (1.4500, 0.1000);	Dispersant R.I. = 1.000)]	
Analysis Model: Polydisperse			Residual: 0.204%
Modifications: Active -	Blended with Record 3;		
Result Statistics			
Distribution Type: Volume	Concentration = 0.0005 % Vol		Uniformity = 3.518E + 01
D (v. 0.1) = 1.62 µm	Median, D (v, 0.5) = 7.27 µm		D (V, 0.9) = 1191.10 µm
Mean, D [4, 3] = 259.27 µm	Span = 1.637E + 02		

Table 38 provides the composition of two Citalopram HBr CR Tablet formulations wherein the Citalopram HBr is provided by two different suppliers [Formulation 40 (Supplier 1) and Formulation 41 (Supplier 2)].

Table 38: Citalopram HBr CR Tablet Formulations		
Ingredients	**Formulation 40 (Supplier 1) (% w/w)**	**Formulation 41 (Supplier 2) (% w/w)**
Citalopram HBr	6.25	6.25
HPMC (K4MPrem CR)	26.25	26.25
Lactose Anhydrous	56.75	56.75
MCC	8.00	8.00
PVP (90F)	1.75	1.75
Magnesium Stearate	1.00	1.00

In vitro dissolution studies were conducted on 20 mg Citalopram HBr CR Tablets formulated according Formulations 40 and 41. Table 39 provides the *in vitro* dissolution data of 20 mg Citalopram HBr CR Tablets formulated according to Formulations 40 and 41.

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Table 39: *In vitro* Dissolution Data of 20 mg Citalopram HBr Tablets Formulated According to Formulations 40 and 41

Time (hrs)	Formulation 40 (Supplier 1) (% dissolved)	Formulation 41 (Supplier 2) (% dissolved)
0	0	0
1	21.46	16.8
2	34.47	30.6
3	45.28	40.2
4	54.69	49.6
5	63.11	57.3
6	70.44	64.4
7	76.49	71
8	81.94	77.3
9	86.59	82.6
10	90.43	87.1
11	93.66	91
12	96.33	94.4
13	98.54	97.2
14	100.51	99.4
15	103.68	101.1
16	104.46	102.5
17	104.04	103.8
18	104.33	104.3
19	104.49	104.2
20	104.92	105.2

Figure 16 compares the *in vitro* dissolution profiles of 20 mg Citalopram HBr CR Tablets formulated according to Formulations 40 and 41.

EXAMPLE 11:

Particle size measurements were conducted on Paroxetine HCl. Table 40 provides the particle size measurement data of Paroxetine HCl.

Table 40: Particle Size Measurement Data of Paroxetine HCl

System Details

Dispersed in air
1% - 12% Obscuration, 1 000 sweeps
Range Lens: 100 mm Beam Length: 10.00 mm Sampler: MS64 Obscuration: 6.9%
Presentation: 2RHA [Particle R.I = (1.4500, 0.1000); Dispersant R.I. = 1.000)]
Analysis Model: Polydisperse Residual: 0.204%
Modifications: None

Result Statistics

Distribution Type: Volume	Concentration = 0.0005 % Vol	Uniformity = 1.980E + 00
D (v. 0.1) = 0.85 µm	Median, D (v. 0.5) = 4.44 µm	D (v, 0.9) = 16.56 µm
Mean, D [4, 3] = 11.02 µm	Span = 3.541E + 00	

Table 41 provides the composition of one Paroxetine HCl CR Tablet formulation (Formulation 42).

Table 41: Paroxetine HCl CR Tablet Formulation

Ingredients	**Formulation 42 (% w/w)**
Paroxetine HCl	5.6
HPMC (K4MPrem CR)	26.43
Lactose Anhydrous	57.14
MCC	8.05
PVP (90F)	1.76
Magnesium Stearate	1.02

In vitro dissolution studies were conducted on 20 mg Paroxetine HCl CR Tablets formulated according to Formulation 42. Table 42 provides the *in vitro* dissolution data of 20 mg Paroxetine HCl CR Tablets formulated according to Formulation 42.

Table 42: *In vitro* Dissolution Data of 20 mg Paroxetine HCl CR Tablets Formulated According to Formulation 42	
Time (Hrs)	**Formulation 42 (% dissolved)**
0	0
1	12.8
2	22.59
3	31.59
4	39.47
5	46.8
6	53.6
7	59.9
8	65.66
9	71.12
10	76.17
11	80.97
12	85.58
13	90.08
14	94.38
15	98.56
16	102.49

Figure 17 provides the *in vitro* dissolution profile of 20 mg Paroxetine HCl CR Tablets formulated according to Formulation 42.

A randomized, two-way, single-does, open-label, cross-over pilot study was conducted to compare the rate and extent of absorption of the test product, 20 mg Paroxetine HCl CR Tablets versus the reference product, 20 mg PAXIL® Tablets (GlaxoSmithKline) under fasting conditions. The two study periods were separated by a three-week washout period. Twenty-four (24) blood samples were drawn for drug content analysis at 0.0 (pre-drug), 1.0, 2.0, 3.0, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 8.0, 10.0, 12.0, 14.0, 16.0, 24.0, 36.0, 48.0, 60.0, 72.0, 96.0, and 120.0 hours post-drug administration during each study period. Upon completion of the clinical portion of the study, all plasma samples were delivered to the analytical facility for the determination Paroxetine concentrations. Thirteen (13) qualified subjects were entered into the study.

Pharmacokinetic and statistical analyses were conducted on the first twelve (12) evaluable subjects that completed the study.

Table 43 provides the mean plasma Paroxetine concentrations (ng/ml) over time after a single dose of one 20 mg Paroxetine HCl CR Tablet formulated according to Formulation 42 or after a single dose of one 20 mg PAXIL® tablet under fasting conditions.

Table 43: Mean Plasma Paroxetine Concentrations (n=12)

Time (hours)	Formulation 42 1 x 20 mg (ng/ml)	PAXIL® Tablet 1 x 20 mg (ng/ml)
1	1.79	1.27
2	4.47	3.03
3	7.56	5.86
4	10.50	8.68
4.5	10.75	9.51
5	14.19	12.28
5.5	13.61	14.06
6	15.37	14.00
6.5	14.93	15.21
7	14.33	13.78
8	13.92	13.53
10	11.87	11.75
12	10.29	9.33
14	9.65	8.96
16	8.53	8.14
24	7.14	6.33
36	3.98	4.22
48	2.84	2.52
60	2.09	2.08
72	1.69	1.57
96	1.29	1.08
120	0.89	0.93

Figure 18 illustrates the mean plasma Paroxetine concentrations (ng/ml) over time after a single-dose of one 20 mg Paroxetine HCl CR Tablet formulated according to

Formulation 42 or after a single dose of one 20 mg PAXIL® tablet under fasting conditions.

Table 44 provides the mean pharmacokinetic parameters for plasma Paroxetine after a single dose of one 20 mg Paroxetine HCL CR Tablet formulated according to Formulation 42 or after a single dose of one 20 mg PAXIL® tablet under fasting conditions.

Table 44: Mean Pharmacokinetic Parameters for Plasma Paroxetine (n=12)

	Formulation 42 1 x 20 mg			PAXIL® Tablet 1 x 20 mg			Formulation 42/ PAXIL® Ratio	
	AUC	C_{max}	T_{max}	AUC	C_{max}	T_{max}	AUC	C_{max}
Mean	440.50	16.61	6.13	421.60	16.39	6.58	1.08	1.11
Std. Dev.	567.89	10.52	1.23	540.40	11.50	1.33	0.27	0.29
CV (%)	128.92	63.31	20.03	128.18	70.17	20.18	25.24	25.88
GeoMean	249.14	13.44	6.01	237.52	12.48	6.48	1.05	1.08

Formulation 42/PAXIL®

	Arith.Mean	GeoMean	90% C.I.
AUC	1.04	1.05	91-121
C_{max}	1.01	1.08	94-123

Based on the 20 mg Paroxetine HCl CR Tablet formulated according to Formulation 42 to the 20 mg PAXIL® Tablet comparison of plasma data for Paroxetine for the twelve (12) evaluable subjects, the 90% geometric confidence intervals for AUC and C_{max} were found to be within the 80% - 125% range. Therefore the 20 mg Paroxetine HCl CR Tablet formulated according to Formulation 42 are bioequivalent to the 20 mg PAXIL® Tablet.

EXAMPLE 12:

Fluoxetine HCl was provided by two different suppliers (Supplier 1 and Supplier 2). Particle size measurements were conducted on Fluoxetine HCl provided by Supplier 1 and Supplier 2. Tables 45A and 45B provide the particle size measurement data of Fluoxetine HCl provided by Supplier 1 and Supplier 2, respectively.

Table 45A: Particle Size Measurement Data of Fluoxetine HCl Provided by Supplier 1

Condition					
T% (He-Ne):	97.0%	Dist. Form:	Std.	Sampling times:	10
Trigger:	NO	R.R. Index:	1.64-0.00i		
Shaker:	170	Air P.:	LOW	Vacuum:	ON
Format					
Dist. Base:	Volume	Scalling:	Auto	Axis:	LogX - Linear Y
Data					
Median:	19.672µm	SP. Area:	3861cm²/cm²	S.D.:	73.374µm
Mode:	18.600µm	Mean:	45.505µm		
C.V.:	161.24%				
Span:	(D 20.0-D 10.0)/D50=0.158				
Dia.on %	(90.0%):	118.199µm	% on Dia.	(2.000µm):	0.1%
Dia.on %	(70.0%):	29.4885µm	% on Dia.	(10.000µm):	16.7%
Dia.on %	(35.0%):	15.114µm	% on Dia.	(20.000µm):	51.0%
Dia.on %	(20.0%):	10.941µm	% on Dia.	(100.000µm):	88.6%
Dia.on %	(10.0%):	7.877µm	% on Dia.	(550.000µm):	99.9%

Table 45B: Particle Size Measurement Data of Fluoxetine HCl Provided by Supplier 2					
Condition					
T% (He-Ne):	97.2%	Dist. Form:	Std.	Sampling times:	10
Trigger:	NO	R.R. Index:	1.64-0.00i		
Shaker:	170	Air P.:	HIGH	Vacuum:	ON
Format					
Dist. Base:	Volume	Scaling:	Auto	Axis:	LogX – Linear Y
Data					
Median:	20.638µm	SP. Area:	5004cm²/cm²	S.D.:	124.996µm
Mode:	18.612µm	Mean:	86.383µm		
C.V.:	144.70%				
Span: (D 20.0-D 10.0)/D50=0.178					
Dia.on %	(90.0%):	296.388µm	% on Dia.	(2.000µm):	2.1%
Dia.on %	(70.0%):	42.5575µm	% on Dia.	(10.000µm):	21.9%
Dia.on %	(35.0%):	14.546µm	% on Dia.	(20.000µm):	48.6%
Dia.on %	(20.0%):	9.337µm	% on Dia.	(100.000µm):	74.6%
Dia.on %	(10.0%):	5.668µm	% on Dia.	(580.000µm):	99.9%

Table 46 provides the composition of two Fluoxetine HCl CR Tablet formulations, wherein the Fluoxetine HCl is provided by two different suppliers [Formulation 43 (Supplier 1) and Formulation 44 (Supplier 2)].

Table 46: Fluoxetine HCl CR Tablet Formulations		
Ingredients	**Formulation 43 (Supplier 1) (%w/w)**	**Formulation 44 (Supplier 2) (%w/w)**
Fluoxetine	5.64	5.64
HPMC (K4M Prem CR)	26.42	26.42
Lactose Anhydrous	57.12	57.12
MCC	8.05	8.05
PVP	1.76	1.76
Magnesium Stearate	1.01	1.01

In vitro dissolution studies were conducted on 40 mg Fluoxetine HCl CR Tablets formulated according to Formulations 43 and 44. Table 47 provides the *in vitro* dissolution data of 40 mg Fluoxetine HCl CR Tablets formulated according to Formulations 43 and 44.

Table 47: *In vitro* Dissolution Data of 20 mg Fluoxetine HCl CR Tablets Formulated According to Formulations 43 and 44

Time (hrs)	Formulation 43 (Supplier 1) (% dissolved)	Formulation 44 (Supplier 2) (% dissolved)
0	0	0
1	16.44	15.32
2	28.35	27.36
3	38.4	37.37
4	46.85	45.93
5	54.35	53.38
6	61.12	59.99
7	67.14	65.92
8	72.49	71.23
9	77.44	76.11
10	82.01	80.65
11	86.31	84.83
12	90.37	88.71
13	94.07	92.21
14	97.36	95.19
15	99.97	97.8
16	102.01	99.89
17	103.64	101.35
18	104.96	102.77
19	106.42	103.97

Figure 19 compares the *in vitro* dissolution profiles of 40 mg Fluoxetine HCl CR Tablets formulated according to Formulations 43 and 44.

A randomized, two-way, single-dose, open-label, cross-over pilot study was conducted to compare the rate and extent of absorption of the test product, 40 mg Fluoxetine HCl CR Tablets versus the reference product, 40 mg PROZAC® PULVULES® (Eli Lilly and Company for Dista; Lot Number: 3MA11; Expiry Date: Dec. 1, 2001) under fasting conditions. The two study periods were separated by a three-week washout period. Twenty-four (24) blood samples were drawn for drug content analysis at 0.0 (pre-drug), 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 12.0, 14.0, 16.0, 24.0, 36.0, 48.0, 60.0, 72.0, 84.0, 96.0, 120.0, 168.0, and 288.0 hours post-drug

administration during each study period. Upon completion of the clinical portion of the study, all plasma samples were delivered to the analytical facility for the determination of Fluoxetine and Norfluoxetine concentrations. Sixteen (16) qualified subjects were entered into the study. Pharmacokinetic and statistical analyses were conducted on first twelve (12) evaluable subjects that completed the study.

Table 48 provides the mean plasma Fluoxetine concentrations (ng/ml) over time after a single dose of one 40 mg Fluoxetine HCl CR Tablet formulated according to Formulation 43 or after a single dose of one 40 mg PROZAC® PULVULE® under fasting conditions.

Table 48: Mean Plasma Fluoxetine Concentrations (n=12)		
	Formulation 43 1 x 40 mg (ng/ml)	PROZAC® PULVULE® 1 x 40 mg (ng/ml)
SAMPLE TIME (hours)	MEAN VALUE ± SD	MEAN VALUE ± SD
0.00	0.00 ± 0.00	0.00 ± 0.00
1.00	0.49 ± 0.35	0.96 ± 0.68
2.00	2.63 ± 1.78	6.06 ± 4.67
3.00	7.55 ± 4.07	12.20 ± 5.90
4.00	12.99 ± 7.20	18.12 ± 8.68
5.00	18.67 ± 8.57	23.20 ± 8.32
6.00	22.45 ± 8.55	26.43 ± 6.95
7.00	23.73 ± 7.22	27.11 ± 5.75
8.00	24.70 ± 7.83	28.49 ± 7.16
9.00	25.05 ± 7.35	29.62 ± 7.39
10.00	26.43 ± 8.09	26.70 ± 7.82
12.00	25.93 ± 6.90	25.79 ± 7.07
14.00	24.51 ± 7.21	25.87 ± 7.65
16.00	22.65 ± 7.60	23.22 ± 7.91
24.00	16.54 ± 5.73	17.44 ± 5.90
36.00	14.47 ± 5.88	15.24 ± 5.79
48.00	10.59 ± 4.79	11.28 ± 5.14
60.00	7.92 ± 4.59	8.68 ± 3.98
72.00	6.03 ± 3.21	7.14 ± 3.90
84.00	5.58 ± 3.26	5.57 ± 3.16
96.00	4.42 ± 2.70	4.66 ± 2.91
120.00	2.83 ± 2.14	3.01 ± 2.13
168.00	1.21 ± 1.21	1.27 ± 1.15
288.00	0.16 ± 0.32	0.17 ± 0.27

Figure 20 illustrates the mean plasma Fluoxetine concentrations (ng/ml) over time after a single dose of one 40 mg Fluoxetine HCl CR Tablet formulated according to Formulation 43 or after a single dose of one 40 mg PROZAC® PULVULE® under fasting conditions.

Table 49 provides the mean pharmacokinetic parameters for plasma Fluoxetine after a single dose of one 40 mg Fluoxetine HCl CR Tablet formulated according to

Formulation 43 or after a single dose of one 40 mg PROZAC® PULVULE® under fasting conditions.

Table 49: Mean Pharmacokinetic Parameters for Plasma Fluoxetine (n = 12)

Parameter	Formulation 43 (Fasting) 1 x 40 mg Mean ± SD	PROZAC® PULVULE® (Fasting) 1 x 40 mg Mean ± SD
$AUC_{(0-t)}$ (ng. hr/ml)	1385.34 ± 633.25	1475.84 ± 634.93
$AUC_{(0-inf)}$ (ng.hr/ml)	1412.00 ± 647.76	1502.66 ± 638.92
C_{max} (ng/ml)	28.32 ± 7.84	30.55 ± 7.46
T_{max} (hours)	10.00 ± 2.30	8.00 ± 1.41
$t_{½}$ (hours)	36.13 ± 9.00	35.91 ± 9.04
K_{el} ($hour^{-1}$)	00.20 ± 0.004	0.020 ± 0.005

Table 50 provides the comparison of plasma Fluoxetine data after a single dose of one 40 mg Fluoxetine HCl CR Tablet formulated according to Formulation 43 versus after a single dose of one 40 mg PROZAC® PULVULE® under fasting conditions.

Table 50: Comparison of Plasma Fluoxetine Data (Formulation 43 vs. PROZAC® PULVULE®)

	$AUC_{(0-t)}$	$AUC_{(0-inf)}$	C_{max}
90% Geometric C.I.[1]	87% - 100%	87% - 99%	88% - 95%
Ratio of Means[2]	93%	93%	92%
CV[3]	9.14%	8.73%	5.18%

1. 90% Geometric Confidence Interval using log-transformed data and PROZAC® PULVULES® as the reference calculated based on two-way Formulation 43 vs. PROZAC® PULVULES® comparison.
2. Calculated using geometric means according to the formula: $e^{(Formulation\ 43\ -\ PROZAC®\ PULVULES®)}$ x 100% calculated based on two-way Formulation 43 vs. PROZAC® PULVULES® comparison.
3. Intra-subject coefficient of variation for log-transformed pharmacokinetic parameter, calculated based on two-way Formulation 43 vs. PROZAC® PULVULES® comparison.

Table 51 provides the mean plasma Norfluoxetine concentrations (ng/ml) over time after a single dose of one 40 mg Fluoxetine HCl CR Tablet formulated according to Formulation 43 or after a single dose of one 40 mg PROZAC® PULVULE® under fasting conditions.

Table 51: Mean Plasma Norfluoxetine Concentrations (n=12)

	Formulation 43 (1x 40 mg) (ng/ml)	PROZAC® PULVULE® (1 x 40 mg) (ng/ml)
SAMPLE TIME (hours)	**MEAN VALUE ± SD**	**MEAN VALUE ± SD**
0.00	1.85 ± 3.71	1.43 ± 1.78
1.00	1.92 ± 4.06	1.50 ± 1.61
2.00	2.04 ± 3.27	2.76 ± 1.80
3.00	3.36 ± 3.39	4.66 ± 2.33
4.00	5.02 ± 3.50	6.10 ± 2.66
5.00	7.39 ± 4.05	7.94 ± 3.16
6.00	8.79 ± 3.67	9.82 ± 3.44
7.00	10.77 ± 3.10	10.65 ± 4.01
8.00	11.56 ± 4.03	12.57 ± 4.53
9.00	11.84 ± 4.20	13.24 ± 4.25
10.00	13.53 ± 5.34	12.62 ± 4.05
12.00	13.93 ± 3.64	15.15 ± 4.85
14.00	15.41 ± 4.75	16.68 ± 5.05
16.00	16.02 ± 5.24	16.72 ± 5.40
24.00	14.98 ± 4.03	15.26 ± 4.53
36.00	19.77 ± 4.48	20.78 ± 4.58
48.00	19.91 ± 5.09	20.33 ± 5.22
60.00	19.58 ± 4.53	21.59 ± 4.98
72.00	21.03 ± 6.06	21.57 ± 5.11
84.00	21.53 ± 6.08	20.51 ± 3.80
96.00	20.12 ± 5.33	20.04 ± 4.93
120.00	18.91 ± 5.85	20.03 ± 6.16
168.00	16.08 ± 6.92	16.37 ± 5.16
288.00	10.23 ± 6.72	10.49 ± 4.80

Figure 21 illustrates the mean plasma Norfluoxetine concentrations (ng/ml) over time after a single dose of one 40 mg Fluoxetine HCl CR Tablet formulated according to

Formulation 43 or after a single dose of one 40 mg PROZAC® PULVULE® formulation under fasting conditions.

Table 52 provides the mean pharmacokinetic parameters for plasma Norfluoxetine after a single dose of one 40 mg Fluoxetine HCl CR Tablet formulated according to Formulation 43 or after a single dose of one 40 mg PROZAC® PULVULE® under fasting conditions.

Table 52: Mean Pharmacokinetic Parameters for Plasma Norfluoxetine (n=12)

Parameter	Formulation 43 (Fasting) 1 x 40 mg Mean ± SD	PROZAC® PULVULE® (Fasting) 1 x 40 mg Mean ± SD
$AUC_{(0-t)}$ (ng. hr/ml)	4673.09 ± 1549.55	4586.11 ± 1122.06
$AUC_{(0-inf)}$ (ng.hr/ml)	7843.69 ± 3837.59	6619.57 ± 2390.69
C_{max} (ng/ml)	23.91 ± 5.79	25.01 ± 5.06
T_{max} (hours)	84.06 ± 19.90	84.04 ± 39.30
$t_{\frac{1}{2}}$ (hours)	189.63 ± 87.67	172.25 ± 62.06
K_{el} ($hour^{-1}$)	0.005 ± 0.003	0.005 ± 0.002

Table 53 provides the comparison of plasma Norfluoxetine data after a single dose of one 40 mg Fluoxetine HCl CR Tablet formulated according to Formulation 43 versus after a single dose of one 40 mg PROZAC® PULVULE® under fasting conditions.

Table 53: Comparison of Plasma Fluoxetine Data (Formulation 43 vs. PROZAC® PULVULE®)

	$AUC_{(0-t)}$	**$AUC_{(0-inf)}$**	**C_{max}**
90% Geometric C.I.[1]	89% - 112%	77% - 101%	87% - 103%
Ratio of Means[2]	100%	88%	95%
CV[3]	16.09%	8.75%	11.47%

1. 90% Geometric Confidence Interval using log-transformed data and PROZAC® PULVULES® as the reference calculated based on two-way Formulation 43 vs. PROZAC® PULVULES® comparison.

2. Calculated using geometric means according to the formula: $e^{(\text{Formulation 43} - \text{PROZAC® PULVULES®})}$ x 100% calculated based on two-way Formulation 43 vs. PROZAC® PULVULES® comparison.
3. Intra-subject coefficient of variation for log-transformed pharmacokinetic parameter, calculated based on two-way Formulation 43 vs. PROZAC® PULVULES® comparison.

Based on the 40 mg plasma data for Fluoxetine for the twelve (12) evaluable subjects, the 40 mg Fluoxetine HCl CR Tablet formulated according to Formulation 43 to the 40 mg PROZAC® PULVULE®, the 90% geometric confidence intervals for $AUC_{(0-t)}$, $AUC_{(0-inf)}$, and C_{max} were found to be within the 80% - 125% range.

Based on the 40 mg Fluoxetine HCl CR Tablet formulated according to Formulation 43 to the 40 mg PROZAC® PULVULE® comparison of plasma data for Norfluoxetine for the twelve (12) evaluable subjects, the 90% geometric confidence intervals for $AUC_{(0-t)}$ and C_{max} were found to be within the 80% - 125% range. Therefore, the 40 mg Fluoxetine HCl CR Tablets formulated according to Formulation 43 are bioequivalent to the 40 mg PROZAC® PULVULES®.

A randomized pilot, two-way, single dose, open-label, cross over study was conducted to compare the rate and extent of absorption of the test product, 40 mg Fluoxetine HCl CR Tablets versus the reference product, 40 mg PROZAC® PULVULES® (By: Eli Lilly and Company For: Dista; Lot Number: 3MA11M; Expiry Date: Dec. 1, 2001) under fasting conditions. The two study periods were separated by a three-week washout period. Twenty-four (24) blood samples were drawn for drug content analysis on Day 1 at 0.0 (pre-drug), 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 12.0, 14.0 and 16.0 hours post-drug administration; on Day 2 at 24.0 and 36.0 hours post-drug administration; on Day 3 at 48.0 and 60.0 hours post-drug administration; on Day 4 at 72.0 and 84.0 hours post-drug administration; on Day 5 at 96.0 hours post-drug administration; on Day 6 at 120.0 hours post-drug administration; on Day 8 at 168.0 hours post-drug administration; and on Day 13 at 288.0 hours post-drug administration.

Upon completion of the clinical portion of the study, all plasma samples were delivered to the analytical facility for the determination the concentrations of Fluoxetine and its metabolite, Norfluoxetine. Eleven (11) qualified subjects and four (4) alternates were entered into the study. Pharmacokinetic and statistical analyses were conducted on twelve (12) evaluable subjects that completed the study.

Table 54 provides the mean plasma Fluoxetine concentrations (ng/ml) over time after a single dose of one 40 mg Fluoxetine HCl CR Tablet formulated according to Formulation 43 or after a single dose of one 40 mg PROZAC® PULVULE® under fasting conditions.

Table 54: Mean Plasma Fluoxetine Concentrations (n=12)		
	Formulation 43 (1 x 40 mg) (ng/ml)	PROZAC® PULVULE® (1 x 40 mg) (ng/ml)
SAMPLE TIME (hours)	MEAN VALUE ± SD	MEAN VALUE ± SD
0.00	0.00 ± 0.00	0.00 ± 0.00
1.00	1.06 ± 0.80	1.28 ± 1.06
2.00	3.88 ± 1.98	4.68 ± 3.00
3.00	10.01 ± 5.38	10.89 ± 4.96
4.00	14.06 ± 5.87	14.63 ± 5.93
5.00	17.79 ± 5.78	18.11 ± 7.77
6.00	21.42 ± 4.70	18.94 ± 7.48
7.00	22.83 ± 4.92	20.00 ± 7.52
8.00	22.99 ± 5.11	23.16 ± 5.74
9.00	23.75 ± 5.36	21.84 ± 4.14
10.00	21.76 ± 3.95	21.26 ± 4.14
12.00	21.76 ± 4.96	22.01 ± 5.50
14.00	19.41 ± 5.13	19.85 ± 4.52
16.00	17.06 ± 3.43	17.03 ± 4.70
24.00	13.13 ± 2.99	12.87 ± 3.66
36.00	11.28 ± 3.33	11.25 ± 3.38
48.00	7.61 ± 2.28	7.85 ± 2.27
60.00	6.44 ± 2.40	6.10 ± 1.90
72.00	4.68 ± 2.06	4.28 ± 1.61
84.00	3.86 ± 1.60	3.57 ± 1.33
96.00	2.68 ± 1.13	2.32 ± 0.97
120.00	1.66 ± 0.74	1.56 ± 0.66
168.00	0.62 ± 0.35	0.45 ± 0.35
288.00	0.00 ± 0.00	0.01 ± 0.05

Figure 22 illustrates the mean plasma Fluoxetine concentrations (ng/ml) over time after a single dose of one 40 mg Fluoxetine HCl CR Tablet formulated according to Formulation 43 or after a single dose of one 40 mg PROZAC® PULVULE®.

Table 55 provides the mean pharmacokinetic parameters for plasma Fluoxetine after a single dose of one 40 mg Fluoxetine HCl CR Tablet formulated according to Formulation 43 or after a single dose of one 40 mg PROZAC® PULVULE® under fasting conditions.

Table 55: Mean Pharmacokinetic Parameters for Plasma Fluoxetine (n = 12)		
Parameter	**Formulation 43 (Fasting) 1 x 40 mg Mean ± SD**	**PROZAC® PULVULE® (Fasting) 1 x 40 mg Mean ± SD**
$AUC_{(0-t)}$ (ng. hr/ml	1000.20 ± 277.33	981.17 ± 240.34
$AUC_{(0-inf)}$ (ng.hr/ml)	1031.25 ± 289.90	1008.24 ± 245.60
C_{max} (ng/ml)	25.86 ± 5.90	24.42 ± 5.39
T_{max} (hours)	8.17 ± 1.53	8.58 ± 2.35
$t_{½}$ (hours)	31.37 ± 4.87	31.74 ± 7.29
K_{el} ($hour^{-1}$)	0.023 ± 0.004	0.023 ± 0.004

Table 56 provides the comparison of plasma Fluoxetine data after a single dose of one 40 mg Fluoxetine HCl CR Tablet formulated according to Formulation 43 versus after a single dose of one 40 mg PROZAC® PULVULE® under fasting conditions.

Table 56: Comparison of Plasma Fluoxetine Data (Formulation 43 vs. PROZAC® PULVULE®)			
	$AUC_{(0-t)}$	**$AUC_{(0-inf)}$**	**C_{max}**
90% Geometric C.I.[1]	96% - 106%	96% - 106%	100% - 112%
Ratio of Means[2]	101%	101%	106%
CV[3]	6.88%	6.79%	7.70%

1. 90% Geometric Confidence Interval using log-transformed data and PROZAC® PULVULES® as the reference calculated based on two-way Formulation 43 vs. PROZAC® PULVULES® comparison.
2. Calculated using geometric means according to the formula: $e^{(\text{Formulation 43 - PROZAC® PULVULES®})} \times 100\%$ calculated based on two-way Formulation 43 vs. PROZAC® PULVULES® comparison.
3. Intra-subject coefficient of variation for log-transformed pharmacokinetic parameter, calculated based on two-way Formulation 43 vs. PROZAC® PULVULES® comparison.

Table 57 provides the mean plasma Norfluoxetine concentrations (ng/ml) over time after a single dose of one 40 mg Fluoxetine HCl CR Tablet formulated according to

Formulation 43 or after a single dose of one 40 mg PROZAC® PULVULE® under fasting conditions.

Table 57: Mean Plasma Norfluoxetine Concentrations (n=12)

	Formulation 43 (1 x 40 mg) (ng/ml)	PROZAC® PULVULE® (1 x 40 mg) (ng/ml)
SAMPLE TIME (hours)	MEAN VALUE ± SD	MEAN VALUE ± SD
0.00	0.78 ± 1.29	0.72 ± 0.91
1.00	1.05 ± 1.35	0.84 ± 0.88
2.00	2.13 ± 1.66	1.84 ± 0.96
3.00	3.60 ± 1.88	3.51 ± 1.30
4.00	4.92 ± 2.09	5.05 ± 1.27
5.00	6.83 ± 2.38	6.71 ± 2.76
6.00	8.78 ± 2.43	8.25 ± 3.15
7.00	9.74 ± 2.78	9.87 ± 3.65
8.00	11.37 ± 2.48	11.49 ± 2.12
9.00	12.25 ± 2.62	12.42 ± 2.26
10.00	12.52 ± 2.78	12.38 ± 2.08
12.00	13.76 ± 3.16	15.72 ± 5.15
14.00	13.76 ± 3.39	14.38 ± 3.08
16.00	13.81 ± 3.15	14.57 ± 3.61
24.00	13.14 ± 2.74	14.71 ± 4.19
36.00	19.26 ± 4.33	20.81 ± 5.12
48.00	16.46 ± 2.67	18.56 ± 2.84
60.00	18.79 ± 3.84	20.59 ± 6.84
72.00	17.12 ± 4.10	16.50 ± 2.39
84.00	17.90 ± 2.93	19.43 ± 2.94
96.00	15.85 ± 3.31	15.13 ± 3.83
120.00	14.65 ± 3.07	14.84 ± 4.35
168.00	12.81 ± 3.56	11.50 ± 3.15
288.00	6.17 ± 2.25	7.23 ± 3.56

Figure 23 illustrates the mean plasma Norfluoxetine concentrations (ng/ml) over time after a single dose of one 40 mg Fluoxetine HCl CR Tablet formulated according to

Formulation 43 or after a single dose of one 40 mg PROZAC® PULVULE® under fasting conditions.

Table 58 provides the mean pharmacokinetic parameters for plasma Norfluoxetine after a single dose of one 40 mg Fluoxetine HCl CR Tablet formulated according to Formulation 43 or after a single dose of one 40 mg PROZAC® PULVULE® under fasting conditions.

Table 58: Mean Pharmacokinetic Parameters for Plasma Norfluoxetine (n=12)

Parameter	Formulation 43 (Fasting) 1 x 40 mg Mean ± SD	PROZAC® PULVULE® (Fasting) 1 x 40 mg Mean ± SD
$AUC_{(0-t)}$ (ng. hr/ml)	3493.60 ± 730.93	3752.49 ± 871.15
$AUC_{(0-inf)}$ (ng.hr/ml)	5190.67 ± 1584.60	5176.36 ± 1622.25
C_{max} (ng/ml)	20.67 ± 3.55	22.63 ± 5.53
T_{max} (hours)	54.01 ± 20.79	59.14 ± 20.86
$t_{½}$ (hours)	148.84 ± 48.99	152.29 ± 60.35
K_{el} ($hour^{-1}$)	0.005 ± 0.002	0.005 ± 0.001

Table 59 provides the comparison of plasma Norfluoxetine data after a single dose of one 40 mg Fluoxetine HCl CR Tablets formulated according to Formulation 43 versus after a single dose of one 40 mg PROZAC® PULVULE® under fasting conditions.

Table 59: Comparison of Plasma Norfluoxetine Data (Formulation 43 vs. PROZAC® PULVULE®)

	$AUC_{(0-t)}$	$AUC_{(0-inf)}$	C_{max}
90% Geometric C.I.[1]	84% - 103%	92% - 104%	86% - 99%
Ratio of Means[2]	93%	98%	92%
CV[3]	13.87%	7.36%	9.28%

1. 90% Geometric Confidence Interval using log-transformed data and PROZAC® PULVULES® as the reference calculated based on two-way Formulation 43 vs. PROZAC® PULVULES® comparison.

2. Calculated using geometric means according to the formula: $e^{(\text{Formulation 43 - PROZAC® PULVULES®})}$ x 100% calculated based on two-way Formulation 43 vs. PROZAC® PULVULES® comparison.
3. Intra-subject coefficient of variation for log-transformed pharmacokinetic parameter, calculated based on two-way Formulation 43 vs. PROZAC® PULVULES® comparison.

Based on the 40 mg Fluoxetine HCl CR Tablet formulated according to Formulation 43 to the 40 mg PROZAC® PULVULE® comparison of plasma data for Fluoxetine and its metabolite Norfluoxetine, the 90% geometric confidence intervals for $AUC_{(0-t)}$, $AUC_{(0-\infty)}$ and C_{max} were found to be within the 80% - 125% range. The results presented herein demonstrate that the test product, 40 mg Fluoxetine HCl CR Tablets formulated according to Formulation 43 is bioequivalent to the reference product, 40 mg PROZAC® PULVULES® (By: Eli Lilly and Company For Dista; Lot Number: 3MA11M; Expiry ate: Dec. 1, 2001) under fasting conditions.

A randomized, pilot study was conducted to compare the rate and extent of absorption of the test product, 40 mg Fluoxetine HCl CR Tablets to the reference product, 40 mg PROZAC® PULVULES® (Eli Lilly and Company for Dista), under fasting conditions. The two (2) study periods were separated by a three (3)-week washout period. Twenty-four (24) blood samples were drawn for drug content analysis at 0.0 (pre-drug), 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 12.0, 14.0, 16.0, 24.0, 36.0, 48.0, 60.0, 72.0, 84.0, 96.0, 120.0, 168.0 and 288.0 hours post-drug administration during each study period. Upon completion of the clinical portion of the study, all plasma samples were delivered to the analytical facility for the determination of Fluoxetine and Norfluoxetine concentrations. Twelve (12) qualified subjects were entered into the study. Pharmaceutical and statistical analyses were conducted on eleven (11) evaluable subjects that completed the study.

Table 60 provides the mean plasma Fluoxetine concentrations (ng/ml) over time after a single dose of one 40 mg Fluoxetine HCl CR Tablet formulated according to

Formulation 43 or after a single dose of one 40 mg PROZAC® PULVULES® formulation under fasting conditions.

Table 60: Mean Plasma Fluoxetine Concentrations (n=11)

	Formulation 43 (1 x 40 mg)	**PROZAC® PULVULE® (1 x 40 mg)**
	(ng/ml)	**(ng/ml)**
SAMPLE TIME (hours)	**MEAN VALUE ± SD**	**MEAN VALUE ± SD**
0.00	0.09 ± 0.29	0.00 ± 0.00
1.00	0.62 ± 0.49	1.46 ± 0.83
2.00	3.50 ± 2.49	6.92 ± 2.83
3.00	11.65 ± 6.83	15.77 ± 5.88
4.00	15.48 ± 6.69	23.71 ± 6.05
5.00	22.31 ± 8.73	25.13 ± 6.56
6.00	25.41 ± 6.31	27.06 ± 5.64
7.00	27.06 ± 6.32	28.08 ± 4.46
8.00	25.16 ± 6.51	28.02 ± 4.46
9.00	26.25 ± 7.08	28.09 ± 5.13
10.00	25.97 ± 6.24	26.70 ± 4.36
12.00	25.87 ± 6.61	27.53 ± 6.22
14.00	23.29 ± 5.59	24.32 ± 6.00
16.00	21.45 ± 5.95	21.83 ± 6.09
24.00	17.39 ± 5.62	17.37 ± 6.15
36.00	14.49 ± 6.40	16.05 ± 6.40
48.00	10.24 ± 5.18	10.60 ± 6.25
60.00	9.11 ± 5.45	9.11 ± 5.99
72.00	6.37 ± 4.50	6.28 ± 4.58
84.00	5.79 ± 4.69	6.24 ± 5.02
96.00	4.73 ± 4.00	4.37 ± 3.92
120.00	2.95 ± 3.10	3.23 ± 3.20
168.00	1.75 ± 2.80	1.66 ± 2.19
288.00	0.48 ± 1.21	0.45 ± 1.07

Figure 24 illustrates the means plasma Fluoxetine concentrations (ng/ml) over time after a single dose of one 40 mg Fluoxetine HCl CR Tablet formulated according to Formulation 43 or after a single dose of one 40 mg PROZAC® PULVULE® under fasting conditions.

Table 61 provides the mean pharmacokinetic parameters for plasma Fluoxetine after a single dose of one 40 mg Fluoxetine HCl CR Tablet formulated according to

Formulation 43 or after a single dose of one 40 mg PROZAC® PULVULE® formulation under fasting conditions.

Table 61: Mean Pharmacokinetic Parameters for Plasma Fluoxetine (n=11)

Parameter	Formulation 43 (Fasting) 1 x 40 mg Mean ± SD	PROZAC® PULVULE® (Fasting) 1 x 40 mg Mean ± SD
$AUC_{(0-t)}$ (ng. hr/ml	1459.68 ± 880.20	1478.01 ± 863.53
$AUC_{(0-inf)}$ (ng.hr/ml)	1534.26 ± 1033.14	1560.25 ± 987.47
C_{max} (ng/ml)	29.04 ± 6.39	31.39 ± 4.86
T_{max} (hours)	8.27 ± 2.72	7.27 ± 2.80
$t_{½}$ (hours)	39.17 ± 23.85	40.59 ± 23.07
K_{el} ($hour^{-1}$)	0.021 ± 0.007	0.020 ± 0.007

Table 62 provides the comparison of plasma Fluoxetine data after a single dose of one 40 mg Fluoxetine HCl CR Tablet formulated according to Formulation 43 versus after a single dose of one 40 mg PROZAC® PULVULE® under fasting conditions.

Table 62: Comparison of Plasma Fluoxetine Data (Formulation 43 vs. PROZAC® PULVULE®)

	$AUC_{(0-t)}$	$AUC_{(0-inf)}$	C_{max}
90% Geometric C.I.[1]	89% - 106%	89% - 105%	83% - 100%
Ratio of Means[2]	97%	97%	91%
CV[3]	10.96%	10.72%	11.87%

1. 90% Geometric Confidence Interval using log-transformed data and PROZAC® PULVULES® as the reference calculated based on two-way Formulation 43 vs. PROZAC® PULVULES® comparison.
2. Calculated using geometric means according to the formula: $e^{(Formulation\ 43\ -\ PROZAC®\ PULVULES®)}$ x 100% calculated based on two-way Formulation 43 vs. PROZAC® PULVULES® comparison.
3. Intra-subject coefficient of variation for log-transformed pharmacokinetic parameter, calculated based on two-way Formulation 43 vs. PROZAC® PULVULES® comparison.

Table 63 provides the mean plasma Norfluoxetine concentrations (ng/ml) over time after a single dose of one 40 mg Fluoxetine HCl CR Tablet formulated according to Formulation 43 or after a single dose of one 40 mg PROZAC® PULVULE® under fasting conditions.

Table 63: Mean Plasma Norfluoxetine Concentrations (n=11)

	Formulation 43 (1 x 40 mg) (ng/ml)	PROZAC® PULVULE® (1 x 40 mg) (ng/ml)
SAMPLE TIME (hours)	MEAN VALUE ± SD	MEAN VALUE ± SD
0.00	0.87 ± 1.04	1.86 ± 2.75
1.00	1.11 ± 1.18	2.03 ± 2.68
2.00	1.84 ± 1.48	3.60 ± 2.61
3.00	4.27 ± 2.10	6.12 ± 3.17
4.00	5.73 ± 2.76	8.78 ± 4.23
5.00	8.14 ± 3.53	11.08 ± 4.19
6.00	10.47 ± 4.90	12.55 ± 4.87
7.00	11.78 ± 4.85	14.61 ± 5.18
8.00	13.12 ± 4.82	15.00 ± 4.94
9.00	12.63 ± 4.77	15.46 ± 5.64
10.00	14.56 ± 6.10	16.87 ± 5.58
12.00	16.19 ± 6.56	18.70 ± 6.24
14.00	16.26 ± 5.97	19.28 ± 7.13
16.00	16.74 ± 6.72	18.95 ± 6.72
24.00	17.67 ± 7.00	19.24 ± 7.49
36.00	21.15 ± 6.47	24.39 ± 8.58
48.00	20.80 ± 7.38	21.91 ± 7.53
60.00	19.85 ± 7.11	24.97 ± 8.18
72.00	20.85 ± 9.54	21.17 ± 6.34
84.00	22.72 ± 7.09	25.54 ± 8.65
96.00	22.17 ± 7.07	22.09 ± 6.46
120.00	20.29 ± 6.83	20.61 ± 7.73
168.00	16.04 ± 6.15	16.74 ± 6.69
288.00	9.55 ± 4.48	10.48 ± 5.18

Figure 25 illustrates the mean plasma Norfluoxetine concentrations (ng/ml) over time after a single dose of one 40 mg Fluoxetine HCl CR Tablet formulated according to Formulation 43 or after a single dose of one 40 mg PROZAC® PULVULE® under fasting conditions.

Table 64 provides the mean pharmacokinetic parameters for plasma Norfluoxetine after a single dose of one 40 mg Fluoxetine HCl CR Tablet formulated according to Formulation 43 or after a single dose of one 40 mg PROZAC® PULVULE® under fasting conditions.

Table 64: Mean Pharmacokinetic Parameters for Plasma Norfluoxetine (n=11)

Parameter	**Formulation 43 (Fasting) 1 x 40 mg Mean ± SD**	**PROZAC® PULVULE® (Fasting) 1 x 40 mg Mean ± SD**
$AUC_{(0-t)}$ (ng. hr/ml	4606.15 ± 1582.52	5083.98 ± 1692.52
$AUC_{(0-inf)}$ (ng.hr/ml)	7249.74 ± 2916.95	8348.86 ± 4502.44
C_{max} (ng/ml)	25.69 ± 6.88	27.36 ± 8.49
T_{max} (hours)	68.87 ± 20.83	64.19 ± 24.01
$t_{½}$ (hours)	164.75 ± 64.02	183.18 ± 85.51
K_{el} ($hour^{-1}$)	0.005 ± 0.002	0.004 ± 0.001

Table 65 provides the comparison of plasma Norfluoxetine data after a single dose of one 40 mg Fluoxetine HCl CR Tablet formulated according to Formulation 43 versus after a single dose of one 40 mg PROZAC® PULVULE® under fasting conditions.

Table 65: Comparison of Plasma Norfluoxetine data (Formulation 43 vs. PROZAC® PULVULE®)			
	$AUC_{(0-t)}$	**$AUC_{(0-inf)}$**	**C_{max}**
90% Geometric C.I.[1]	82% - 98%	79% - 102%	91% - 100%
Ratio of Means[2]	90%	90%	95%
CV[3]	11.32%	15.00%	6.51%

1. 90% Geometric Confidence Interval using log-transformed data and PROZAC® PULVULES® as the reference calculated based on two-way Formulation 43 vs. PROZAC® PULVULES® comparison.
2. Calculated using geometric means according to the formula: $e^{(\text{Formulation 43 - PROZAC® PULVULES®})}$ x 100% calculated based on two-way Formulation 43 vs. PROZAC® PULVULES® comparison.
3. Intra-subject coefficient of variation for log-transformed pharmacokinetic parameter, calculated based on two-way Formulation 43 vs. PROZAC® PULVULES® comparison.

Based on the 40 mg Fluoxetine HCl CR Tablet formulated according to Formulation 43 to the 40 mg PROZAC® PULVULE® comparison of the plasma data for Fluoxetine, the 90% geometric confidence intervals for $AUC_{(0-t)}$, $AUC_{(0-infinity)}$ and C_{max} were found to be within the 80% - 125% range. Based on the comparison of the 40 mg Fluoxetine HCl CR Tablet formulated according to Formulation 43 to the 40 mg PROZAC® PULVULE® comparison of plasma data for Norfluoxetine, the 90% geometric confidence intervals for $AUC_{(0-t)}$ and C_{max} were found to be within the 80% - 125% range.

The results presented herein demonstrate that the test product, 40 mg Fluoxetine HCl CR Tablets formulated according to Formulation 43, is bioequivalent to the reference product, 40 mg PROZAC® PULVULES® (Eli Lily and Company for Dista; Lot Number: 3A11M; Expiry Date: Dec. 1, 2001) under fasting conditions.

Table 66 provides a list of the equipment used in the manufacturing process of SSRI CR Tablets formulated according to one embodiment of the present invention.

Table 66: Equipment Used in the Manufacturing Process of SSRI CR Tablets	
Process	**Equipment**
Wet granulation process	High shear mixer
Drying of wet mass	Tray dryer
Size reduction of dry granules	Cone mill
Preparation of bulk blend	V – blender
Tabletting process	Rotary press
Coating process	Perforated coater

The equipment used to manufacture the experimental batch and the pivotal biobatch formulated according to one embodiment of the present invention, although different in size, operate on the same principles as those used in the pilot batches (see Table 67). Commercial batches formulated to one embodiment of the present invention are manufactured using the same equipment used for the pivotal biobatch.

Table 67: Comparison of Critical Equipment Used in the Manufacturing Process of SSRI CR Tablets		
Lab Scale Equipment	**Scale up Equipment**	**Process Stage**
High Shear Granulator Model: Aeromatic fielder	High Shear Granulator Model: PMA 600	Mixing and Granulation
Tray Drying Oven Blue M electric	Tray Drying Oven Model: O'Hara 400	Drying the granules
Cone Mill Model: Model 197S	Cone Mill Model: KEK 220	Sizing of granules
V-Blender Model: 16 qt.	V-Blender Model:40 cu. ft.	Blending of granules
Rotary Tablet Press Model: Riva Pren	Rotary Tablet Press Model: Manesty Unipress	Manufacture of tablets
Polisher/De-duster Model: FMC AV 100	Polisher/De-duster Model: MG2 GTS/E	Removes loose particles from tablets
	Metal Detector Model: LOMA	Rejects tablets with metal contaminant
Mixer Model: Craframo	Propeller Mixer: ID# DTR-1/DTR-9	Preparation of Coating Suspension
Mixer Model: Craframo	Mixer Model: Craframo	Mixing of coating Solution
Tablet Coater Model: Labcoat 11 system	Tablet Coater Model: O'Hara FastCoat 60''	Coating of tablets

The manufacture of SSRI CR Tablets, in one embodiment, is based on the wet granulation process. The manufacturing process can be divided into ten (10) unit operations as follows.

1. Weighing of active ingredients and excipients;
2. Blending of active ingredient and retardant excipient (polymer) in a high shear mixer;
3. Granulation of active ingredient and retardant excipient blend with alcoholic solution of Povidone in the high shear mixer;
4. Drying of wet granulation in a tray dryer;
5. Size reduction of dry granules in a cone mill;
6. Blending of dry granules with lubricants in a V-blender.
7. Tabletting of final blend in a Rotary press;
8. Preparation of coating solution;
9. Coating of tablets;
10. Packaging.

A brief description of various processes in the manufacture of SSRI CR Tablets formulated according to one embodiment of the present invention is as follows:

A) Wet granulation process: The weighed materials were transferred to the high shear mixer and materials were dry blended with samples removed for in-process quality control testing for potency in order to determine blend uniformity (homogeneity). Once blend uniformity was determined to be appropriate alcohol was added to the dry blend and granulated under high shear. The wet granules were discharged into trays and loaded into the tray dryer. The granules were dried for 10 hours at 60°C. Samples were removed for

in-process quality control testing for residual of isopropyl alcohol and loss on drying. The tray dryer was unloaded based on whether specifications were met.

B) Preparation of bulk blend: The dried granules were passed through a 2mm round screen in a cone mill for the purpose of size reduction. The size reduced granules were transferred into a V-blender. Magnesium stearate was added to the granules in the V-blender and blended. Samples were taken from the lubricated blend for in-process quality control testing for potency determination and blending uniformity. The samples were also used to measure flowability, compressibility, granule size and distribution of the granules.

C) Tabletting Process: The amount of granules required to give the potency of 20 mg active ingredient was calculated after which the hopper of a tablet press was charged. Compression force and fill weight were set by adjusting the relevant controls on the tablet press. A few tablets were compressed by manual turning of the drive shaft. Physical specifications were checked and when ten tablets met the required specifications of weight, hardness, thickness, and friability automated tabletting was started.

D) Manufacture of Coating Suspension: The coating suspension was prepared by mixing OPADRY® II White in purified water to produce a suspension with the help of a propeller mixer. Samples were taken in order to measure total solids for quality control release testing.

E) Coating process: The amount of tablets to be coated were accurately weighed and charged into the coating pan. The tablets were then coated by spray coating with the coating suspension. Samples were taken to test for appearance, identification, potency, content uniformity, impurity levels, moisture content and dissolution for the purpose of quality control release testing.

F) Packaging process: The coated tablets are quarantined and released for packaging after quality control testing.

Figure 26 illustrates a schematic diagram for the bio-batch manufacture of SSRI CR Tablets formulated according to one embodiment of the present invention.

The following parameters were identified as critical to successful formulation during the development of SSRI CR Tablets formulated according to one embodiment of the present invention, and in-process testing procedures were set to check these parameters during the relevant procedures. The tests were carried out and shown to conform to the set standards during manufacturing, as documented in the QA release testing data, before progressing to the next stage.

1. Homogeneity of blend during initial dry mixing: this was shown by content uniformity as evidenced from potency determination with low standard deviation;

2. Drying time and temperature: Adequate drying was checked by determination of loss on drying and possible volatile impurities.

3. Milling and lubrication in V-blender: Potency determination showed homogeneity of blend in the V-blender, while flowability and compressibility of the blend as evidenced by Carr Index was an indicator of adequate lubrication. Particle size analysis of granules showed that the required size reduction was achieved by milling.

4. Tabletting: Tablets were within the specified limits for weight variability, hardness, thickness and friability. Assay showed that content uniformity and impurities all conformed to standards, while dissolution showed that the release rates were also within set limits.

5. Coating: The coated tablets were within specified limits for weight gain after the coating process. As expected, dissolution data of the coated tablets showed that the coating had no significant effect on the dissolution rate of the uncoated tablet.

Table 68 provides the in-process and finished product testing specifications established for the biobatches and proposed for the commercial batches of SSRI CR Tablets formulated according to one embodiment of the present invention.

Table 68: Quality Standard Data for 20 mg SSRI Coated CR Tablets

Tests and methods	Specifications	Results
DESCRIPTION STM: 0006.00, Rev. 03	White oblong coated tablet	White oblong coated tablet
IDENTIFICATION STM: 0022.27	HPLC retention time of major peak in sample conforms with that of the Standard	HPLC retention time of major peak in sample conforms with that of the Standard
POTENCY STM: 0022.07	90.0-110.0%	101.0%
CONTENT UNIFORMITY <0022.27>	Min: 85.0% of LC Max: 115.0% of LC	102.7%
	%RSD < 6.0%	1.2%
DISSOLUTION STM: 0021.14	1 Hour: 10-30% Range	23%
	4 Hour: 46-66% Range	54%
	8 Hour: 70-90% Range	80%
	12Hour:NLT 80% Range	93%
IMPURITIES STM: 0022.13	[Lu 14-017]:NMT 0.1%	0.0%
	[Lu 29-215]:NMT 0.25%	0.07%
	[Lu 11-305]:NMT:0.1%	0.02%
	[Lu 29-075]:NMT 0.25%	0.07%
	Single Unknown Impurity: NMT 0.1%	None > 0.1%
	Total Impurities: NMT 0.5%	0.22%
Moisture Content STM: 0009.01	NMT 5%	1%

While the foregoing provides a detailed description of a preferred embodiment of the invention, it is to be understood that this description is illustrative only of the principles of the invention and not limitative. Furthermore, as many changes can be

made to the invention without departing from the scope of the invention, it is intended that all material contained herein be interpreted as illustrative of the invention and not in a limiting sense.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE AS FOLLOWS:

1. A modified release pharmaceutical composition for oral administration, for once daily dosing comprising:

(a) from about 4.0% (w/w) to about 8.0% (w/w) of a form of at least one selective serotonin re-uptake inhibitor (SSRI) selected from the group consisting of Fluoxetine, Fluvoxamine, Paroxetine, Sertraline, Venlafaxine, Citalopram, racemic mixtures thereof, enantiomers thereof, pharmaceutically-acceptable salts thereof, and combinations thereof;

(b) from about 10% (w/w) to about 42% (w/w) of at least one release rate controlling polymer, wherein the at least one release rate controlling polymer is selected from the group consisting of cellulose derivatives, dextrans, starches, carbohydrates, base polymers, natural or hydrophilic gums, xanthans, alginates, gelatins, polyacrylic acids, polyvinyl alcohol, polyvinyl pyrrolidone, carbomers and combinations thereof;

(c) from about 46% (w/w) to about 70% (w/w) of at least one diluent;

(d) from about 0% (w/w) to about 5% (w/w) of at least one binder;

(e) from about 0% (w/w) to about 5.0% (w/w) of at least one lubricant;

(f) from about 0% (w/w) to about 6.0% (w/w) of at least one surfactant;

(g) from about 0% (w/w) to about 6.0% (w/w) of at least one solubilizing agent;

(h) from about 0% (w/w) to about 6.0% (w/w) of at least one bioavailability enhancer; and

(i) from about 0% (w/w) to about 6.0% (w/w) of at least one acidifying agent;

wherein the pharmaceutical composition is in the form of a matrix tablet.

2. The modified release pharmaceutical composition of Claim 1 wherein the form of the at least one selective serotonin re-uptake inhibitor is selected from the group consisting of Fluoxetine HCl, Fluvoxamine maleate, Paroxetine HCl, Sertraline HCl, Venlafaxine HCl, Citalopram HBr, Escitalopram oxalate and combinations thereof.

3. The modified release pharmaceutical composition of any one of Claims 1 or 2 wherein the form of the at least one SSRI is present in the pharmaceutical composition in an

amount effective to treat at least one condition selected from the group consisting of depression, major depressive disorder, obsessive compulsive disorder, panic disorder, social anxiety disorder, generalized anxiety disorder, posttraumatic stress disorder and combinations thereof.

4. The modified release pharmaceutical composition of any one of Claims 1 to 3 wherein the cellulose derivatives are selected from the group consisting of cellulose ethers, cellulose esters and combinations thereof.

5. The modified release pharmaceutical composition of Claim 4 wherein the cellulose derivatives are selected from the group consisting of alkyl cellulose derivatives, hydroxyalkyl cellulose derivatives and combinations thereof.

6. The modified release pharmaceutical composition of Claim 5 wherein the alkyl and hydroxyalkyl cellulose derivatives are selected from the group consisting of methyl cellulose, ethylcellulose, hydroxyl methylcellulose, hydroxyl ethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylhydroxy ethylcellulose, methylhydroxy propylcellulose, sodium carboxymethyl cellulose and combinations thereof.

7. The modified release pharmaceutical composition of any one of Claims 1 to 3 wherein the at least one release rate controlling polymer is selected from the group consisting of hydroxypropyl methylcellulose, hydroxyl ethylcellulose, ethylcellulose, carbomer and combinations thereof.

8. The modified release pharmaceutical composition of Claim 7 wherein the release rate controlling polymer is hydroxypropyl methylcellulose.

9. The modified release pharmaceutical composition of any one of claims 1 to 8 further comprising at least one other pharmaceutically acceptable excipient selected from the group consisting of at least one granulating aid, at least one colourant, at least one flavourant, at least one pH adjuster, at least one anti-adherent, at least one glidant, at

least one solubility enhancer, at least one surface active agent and combinations thereof.

10. The modified release pharmaceutical composition of any one of claims 1 to 9 wherein the at least one diluent is selected from the group consisting of lactose, microcrystalline cellulose, mannitol and combinations thereof.

11. The modified release pharmaceutical composition of any one of claims 1 to 10 wherein the at least one binder is polyvinyl pyrrolidone.

12. The modified release pharmaceutical composition of any one of claims 1 to 11 wherein the at least one lubricant is selected from the group consisting of magnesium stearate, stearic acid and combinations thereof.

13. The modified release pharmaceutical composition of any one of claims 1 to 12 wherein the at least one surfactant is selected from the group consisting of a bile salt, sodium lauryl sulphate (SLS), polyoxyethylene/polyoxypropylene block copolymers, polyethylene glycol hydrogenated castor oils, polyethylene glycols, saturated polyglycolized glycerides from hydrogenated vegetable oils, saturated polyglycolized glycerides, water soluble derivatives of natural source vitamins, sucrose stearate, mannitol, mono- and diglycerides, lauroyl macrogol glycerides, stearoyl macrogol glycerides, Vitamin E d-α-tocopheryl polyethylene glycol 1000 succinate, propylene glycol monoesters of medium chain fatty acids and combinations thereof.

14. The modified release pharmaceutical composition of any one of claims 1 to 13 wherein the at least one acidifying agent is L-tartaric acid.

15. The modified release pharmaceutical composition of any one of claims 1 to 14 wherein the form of the at least one selective serotonin re-uptake inhibitor is incorporated in a normal release matrix.

16. The modified release pharmaceutical composition of any one of claims 1 to 14 wherein the form of the at least one selective serotonin re-uptake inhibitor is incorporated in a modified release matrix.

17. The modified release pharmaceutical composition of Claim 16 wherein the modified-release matrix is selected from the group consisting of a sustained release matrix and a controlled release matrix.

18. The modified release pharmaceutical composition of any one of claims 15 to 17 further comprising a coating selected from the group consisting of a film coating and a modified release coating.

19. The modified release pharmaceutical composition of Claim 18 wherein the film coating is present in a concentration up to about 5% (w/w) of the core.

20. The modified release pharmaceutical composition of Claim 18 wherein the modified release coating is selected from the group consisting of a delayed-release coating, an extended-release coating and combinations thereof.

21. The modified release pharmaceutical composition of Claim 20 wherein the delayed-release coating is an enteric coating.

22. The modified release pharmaceutical composition of Claim 20 wherein the extended-release coating is selected from the group consisting of a sustained-release coating, a controlled-release coating, and combinations thereof.

23. The modified release pharmaceutical composition of Claim 18 wherein the modified release coating is present in an amount of about 2% (w/w) to about 25% (w/w).

24. The modified release pharmaceutical composition of Claim 18 wherein the modified release coating comprises at least one hydrophobic polymer selected from the group consisting of ethylcellulose, at least one acrylic polymer and combinations thereof.

25. The modified release pharmaceutical composition of Claim 24 wherein the at least one acrylic polymer is selected from the group consisting of acrylic acid copolymers, methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, aminoalkyl methacrylate copolymer, poly (acrylic acid), poly (methacrylic acid, methacrylic acid alkylamide) copolymer, poly (methyl methacrylate), poly (methacrylic acid) (anhydride), methyl methacrylate, polymethacrylate, poly (methyl methacrylate), poly (methyl methacrylate) copolymer, polyacrylamide, aminoalkyl methacrylate copolymer, poly (methacrylic acid anhydride), glycidyl methacrylate copolymers and combinations thereof.

26. The modified release pharmaceutical composition of Claim 18 wherein the modified-release coating is an enteric coating.

27. The modified release pharmaceutical composition of Claim 26 wherein the enteric coating comprises at least one methacrylic acid copolymer.

28. The modified release pharmaceutical composition of Claim 27 wherein the methacrylic acid copolymer is selected from the group consisting of methacrylic acid copolymer Type A, methacrylic acid copolymer Type B, methacrylic acid copolymer Type C and combinations thereof.

29. The modified release pharmaceutical composition of Claim 28 wherein the at least one methacrylic acid copolymer is selected from methacrylic acid copolymer Type A and methacrylic acid copolymer Type B.

30. The modified release pharmaceutical composition of Claim 24 wherein the modified release coating further comprises at least one plasticizer.

31. The modified release pharmaceutical composition of Claim 30 wherein the hydrophobic polymer is ethylcellulose and the at least one plasticizer is selected from the group consisting of dibutyl sebacate, diethyl phthalate, triethyl citrate, tributyl citrate, triacetin, and combinations thereof.

32. The modified release pharmaceutical composition of Claim 30 wherein the at least one hydrophobic polymer is at least one acrylic polymer and the at least one plasticizer is selected from the group consisting of triethyl citrate, tributyl citrate, dibutyl phthalate, polyethylene glycol, propylene glycol, diethyl phthalate, castor oil, triacetin and combinations thereof.

33. The modified release pharmaceutical composition of claim 1 wherein the composition comprises:

(a) from about 4.0% (w/w) to about 8.0% (w/w) of the form of the at least one SSRI;

(b) from about 10.0% (w/w) to about 40.0% (w/w) of hydroxypropyl methylcellulose 2208;

(c) from about 40.0% (w/w) to about 60.0% (w/w) of lactose anhydrous;

(d) from about 6.0% (w/w) to about 10.0% (w/w) of microcrystalline cellulose;

(e) from about 0.0% (w/w) to about 4.0% (w/w) of polyvinyl pyrrolidone;

(f) from about 0.0% (w/w) to about 2.0% (w/w) of magnesium stearate;

(g) from about 0.0% (w/w) to about 2.0% (w/w) of stearic acid;

(h) from about 0.0% (w/w) to about 2.0% (w/w) of a carbomer;

(i) from about 0% (w/w) to about 6.0% (w/w) of at least one surfactant selected from:

from about 0.0% (w/w) to about 3.0% (w/w) of a bile salt;

from about 0.0% (w/w) to about 3.0% (w/w) of sodium lauryl sulphate;

from about 0.0% (w/w) to about 6.0% (w/w) of a poloxamer;

from about 0.0% (w/w) to about 6.0% (w/w) of a polyethylene glycol hydrogenated castor oil;

from about 0.0% (w/w) to about 6.0% (w/w) of a polyethylene glycol;

from about 0.0% (w/w) to about 6.0% (w/w) of a saturated polyglycolized glyceride;

from about 0.0% (w/w) to about 6.0% (w/w) of a water soluble derivative of a natural source vitamin;

from about 0.0% (w/w) to about 6.0% (w/w) of sucrose stearate; and

from about 0.0% (w/w) to about 6.0% (w/w) of mannitol;

(j) from about 0.0% (w/w) to about 6.0% (w/w) of L-tartaric acid; and

combinations thereof.

34. The modified release pharmaceutical composition of any one of claims 1 to 33 wherein the form of the at least one SSRI is selected from Fluoxetine, racemic mixtures thereof, enantiomers thereof, pharmaceutically-acceptable salts thereof, and combinations thereof.

35. The modified release pharmaceutical composition of any one of claims 1 to 33 wherein the form of the at least one SSRI is selected from Fluvoxamine, racemic mixtures thereof, enantiomers thereof, pharmaceutically-acceptable salts thereof, and combinations thereof.

36. The modified release pharmaceutical composition of any one of claims 1 to 33 wherein the form of the at least one SSRI is selected from Paroxetine, racemic mixtures thereof, enantiomers thereof, pharmaceutically-acceptable salts thereof, and combinations thereof.

37. The modified release pharmaceutical composition of any one of claims 1 to 33 wherein the form of the at least one SSRI is selected from Sertraline, racemic mixtures thereof, enantiomers thereof, pharmaceutically-acceptable salts thereof, and combinations thereof.

38. The modified release pharmaceutical composition of any one of claims 1 to 33 wherein the form of the at least one SSRI is selected from Venlafaxine, racemic mixtures thereof, enantiomers thereof, pharmaceutically-acceptable salts thereof, and combinations thereof.

39. The modified release pharmaceutical composition of any one of claims 1 to 33 wherein the form of the at least one SSRI is selected from Citalopram, racemic mixtures thereof, enantiomers thereof, pharmaceutically-acceptable salts thereof, and combinations thereof.

40. The modified release pharmaceutical composition of claim 39 wherein the form of the at least one SSRI is Citalopram HBr.

41. The modified release pharmaceutical composition of claim 39 wherein the form of the at least one SSRI is Escitalopram oxalate.

42. The modified release pharmaceutical composition of Claim 1 wherein the composition comprises:

	Ingredients	**% (w/w)**
(a)	Citalopram HBr	4.0-8.0
(b)	Hydroxypropyl methylcellulose	10.0-40.0
(c)	Lactose Anhydrous	40.0-60.0
(d)	Microcrystalline Cellulose	6.0-10.0
(e)	Polyvinyl pyrrolidone	0.5-3.5
(f)	Magnesium stearate	0.5-2.0.

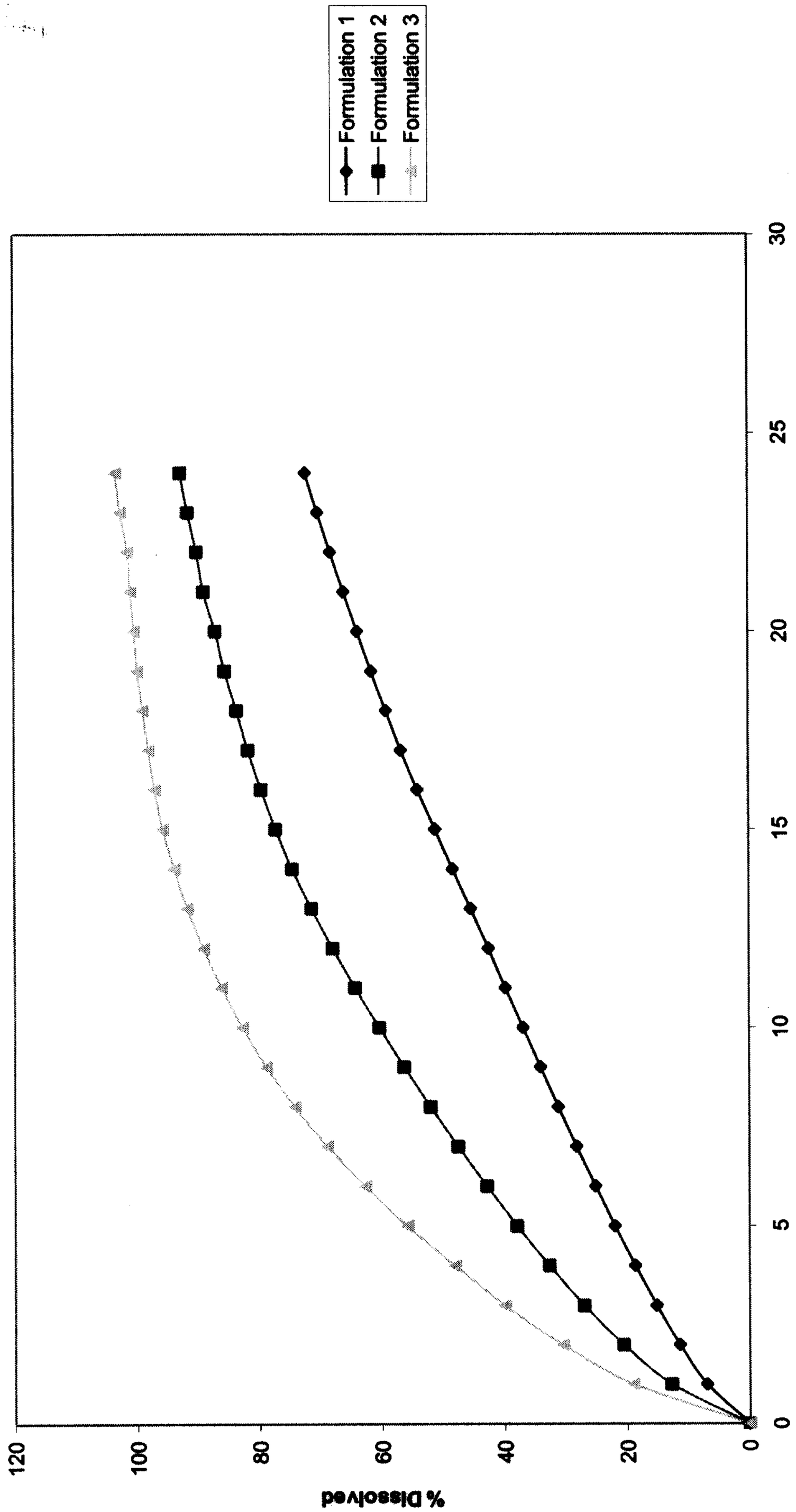
43. The modified release pharmaceutical composition of Claim 1 wherein the composition comprises:

	Ingredients	**% (w/w)**
(a)	Paroxetine HCl	4.0-8.0
(b)	Hydroxypropyl methylcellulose	10.0-40.0
(c)	Lactose Anhydrous	40.0-60.0
(d)	Microcrystalline Cellulose	6.0-10.0
(e)	Polyvinyl pyrrolidone	0.5-3.5
(f)	Magnesium stearate	0.5-2.0.

44. The modified release pharmaceutical composition of Claim 1 wherein the composition comprises:

	Ingredients	**% (w/w)**
(a)	Fluoxetine HCl	4.0-8.0
(b)	Hydroxypropyl methylcellulose	10.0-40.0
(c)	Lactose Anhydrous	40.0-60.0
(d)	Microcrystalline Cellulose	6.0-10.0
(e)	Polyvinyl pyrrolidone	0.5-3.5
(f)	Magnesium stearate	0.5-2.0.

FIGURE 1: In Vitro Dissolution Profiles of 20 mg Citalopram HBr CR Tablets Formulated According to Formulations 1 to 3



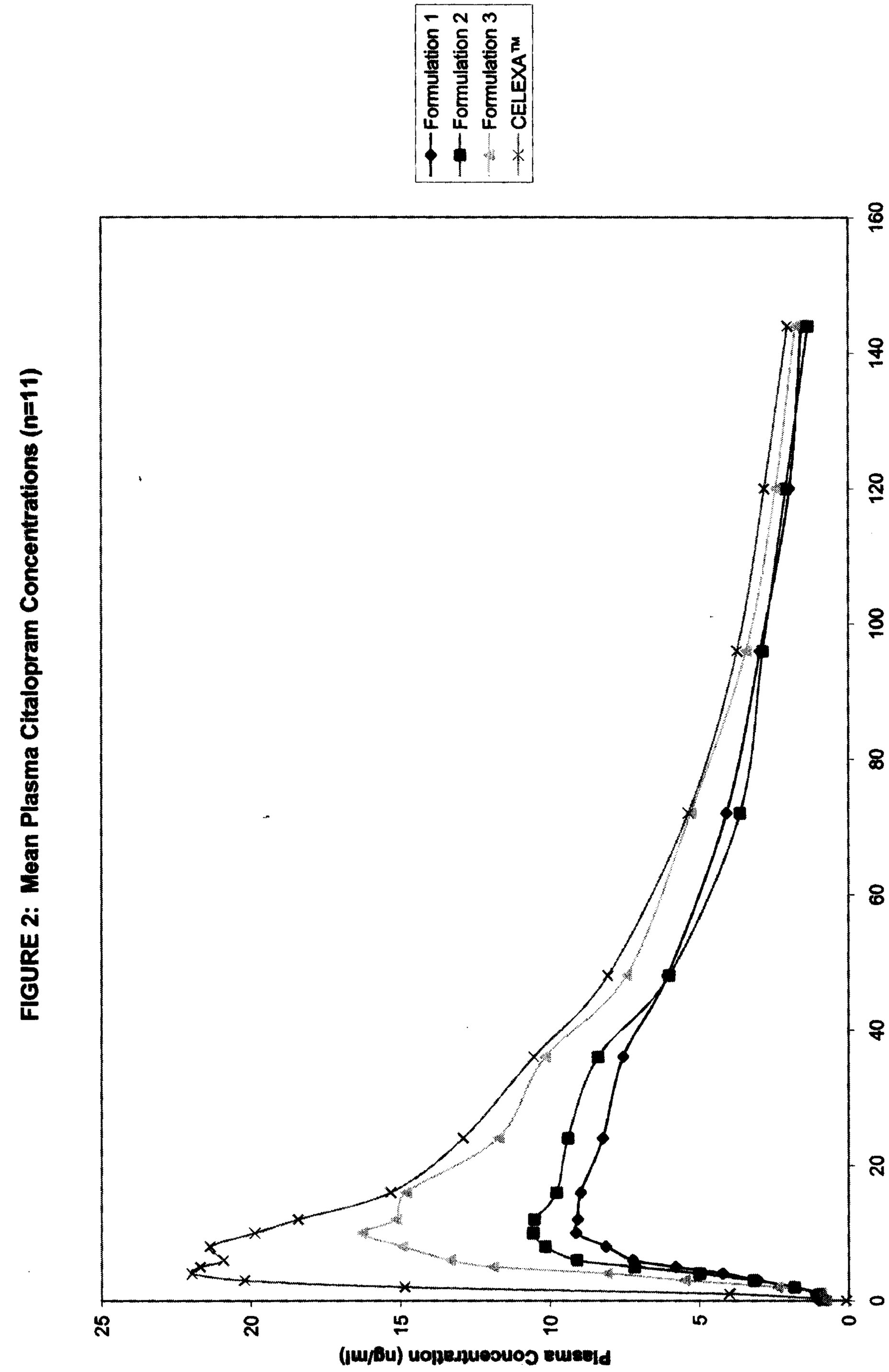


FIGURE 2: Mean Plasma Citalopram Concentrations (n=11)

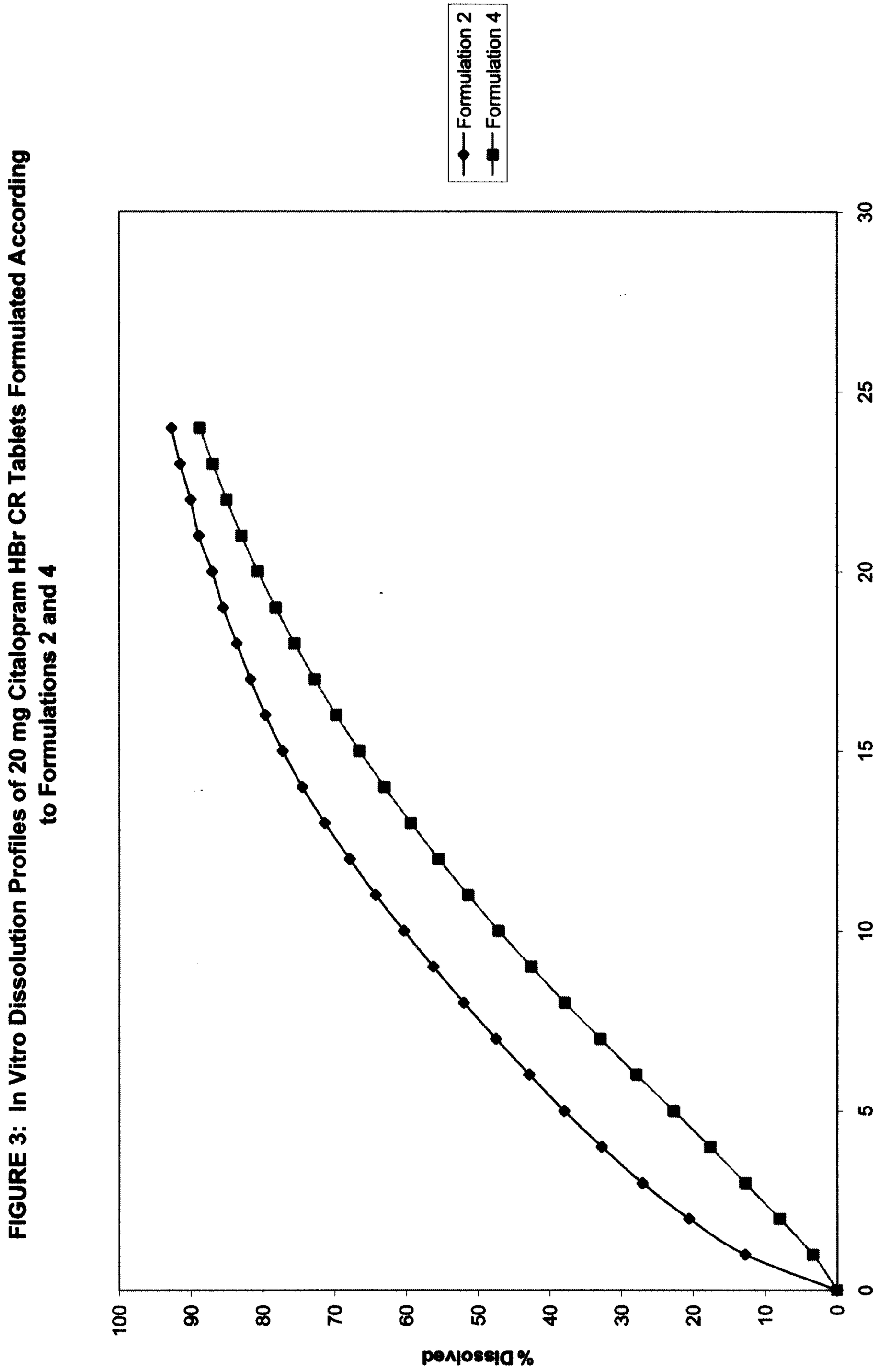


FIGURE 3: In Vitro Dissolution Profiles of 20 mg Citalopram HBr CR Tablets Formulated According to Formulations 2 and 4

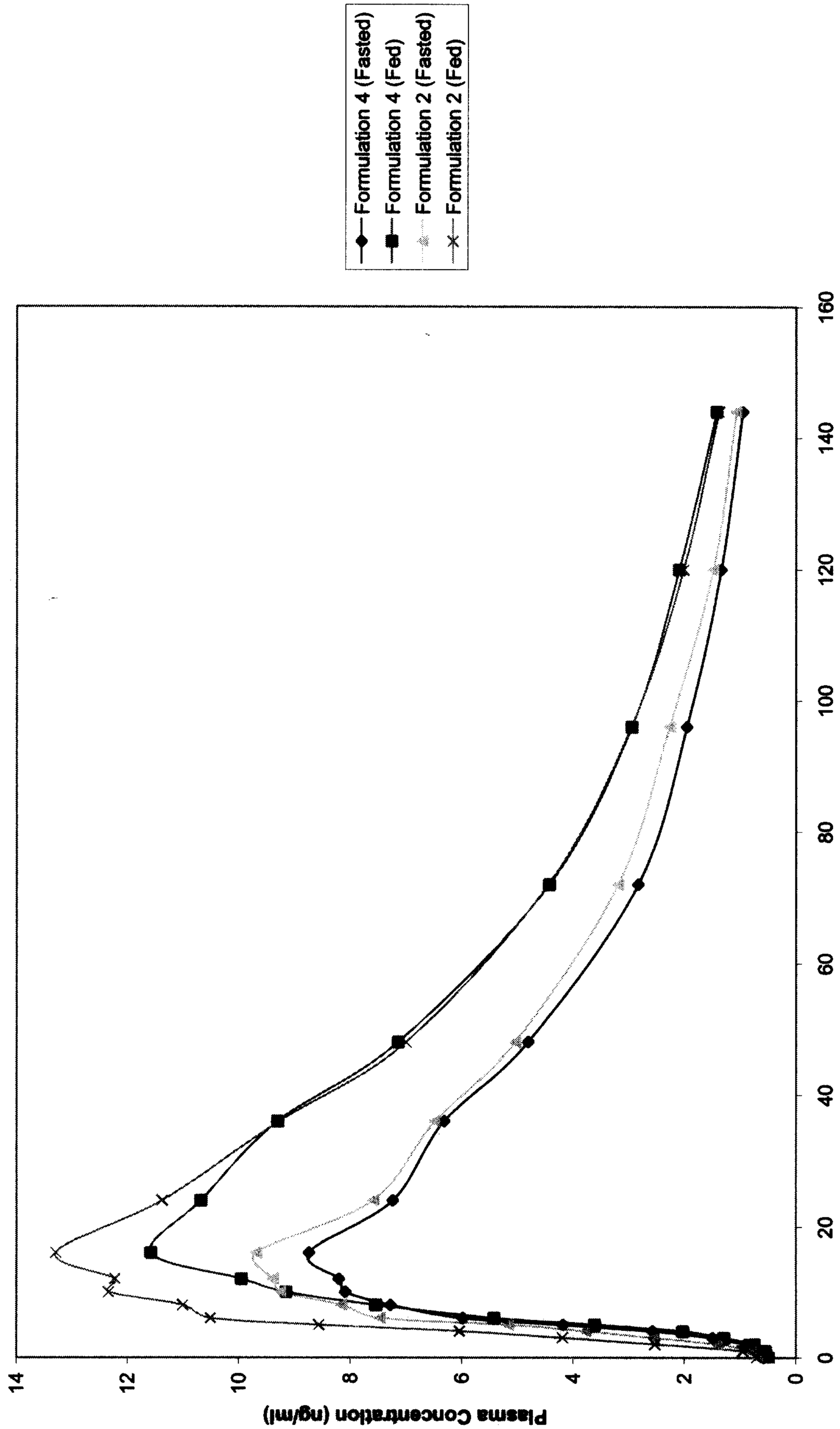
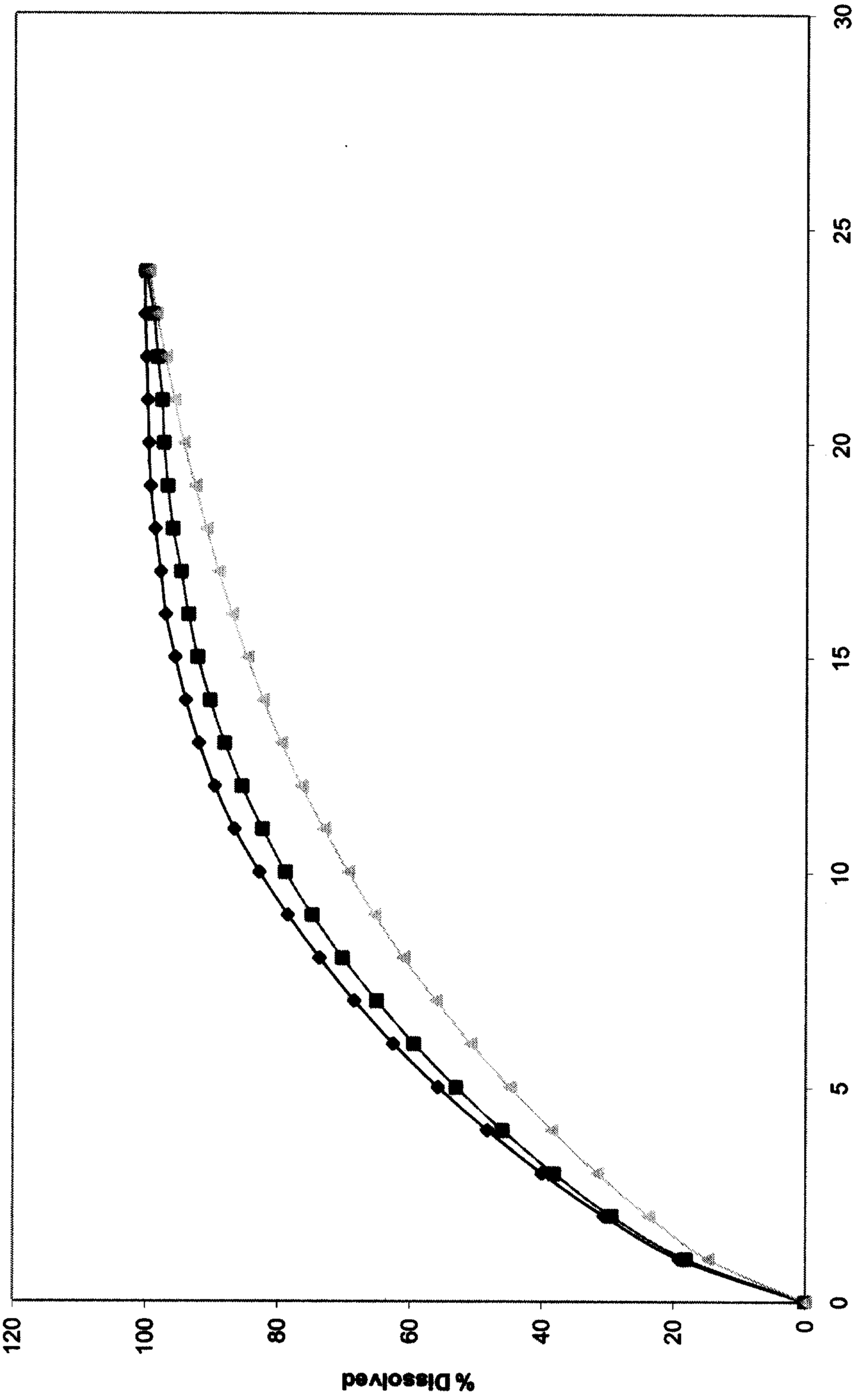


FIGURE 4: Mean Plasma Citalopram Concentrations (n=12)

FIGURE 5: In Vitro Dissolution Profiles of 20 mg Citalopram HBr CR Tablets Formulated According to Formulations 5 to 7



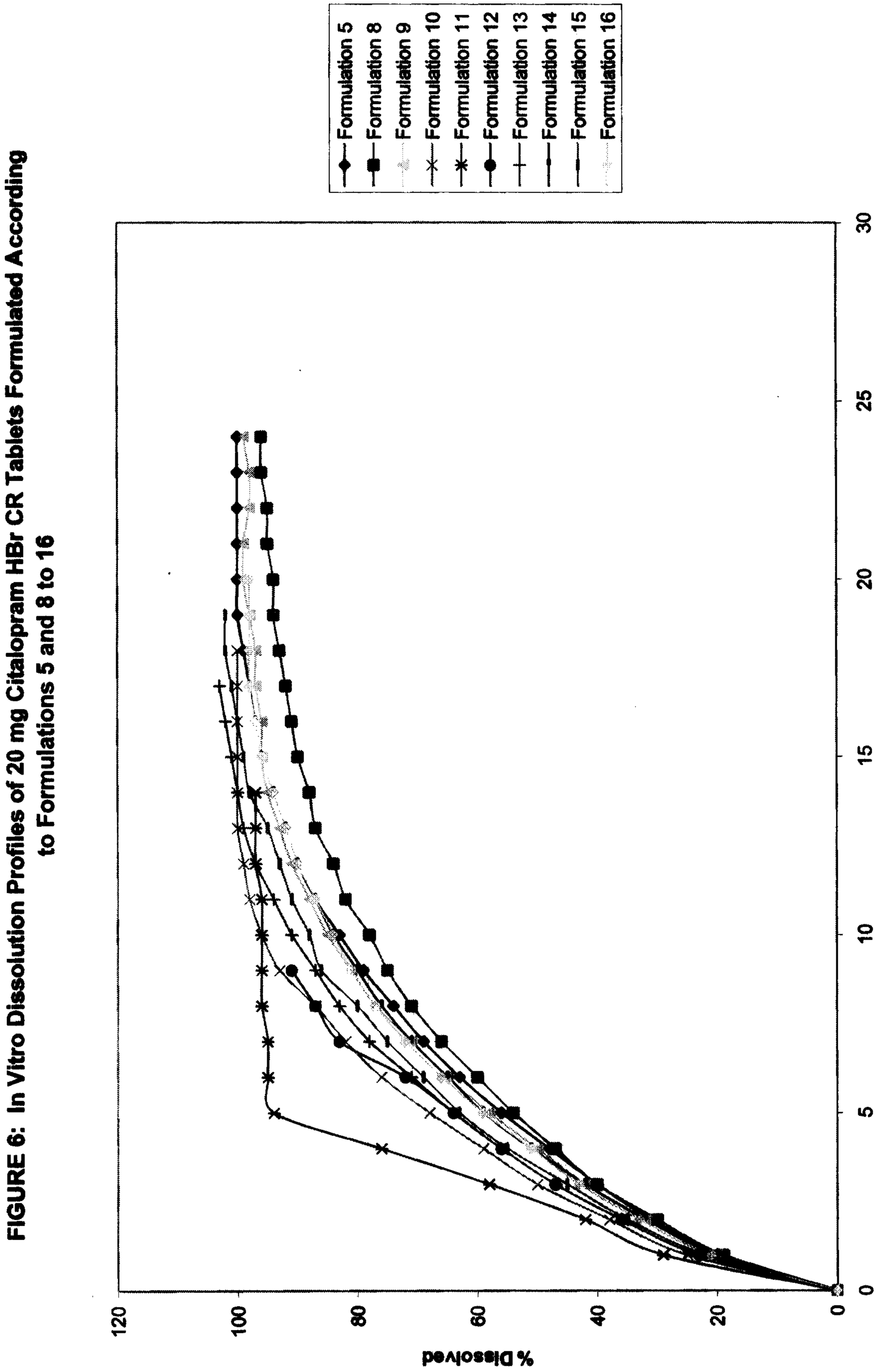


FIGURE 6: In Vitro Dissolution Profiles of 20 mg Citalopram HBr CR Tablets Formulated According to Formulations 5 and 8 to 16

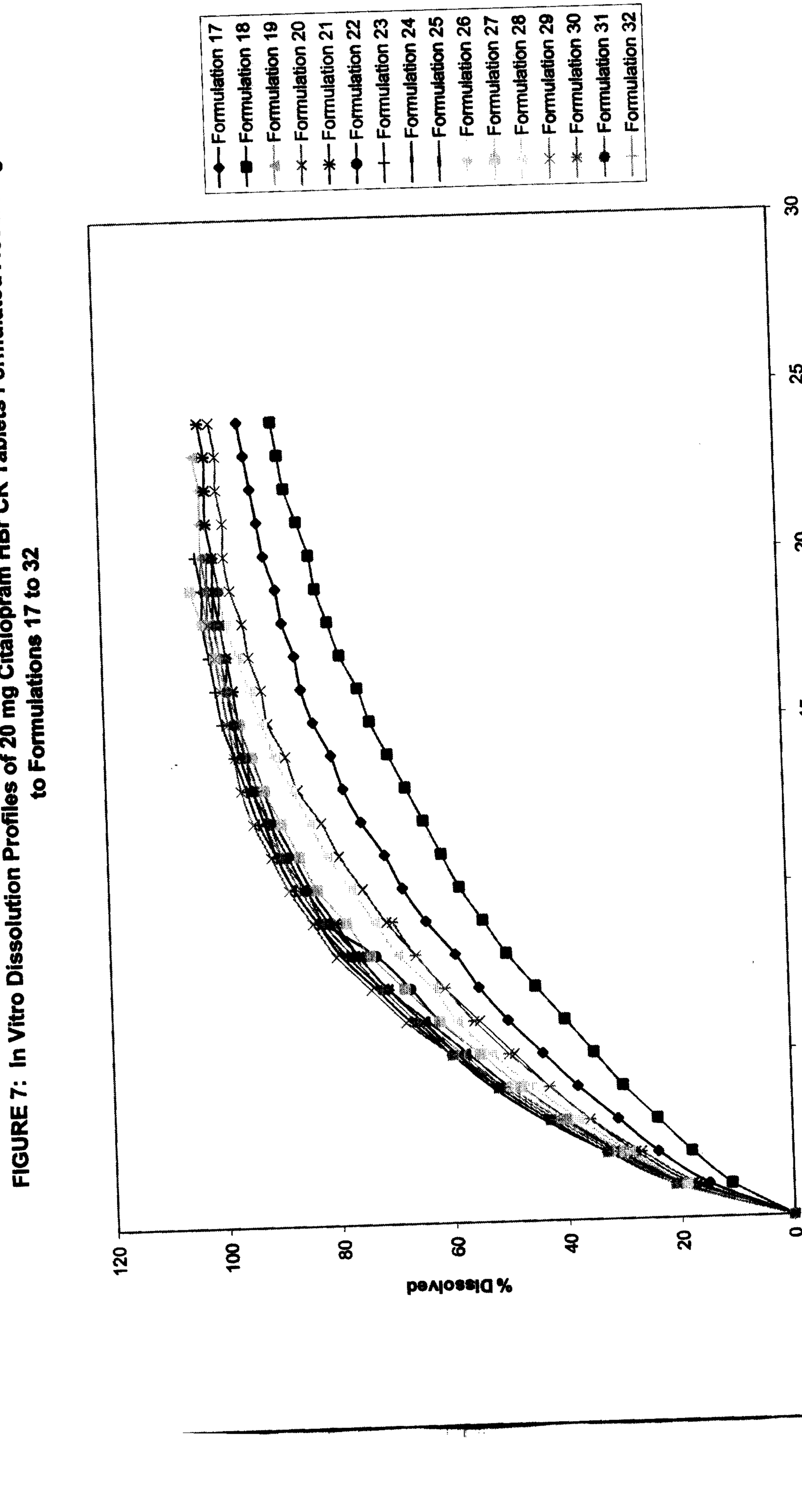

In Vitro Dissolution Profiles of 20 mg Citalopram HBr CR Tablets Formulated According to Formulations 17 to 32
Formulation 17
Formulation 18
Formulation 19
Formulation 20
Formulation 21
Formulation 22
Formulation 23
Formulation 24
Formulation 25
Formulation 26
Formulation 27
Formulation 28
Formulation 29
Formulation 30
Formulation 31
Formulation 32
% Dissolved
Time (hrs)
0
20
40
60
80
100
120
0
5
10
15
20
25
30

FIGURE 7: In

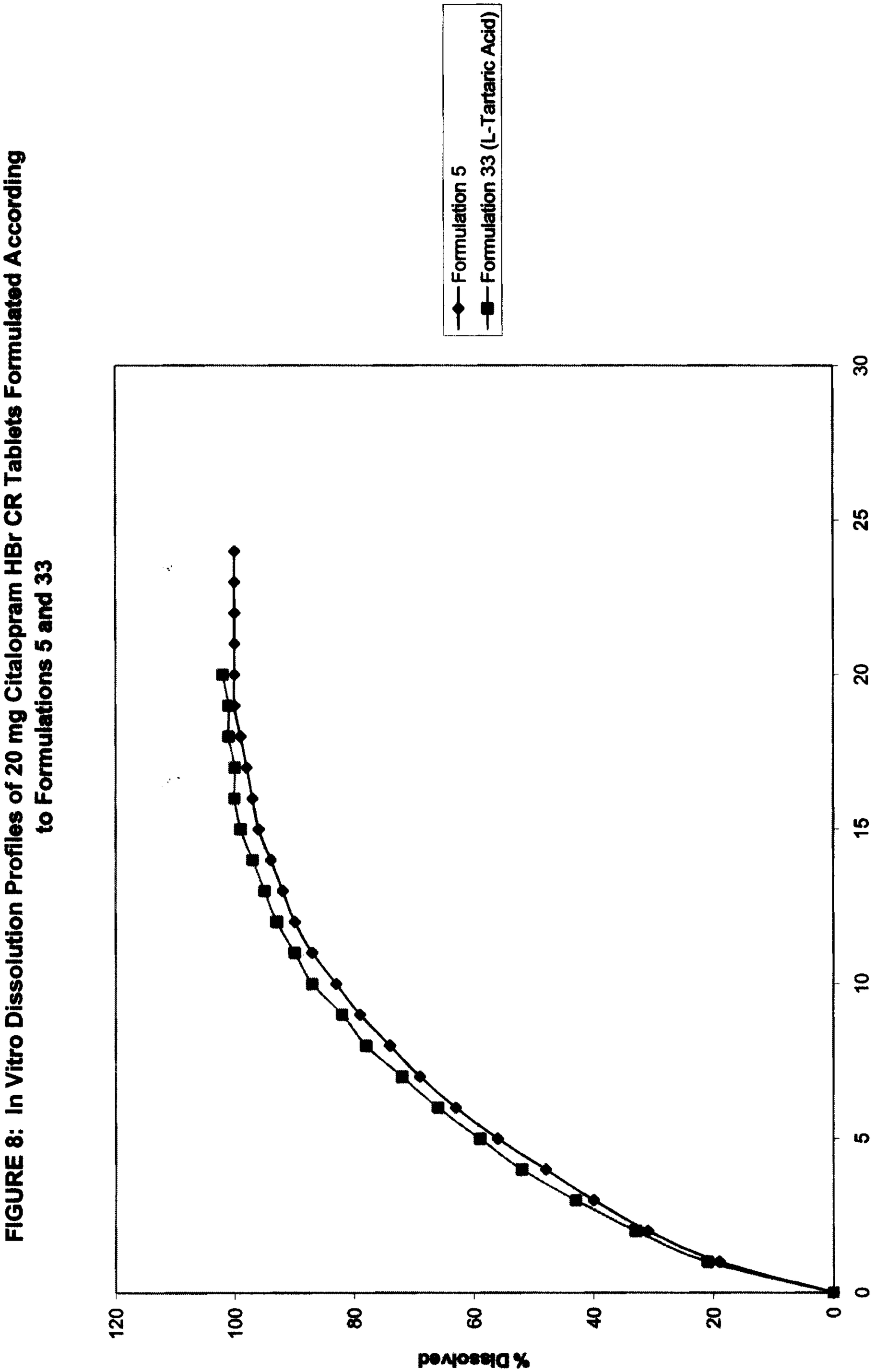


FIGURE 8: In Vitro Dissolution Profiles of 20 mg Citalopram HBr CR Tablets Formulated According to Formulations 5 and 33

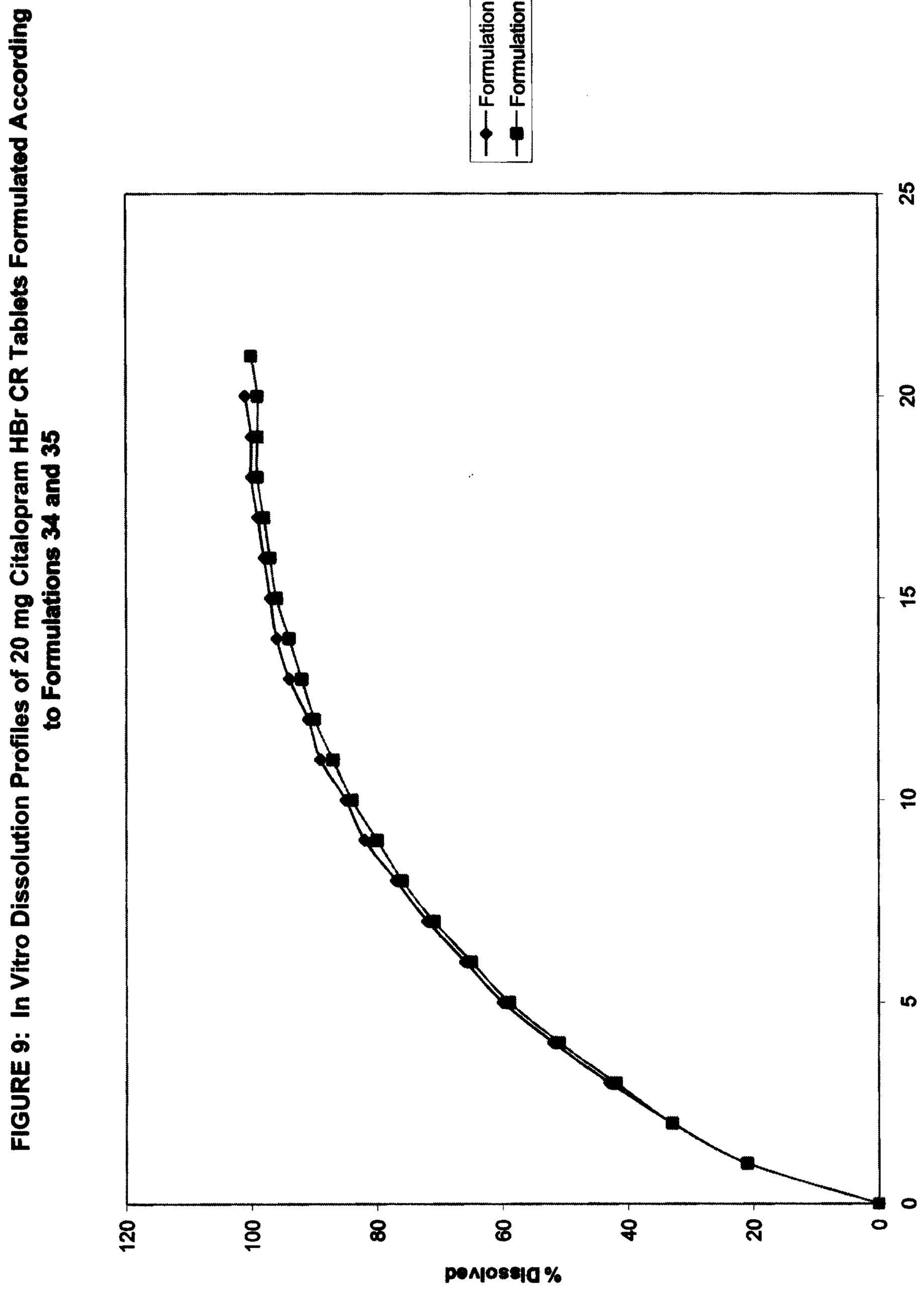
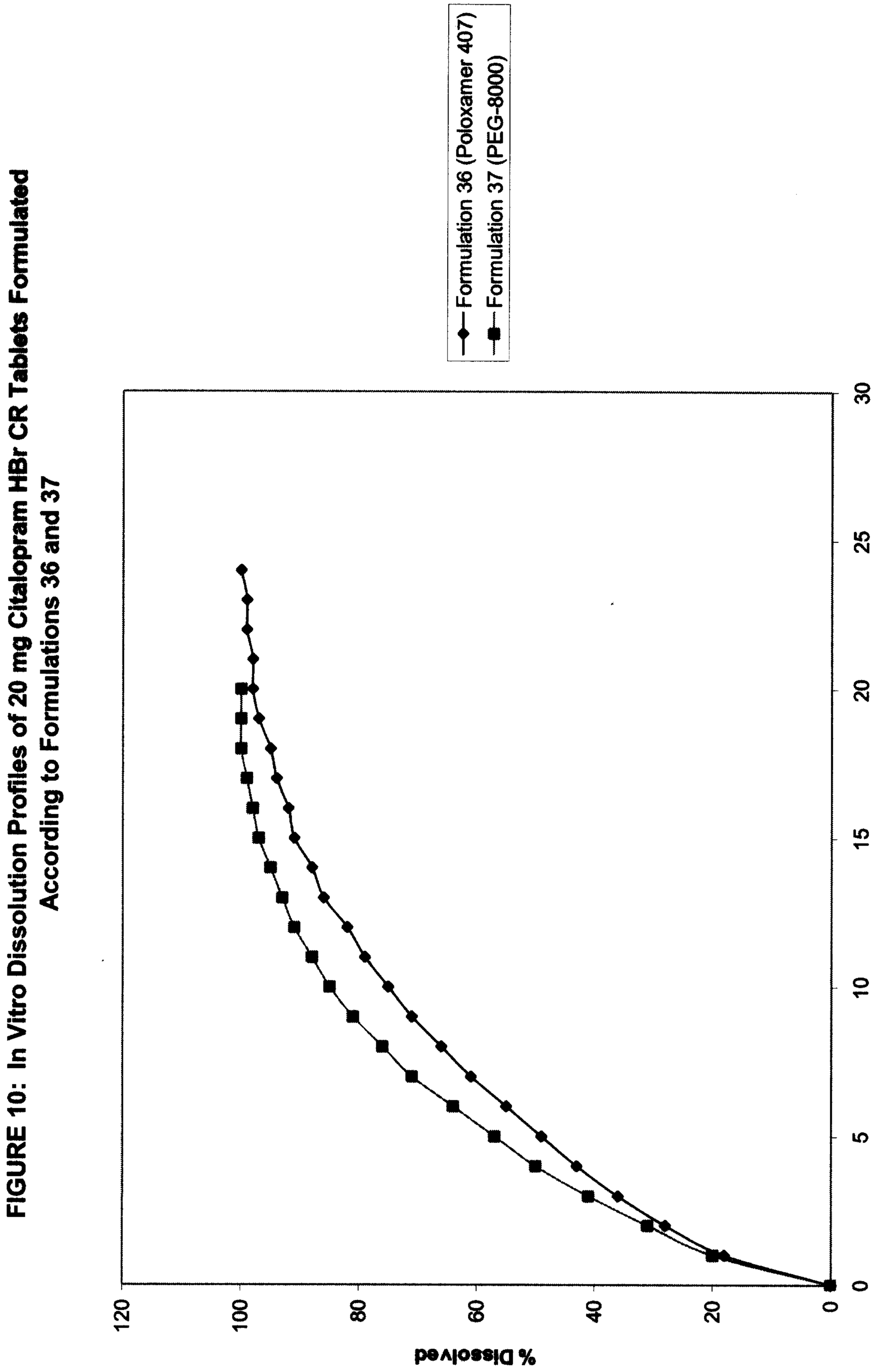


FIGURE 9: In Vitro Dissolution Profiles of 20 mg Citalopram HBr CR Tablets Formulated According to Formulations 34 and 35


FIGURE 10: In Vitro Dissolution Profiles of 20 mg Citalopram HBr CR Tablets Formulated According to Formulations 36 and 37
Formulation 36 (Poloxamer 407)
Formulation 37 (PEG-8000)
% Dissolved
Time (hrs)
120
100
80
60
40
20
0
0
5
10
15
20
25
30

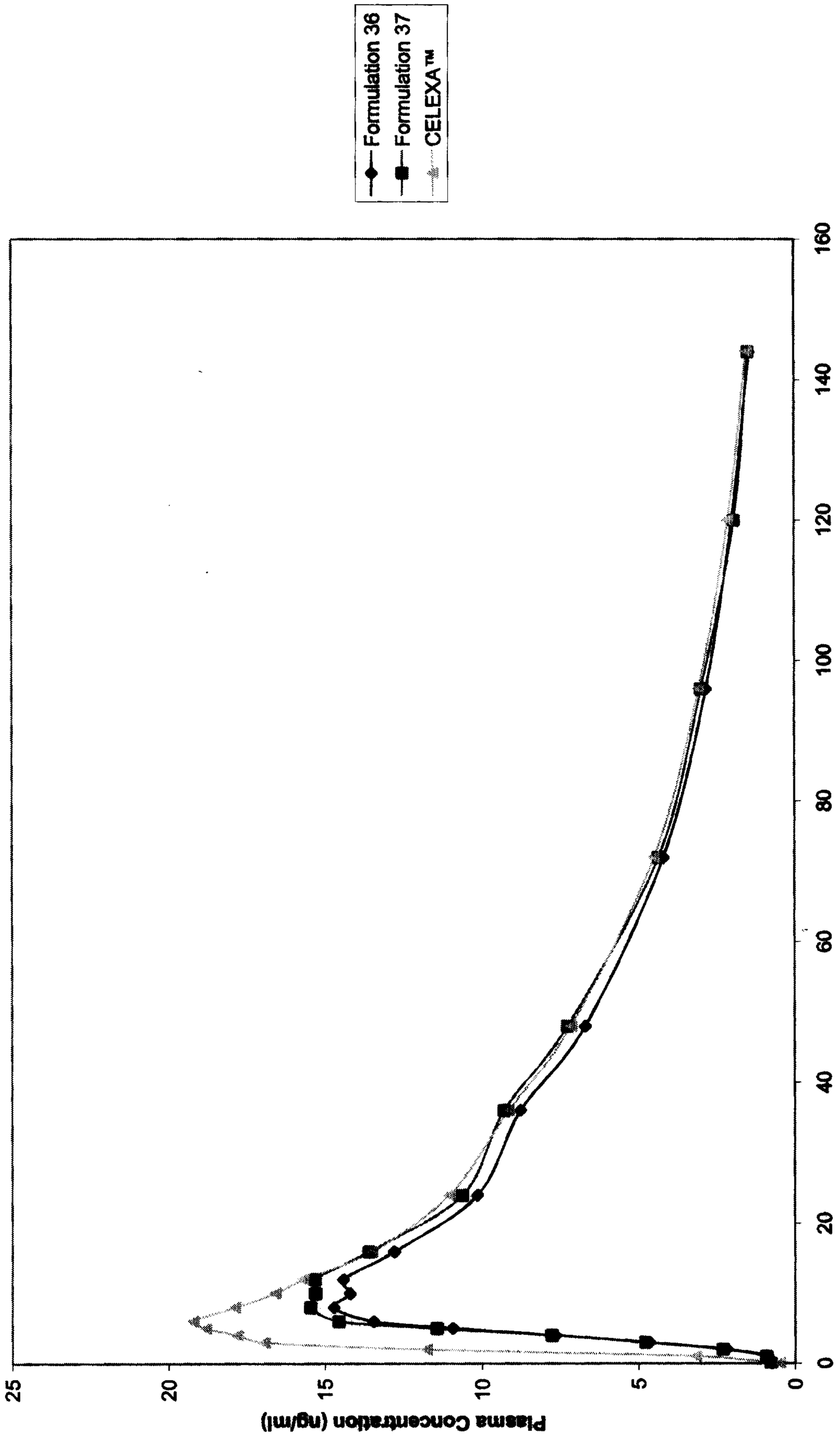
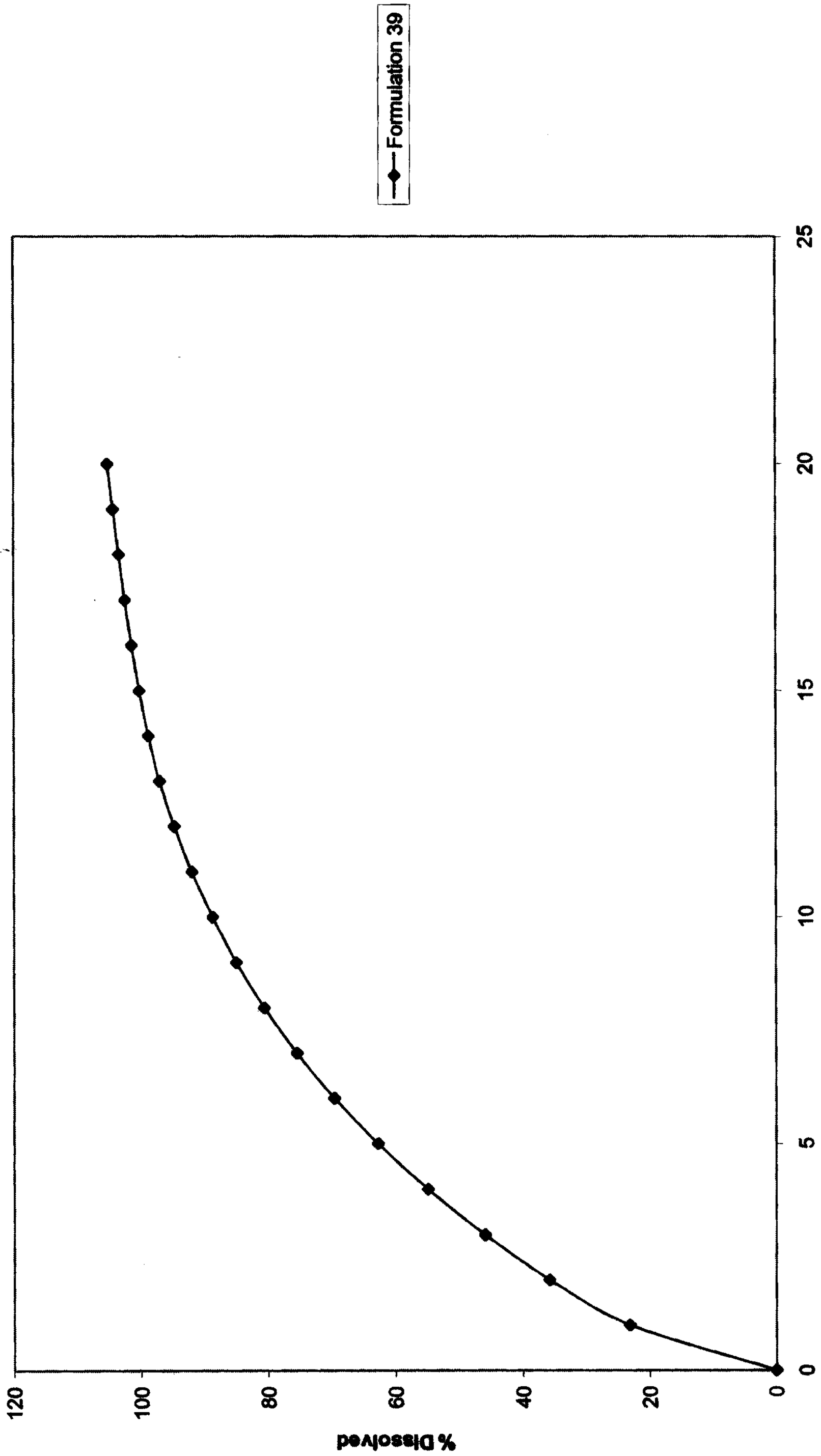


FIGURE 11: Mean Plasma Citalopram Concentrations (n=15)

FIGURE 12: In Vitro Dissolution Profile of 20 mg Citalopram HBr CR Tablets Formulated According to Formulation 39



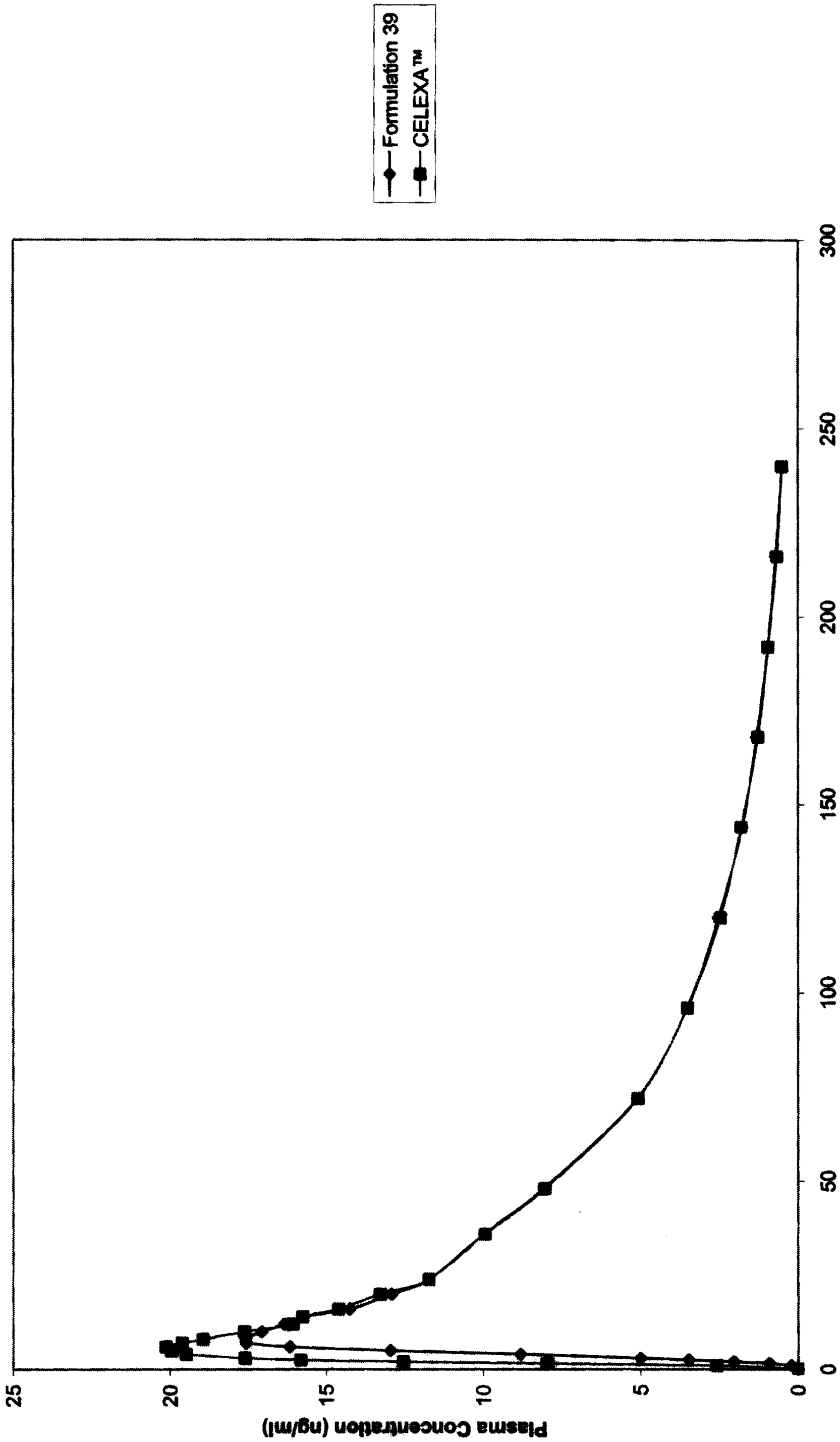


FIGURE 13: Mean Plasma Citalopram Concentrations (n=50)

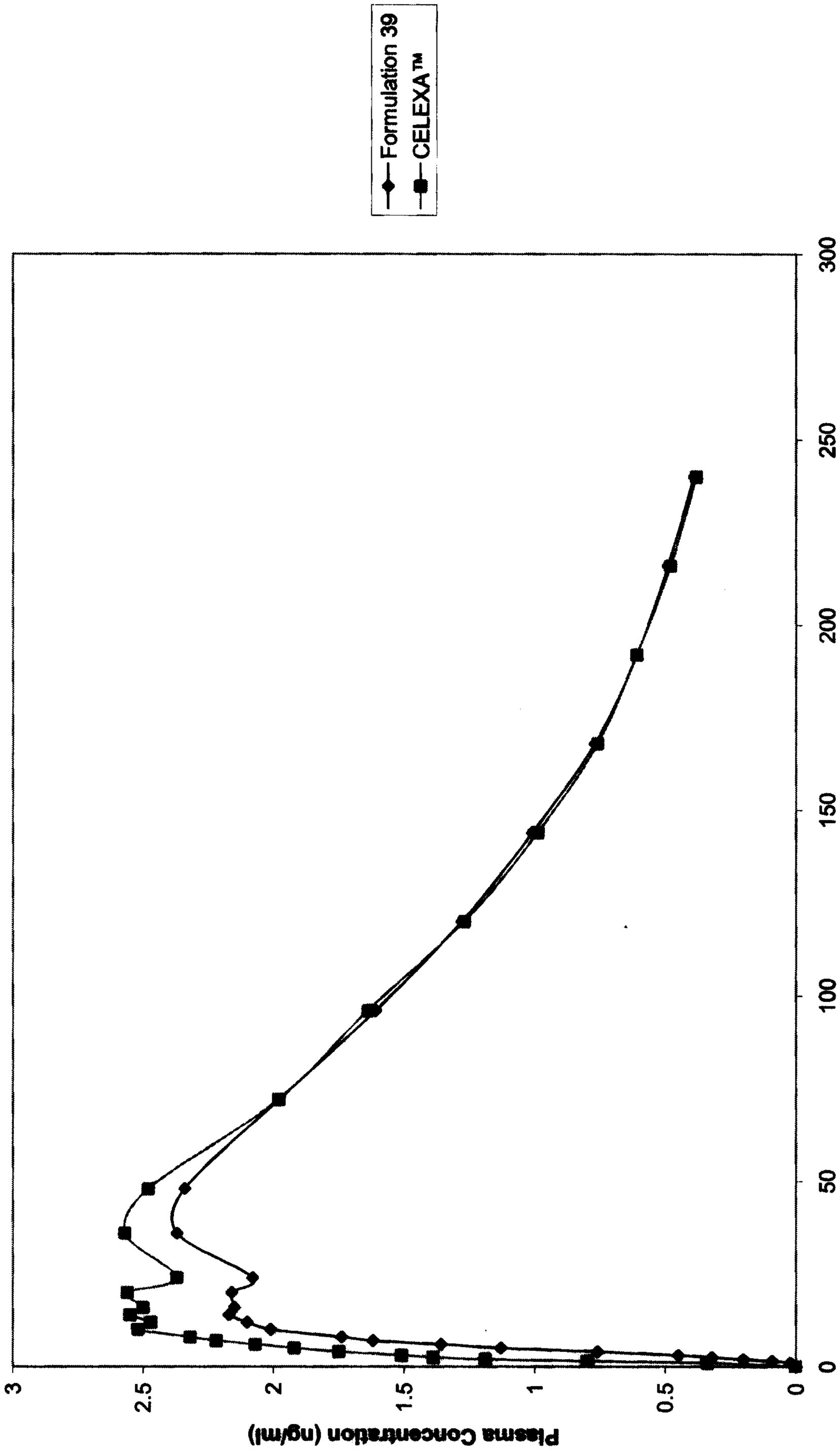


FIGURE14: Mean Plasma Desmethylcitalopram Concentrations (n=50)

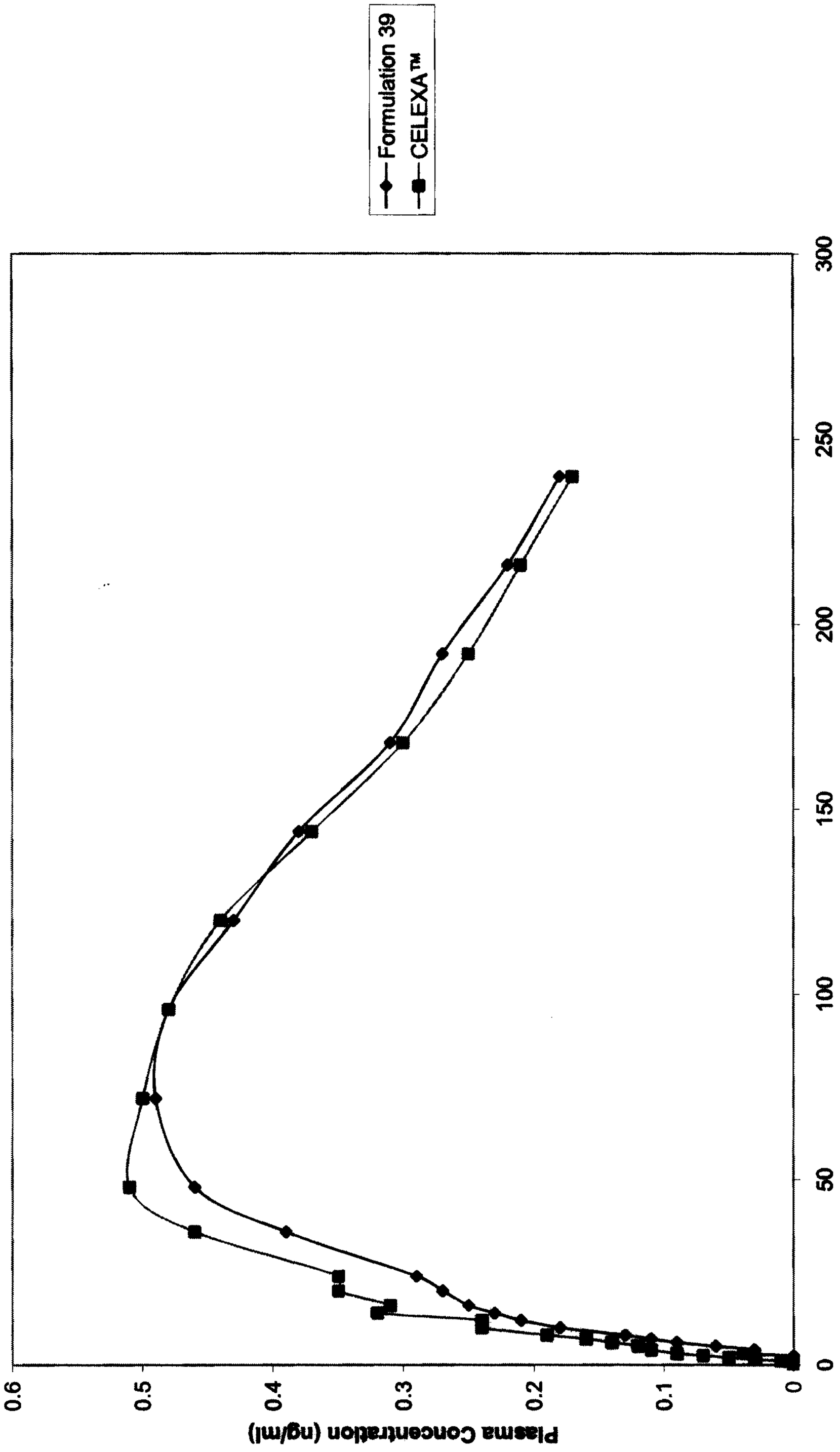


FIGURE 15: Mean Plasma Didesmethylcitalopram Concentrations (n=50)

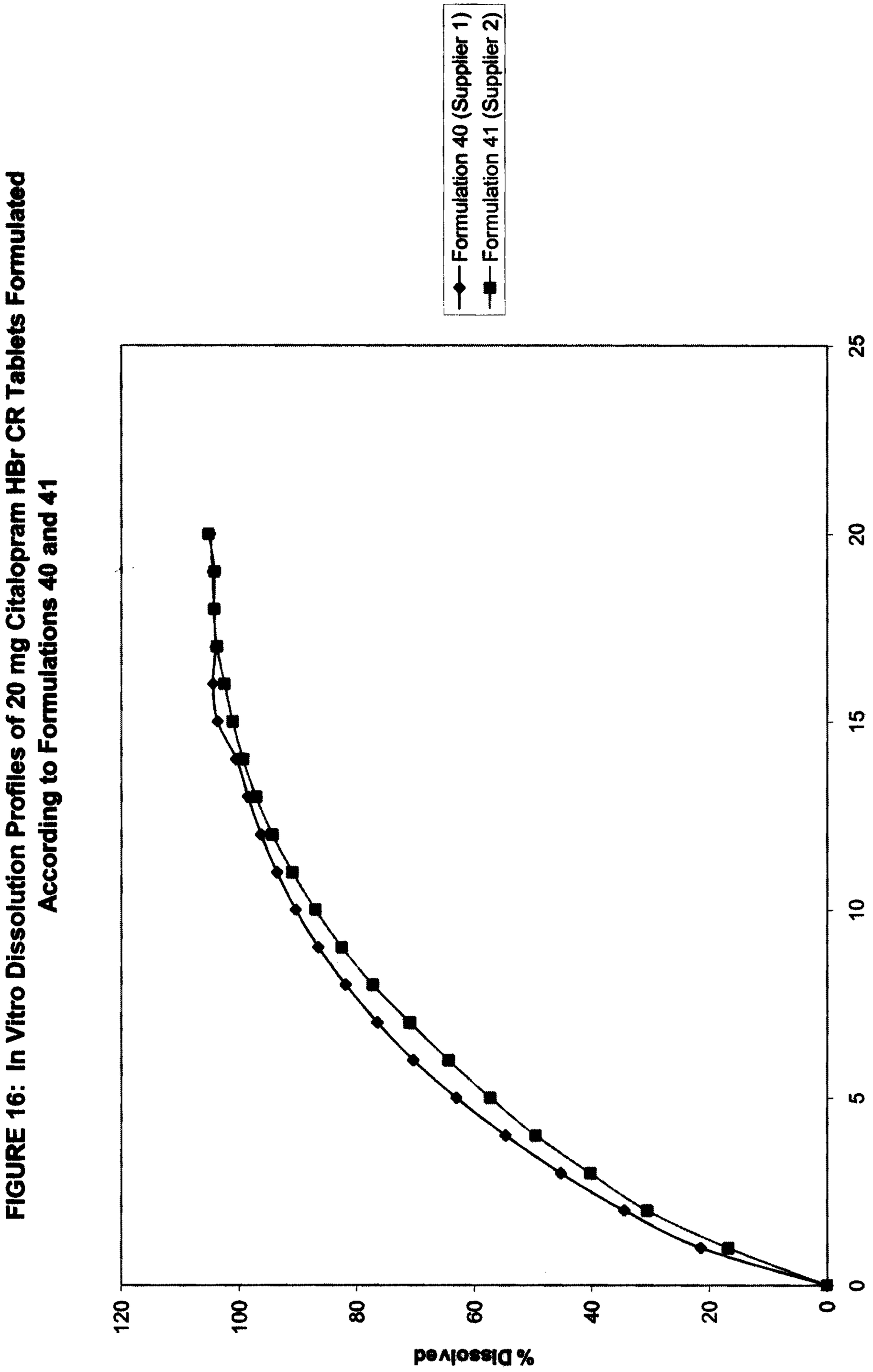


FIGURE 16: In Vitro Dissolution Profiles of 20 mg Citalopram HBr CR Tablets Formulated According to Formulations 40 and 41

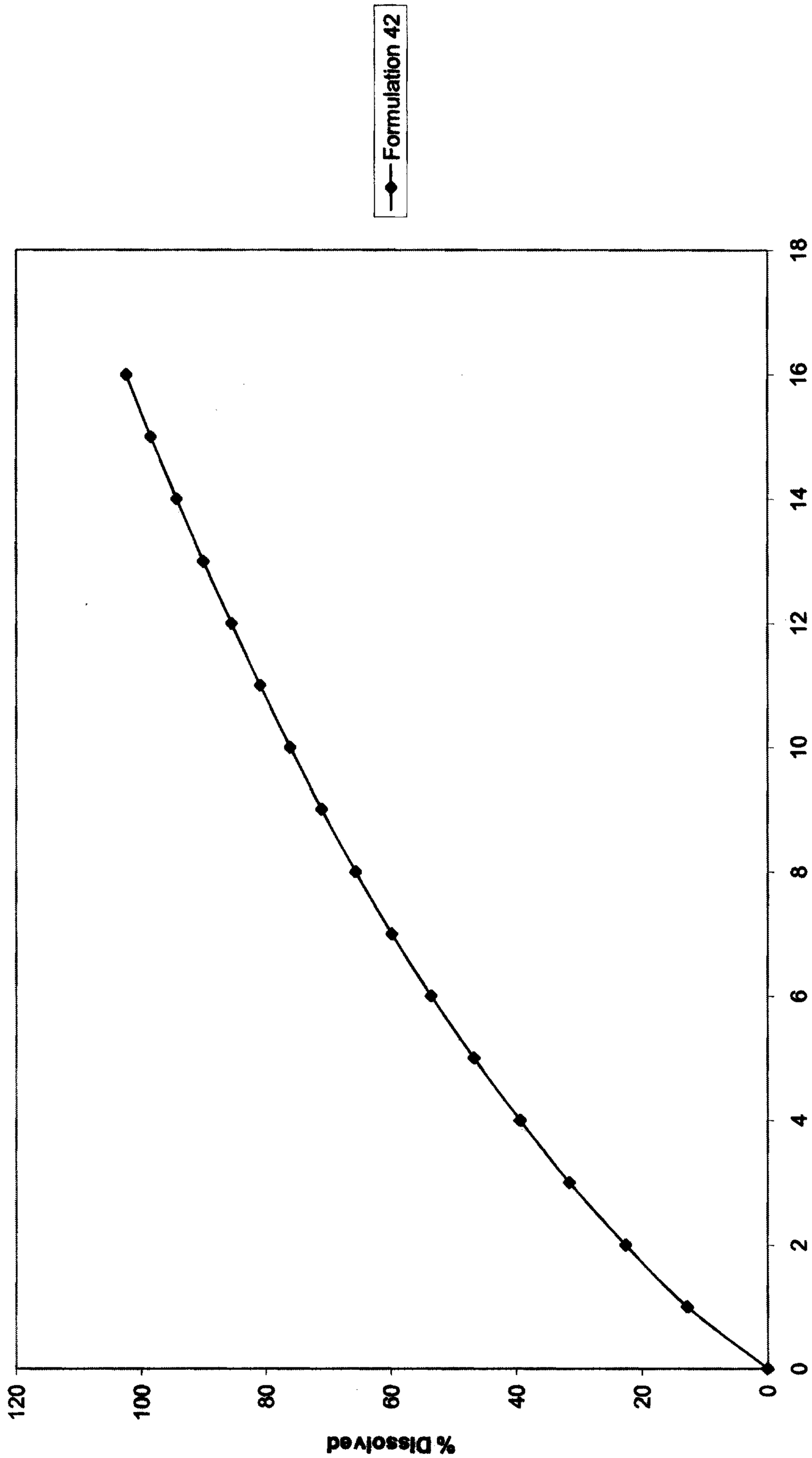


FIGURE 17: In Vitro Dissolution Profile of 20 mg Paroxetine HCl CR Tablets Formulated According to Formulation 42

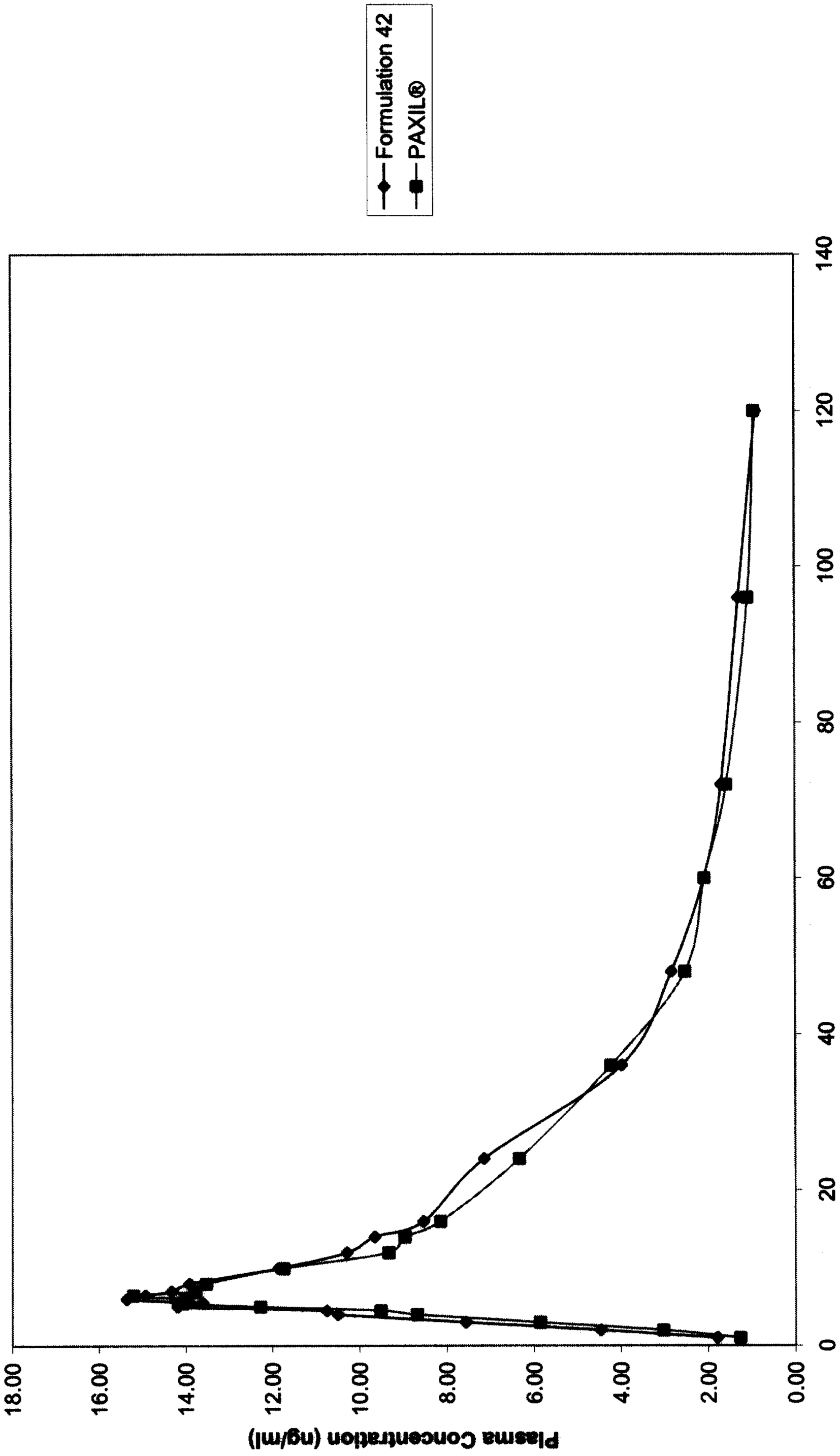
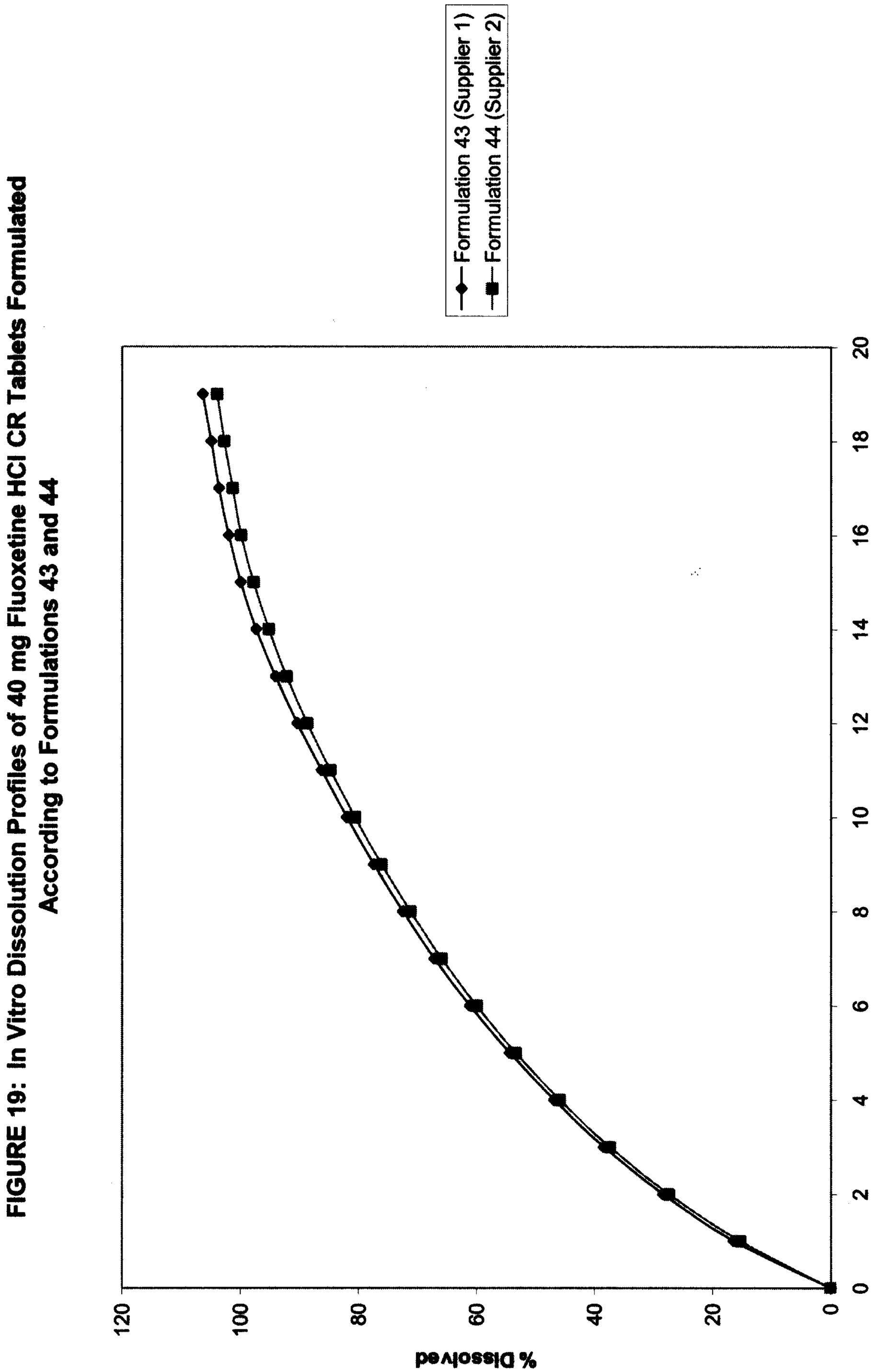


FIGURE 18: Mean Plasma Paroxetine Concentrations (n=12)


FIGURE 19: In Vitro Dissolution Profiles of 40 mg Fluoxetine HCl CR Tablets Formulated According to Formulations 43 and 44
Formulation 43 (Supplier 1)
Formulation 44 (Supplier 2)
% Dissolved
120
100
80
60
40
20
0
Time (hrs)
0
2
4
6
8
10
12
14
16
18
20

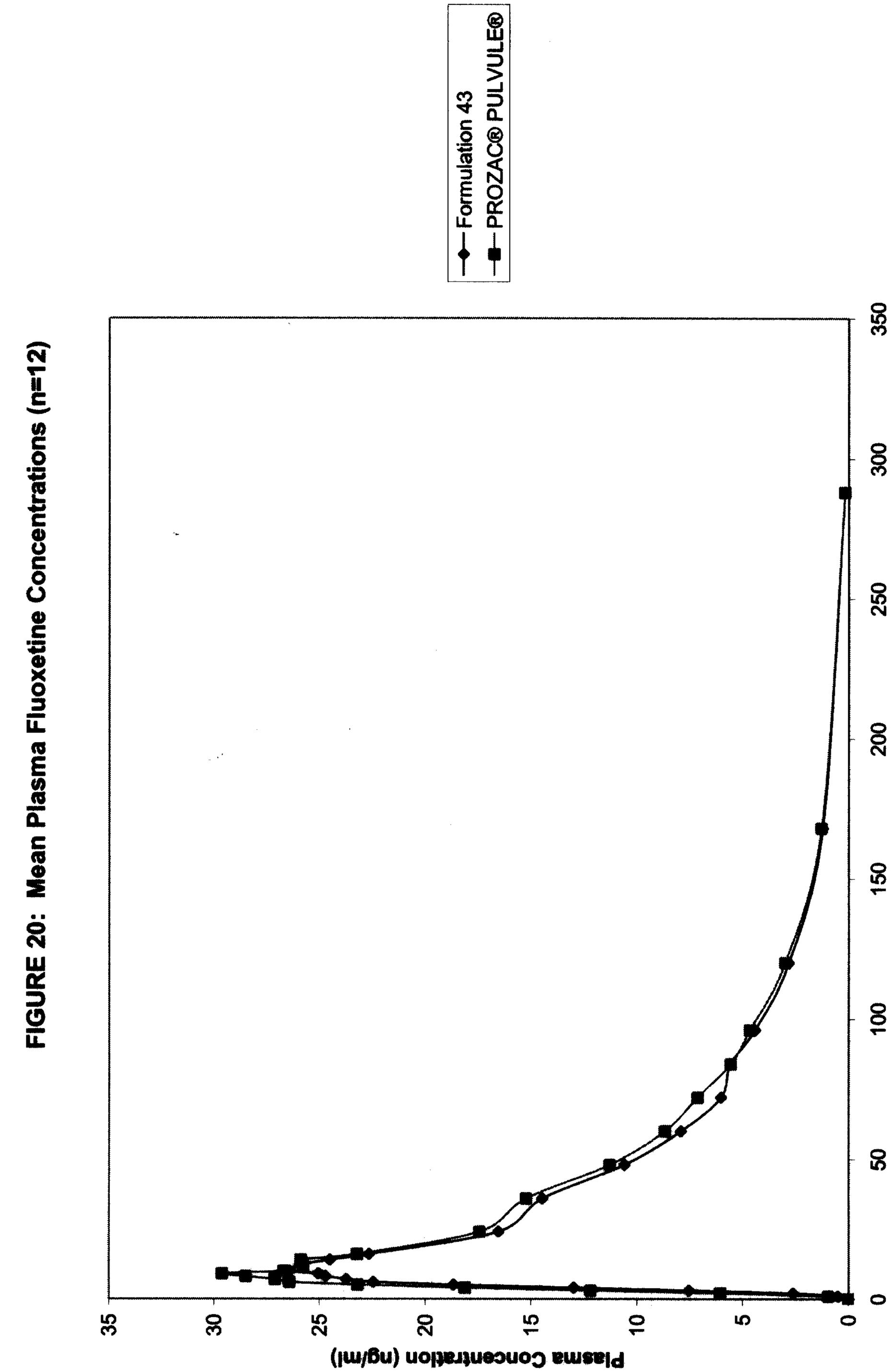


FIGURE 20: Mean Plasma Flu

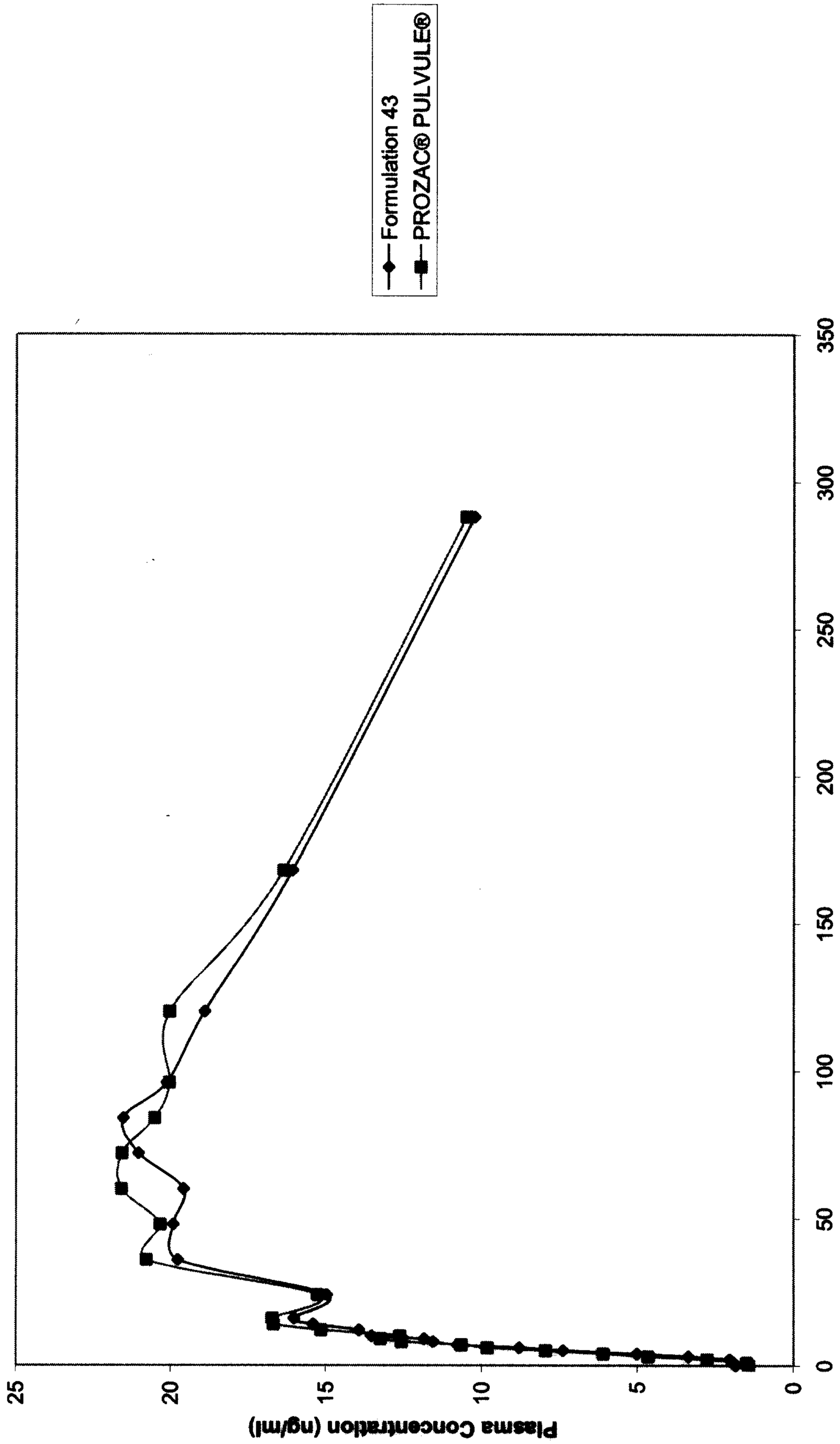


FIGURE 21: Mean Plasma N

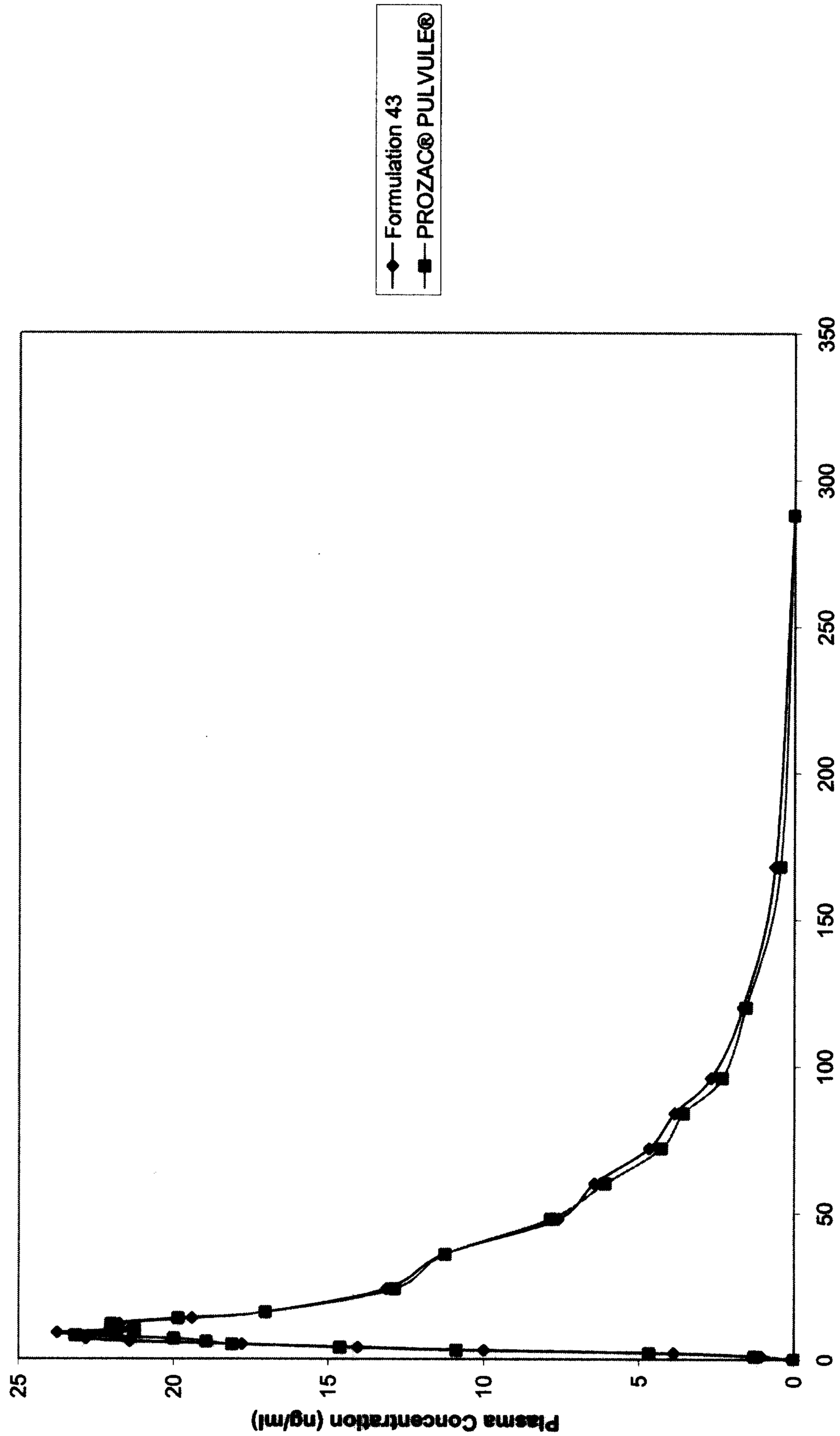


FIGURE 22: Mean Plasma Fluoxetine Concentrations (n=11)

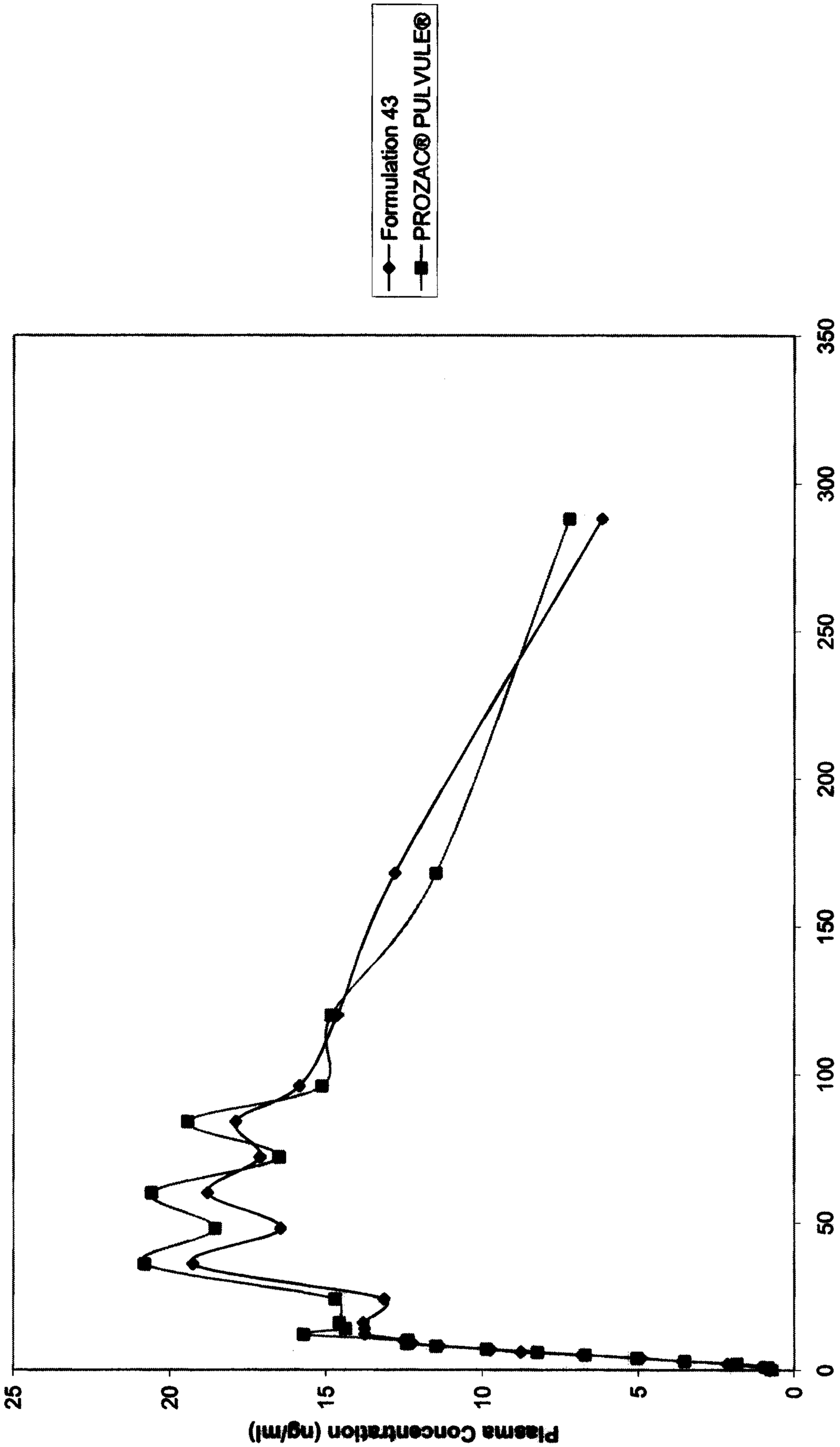


FIGURE 23: Mean Plasma Norfluoxetine Concentrations (n=11)

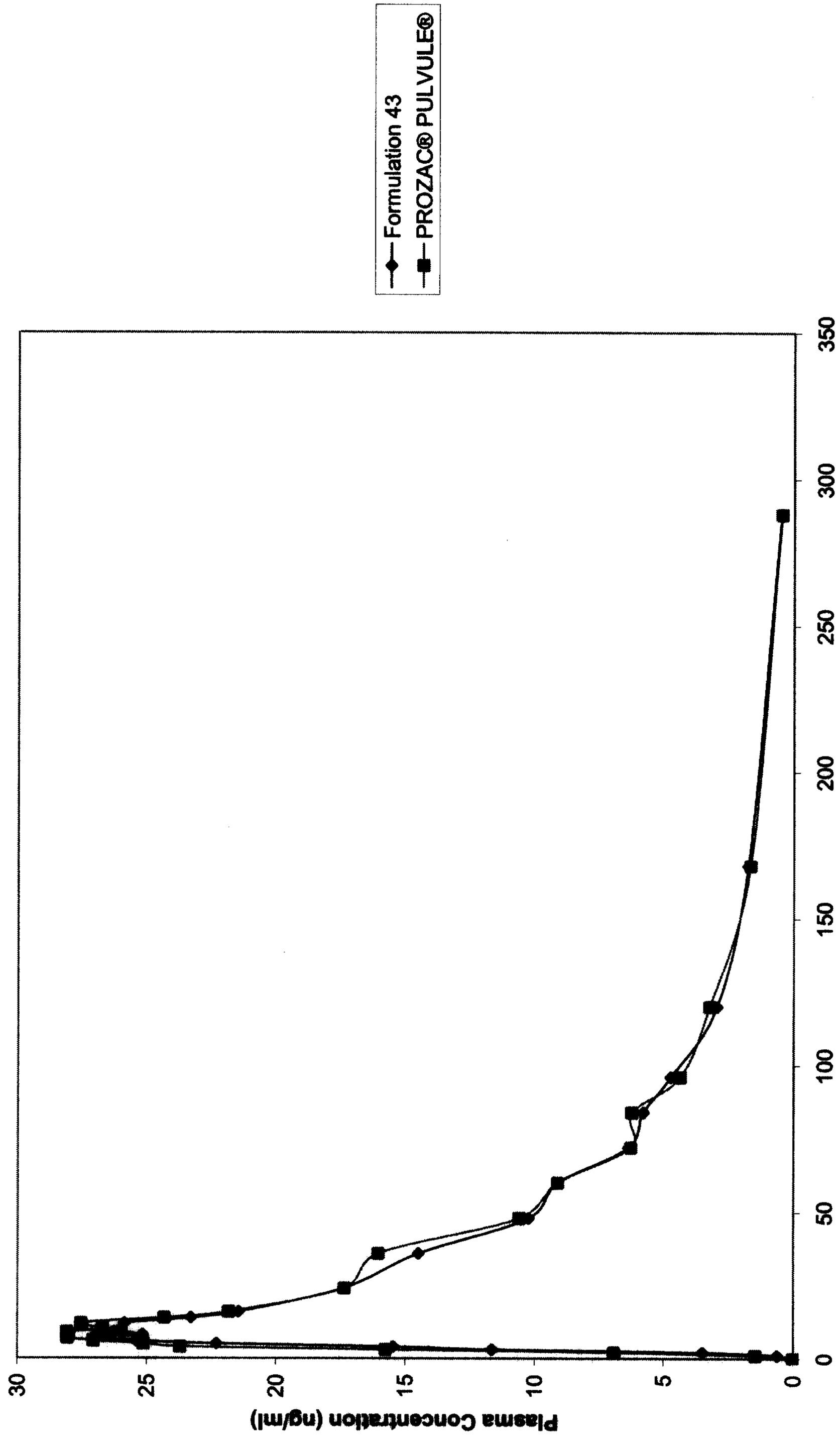


FIGURE 24: Mean Plasma Fluoxetine Concentrations (n=11)

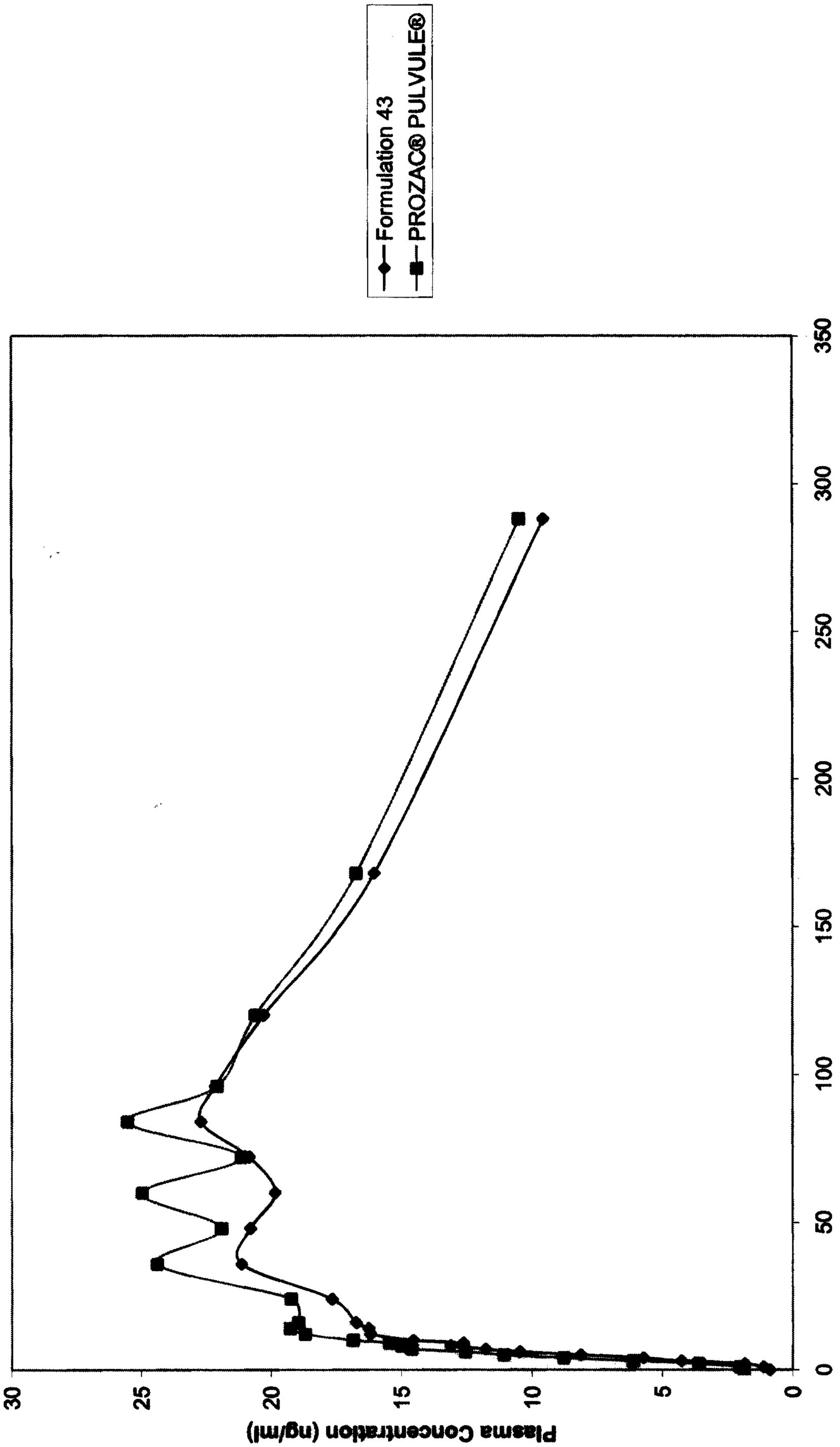


FIGURE 25: Mean Plasma N

SCHEMATIC DIAGRAM FOR THE BIO-BATCH MANUFACTURE OF SSRI CR 20 MG TABLETS

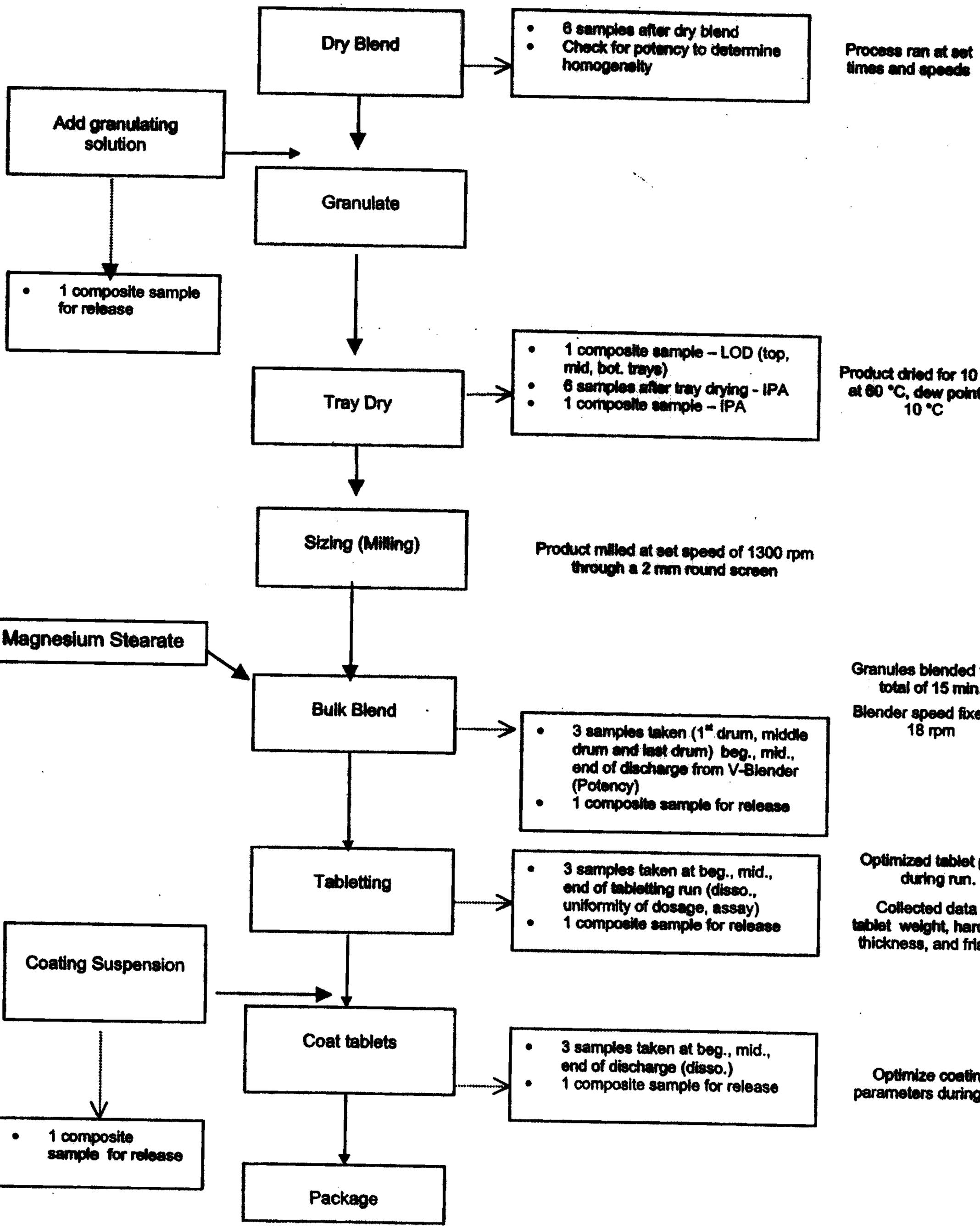


FIGURE 26

Mean Plasma Citalopram Concentrations (n=50)

