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(54) Title: PHARMACEUTICAL DOSAGE FORMS COMPRISING ECOPIPAM FREE BASE OR PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF

(57) Abstract: The present invention relates to novel pharmaceutical dosage forms comprising ecopipam or its pharmaceutically acceptable salt, a process for their preparation, and their use for the treatment of various central nervous system disorders while at the same time reducing or eliminating any adverse side effects.

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PHARMACEUTICAL DOSAGE FORMS COMPRISING ECOPIPAM FREE BASE OR PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of the filing date of U.S. Provisional Application No. 61/671,040, which was filed on July 12, 2012. For the purpose of any U.S. application that may claim the benefit of U.S. Provisional Application No. 61/671,040, the contents of that earlier filed application are hereby incorporated by reference in their entirety.

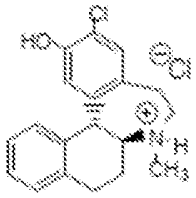
TECHNICAL FIELD OF THE INVENTION

The present invention relates to pharmaceutical dosage forms comprising ecopipam free base or a pharmaceutically acceptable salt thereof, processes for their preparation, and their use in the treatment of various central nervous system (CNS) disorders.

BACKGROUND OF THE INVENTION

Dopamine receptors are a class of receptors expressed in the central nervous system and associated with a number of neurological processes such as pleasure, memory, and motor skills. The receptors are classified by their unique genetic sequence into five types, designated D_1 through D_5 (Civelli *et al.*, *Ann. Rev. Pharmacol. Toxicol.* 32:281-307, 1993). The structural similarities of the receptors allow them to also be classified into two broad families: the D_1 receptor family, which includes D_1 and D_5 receptors, and the D_2 family, which includes D_2, D_3, and D_4 receptors.

Ecopipam free base is a benzazepine derivative that is a selective antagonist of the D_1 family of receptors. Ecopipam hydrochloride (SCH 39166 HCl; $C_{19}H_{20}NOCl{\cdot}HCl$) has the chemical structure shown immediately below.



SCH 39166 HCl

Previous studies have characterized the pharmacokinetics (PK) of ecopipam when delivered as an immediate release (IR) oral tablet. These studies have shown that ecopipam has a

peak plasma level at 2 hours after oral administration and a rather long "tail" giving a calculated half-life of approximately 10 hours. Repeated dose studies have shown little accumulation and little change in the shape of this curve. Previous studies have also shown that the peak adverse (undesirable) sedative effects of ecopipam occur within several hours of dosing. These sedative effects may be related to the high plasma levels at those times since the effects peak at roughly 2-4 hours post dose and dissipate by 6-8 hours thereafter. Likewise, in at least some cases, the efficacy of ecopipam can be related to its plasma levels. For example, studies have been conducted to examine ecopipam's ability to antagonize the euphoric effects of stimulants such as cocaine (Romach *et al.*, *Arch. Gen. Psychiatry* 56:1101-1106, 1999; Haney *et al.*, *Psychopharmacology* (Berl.) 155(4):330-337, 2001; and Nann-Vernotica *et al.*, *Psychopharmacology* (Berl.) 155(4):338-347, 2001). Romach *et al.* has shown that when ecopipam was given in close proximity (~2 hours) to the stimulant dose, there was a blockade of the euphoria stimulation. In contrast, when ecopipam was given earlier (>12 hours before the stimulant) there was no similar antagonism (Haney *et al.*, *supra*, and Nann-Veronica *et al.*, *supra*).

U.S. Patent No. 4,973,586 discloses fused benzazepines, such as ecopipam free base and its pharmaceutically acceptable salts, as selective D_1 antagonists useful in the treatment of various disorders, such as psychoses, depression, and pain. U.S. Patent No. 6,262,049 discloses immediate release (IR) pharmaceutical dosage forms comprising ecopipam free base and its pharmaceutically acceptable salts useful to reduce cravings for nicotine or tobacco in mammals. In addition, U.S. Patent Nos. 7,211,574 and 7,504,391 disclose IR pharmaceutical dosage forms comprising ecopipam free base and its pharmaceutically acceptable salts useful for treating obsessive-compulsive, eating, and somatoform disorders, among others.

Several side effects, however, are associated with the administration of ecopipam, particularly when administered as typical IR pharmaceutical dosage forms (Astrup *et al.*, *Obesity* 15(7):1717–1731, 2007 and Nathan *et al.*, *CNS Neuroscience and Therapeutics* 00:1-16, 2010). For example, the side effects may include fatigue, headache, nausea, and somnolence. In addition, there may be a patient compliance problem with a suboptimal dosing regimen where frequent doses may be required, such as the need for administering a pharmaceutical dosage form three or four times a day.

Sustained or controlled release formulations have been previously developed for the treatment of some CNS disorders. For example, U.S. Patent Nos. 6,322,819, 6,605,300, RE41,148,

RE42,096, 6,919,373, and 6,930,129 disclose controlled release (CR) formulations of stimulants, such as Adderall® and Concert®, for treating attention deficit hyperactivity disorder (ADHD). U.S. Patent Nos. 5,648,093 and 6,224,905 disclose CR formulations for the treatment of schizophrenia, such as depot formulations of risperidone or haloperidol. U.S. Patent No. 7,037,525 discloses CR formulations containing oxcarbazepine for the treatment of epilepsy. No such CR formulations have been disclosed for ecopipam.

SUMMARY OF THE INVENTION

We have recognized the need for a dosage form of ecopipam that conveys the benefits of immediate release (*e.g.*, a fairly rapid onset of action) as well as the advantages of a sustained release form (*e.g.*, in maintaining plasma levels over a longer period of time). Such a controlled-release formulation would not only incorporate the beneficial aspects of both the immediate and sustained release portions, but could also have fewer acute side effects, greater efficacy, and be amenable to dosing optimization. Accordingly, the present invention relates to controlled release pharmaceutical dosage forms that include ecopipam free base or a pharmaceutically acceptable salt thereof, processes for their preparation, and their use in the treatment of various central nervous system disorders. In some instances, it may be preferable to administer a dosage form consisting of just an immediate release component (IRC) or just a controlled release component (CRC). Administering just one or the other in certain instances could further reduce a side effect, such as fatigue, or better control certain acute symptoms. Accordingly, the invention features not only pharmaceutical dosage forms having both immediate release (IR) and controlled release (CR) components, but also pharmaceutical dosage forms of ecopipam having one component or the other. The dosage forms of the invention and component parts thereof can be and generally will be "pharmaceutically acceptable" in that the compounds, materials, compositions, and/or dosage forms are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable benefit/risk ratio.

In one aspect, the invention features pharmaceutical dosage form that includes an IRC comprising from about 20% to about 60% ecopipam free base or its pharmaceutically acceptable salt, by weight, based on the total weight of the immediate release component; and a CRC comprising from about 30% to about 90% ecopipam free base or its pharmaceutically acceptable

salt, by weight, based on the total weight of the controlled release component. Unless the context clearly indicates otherwise, by "about" we mean within 10%, plus or minus, of the specified value. More specifically, the IRC can include from about 12 mg to about 300 mg of ecopipam free base or its pharmaceutically acceptable salt, and the CRC can include from about 30 mg to about 400 mg of ecopipam free base or its pharmaceutically acceptable salt. In some embodiments, the IRC can include about 30% ecopipam free base or its pharmaceutically acceptable salt, by weight, based on the total weight of the immediate release component, and the CRC can include about 63.5% ecopipam free base or its pharmaceutically acceptable salt, by weight, based on a total weight of the CRC. In some embodiments, the IRC can include about 36 mg of ecopipam free base or its pharmaceutically acceptable salt, and the CRC can include about 54 mg of ecopipam free base or its pharmaceutically acceptable salt. In some embodiments, the IRC comprises from about 15% to about 85% (*e.g.*, about 40% or about 50%) of the total weight of the pharmaceutical dosage form, and the CRC comprises from about 15% to about 85% (*e.g.*, about 50% or 60%) of the total weight of the pharmaceutical dosage form.

Ecopipam or a pharmaceutically acceptable salt thereof can constitute about 50% of the IRC and about 50% of the CRC. In some embodiments, the dosage form can include from about 80 mg to about 110 mg (*e.g.*, about 90 mg) of ecopipam free base or its pharmaceutically acceptable salt. In some embodiments, the IRC can include from about 30-40% (*e.g.*, 40%) to about 80% of one or more excipients, by weight, based on the total weight of the immediate release component, and the CRC can include from about 10% to about 60-70% (*e.g.*, 70%) of one or more excipients, by weight, based on a total weight of the controlled release component. In some embodiments, the immediate release component can include about 70% of one or more excipients, by weight, based on the total weight of the immediate release component, and the controlled release component can include about 36.5% of one or more excipients, by weight, based on the total weight of the controlled release component. The one or more excipients can be one or more of: microcrystalline cellulose, hydroxyalkyl alkylcellulose, hydroxyalkyl cellulose, a glycol, sodium lauryl sulfate, a starch or a derivative thereof, a cellulose ether, a cellulose ester, a copolymer of esters of at least one of acrylic acid and methacrylic acid, a sugar or sugar alcohol, an alginate, gelatin, a food coloring, polyvinylalcohol, polyvinyl-pyrrolidone, and stearic acid and salts thereof. In the course of this application, we may provide lists such as this one. It is to be understood that only one item may be selected; that a combination of items may be selected; and

that one or more of the listed items may be excluded. For example, a formulation useful as described herein can include microcrystalline cellulose; a glycol; or both microcrystalline cellulose and a glycol. Further, any of these alternatives can be explicitly excluded. For example, a formulation useful as described herein can include microcrystalline cellulose and a glycol and exclude a sugar.

The pharmaceutically acceptable salt of ecopipam can be hydrochloride. The IRC and/or the CRC can comprise beads. The pharmaceutical dosage form can be a capsule. When administered to a human subject, the pharmaceutical dosage form can provide, on average, a maximum plasma concentration (Cmax) of ecopipam within 2.5 hours of administration and a plasma concentration of ecopipam 12 hours after administration of about 35% to about 50% of Cmax.

In another aspect, the invention features a method of treating a central nervous system disorder in a patient. The method can include administering to the patient an effective amount of a pharmaceutical dosage described herein. The central nervous system disorder can be Lesch-Nyhan disease, pathological gambling, Tourette's syndrome, or Parkinson's disease. In some embodiments, the invention features a method of treating a central nervous system disorder in a patient, the method comprising administering to the patient an effective amount of the pharmaceutical dosage form comprising beads. The central nervous system disorder can be Lesch-Nyhan disease, pathological gambling, Tourette's syndrome, or Parkinson's disease.

In another aspect, the invention features a matrix tablet comprising about 40% to about 90%, by weight, of ecopipam free base or a pharmaceutically acceptable salt thereof, and a pH-dependent or pH-independent polymer. In some embodiments, the tablet can include a pH-dependent polymer. The pH-dependent polymer can be a cross-linked acrylic acid homopolymer, cellulose acetate phthalate (CAP), hydroxypropylmethyl cellulose phthalate (HPMCP), methacrylic acid, a methacrylic ester, or polyvinyl acetate phthalate. In some embodiments, the tablet can include a pH-independent polymer. The pH-independent polymer can be hydroxypropylmethyl cellulose (HPMC), hydroxypropyl cellulose, or polyethylene glycol (PEG). The tablet can include about 5% to about 60% of the polymer and, optionally, a further excipient. The polymer or the further excipient can be microcrystalline cellulose, hydroxyalkyl alkylcellulose, sodium chloride, hydroxyalkyl cellulose, a glycol, sodium lauryl sulfate, a starch or a derivative thereof, a cellulose ether, a cellulose ester, a copolymer of an ester of at least one of

acrylic acid and at least one methacrylic acid, a sugar or sugar alcohol, an alginate, gelatin, a food coloring, polyvinylalcohol, polyvinylpyrrolidone, or stearic acid or a salt thereof.

In another aspect, the invention features a pharmaceutical dosage form that includes a matrix tablet described herein and an immediate release component. In some embodiments, the matrix tablet is encapsulated by the immediate release component or is formulated as a layer adjacent to a layer of the immediate release component. When administered to a human subject, the pharmaceutical dosage form provides on average, a maximum plasma concentration (Cmax) of ecopipam within 2.5 hours of administration and provides a plasma concentration of ecopipam 12 hours after administration of about 35% to about 50% of Cmax.

In another aspect, the invention features a method of treating a central nervous system disorder in a patient. The method can include the step of administering to the patient an effective amount of the matrix tablet or the pharmaceutical dosage form described herein. The central nervous system disorder can be Lesch-Nyhan disease, pathological gambling, Tourette's syndrome, or Parkinson's disease.

In another aspect, the invention features a pharmaceutical dosage form comprising: (a) an immediate release component including from about 25% to about 50% ecopipam free base or a pharmaceutically acceptable salt thereof, by weight, based on the total weight of the immediate release component; and (b) a controlled release component comprising from about 65% to about 95% ecopipam free base or a pharmaceutically acceptable salt thereof, by weight, based on the total weight of the controlled release component; wherein the dosage form is formulated as a tablet. In some embodiments, the immediate release component can include from about 25% to about 35%, by weight, of the total weight of the tablet, and the controlled release component can include from about 37% to about 47%, by weight, of the total weight of the tablet. The tablet can include from about 12% to about 42% of one or more excipients, by weight, based on a total weight of the tablet. The one or more excipients can be selected from those described above (microcrystalline cellulose … or stearic acid and salts thereof) or elsewhere herein. When administered to a human subject, the pharmaceutical dosage form provides, on average, a maximum plasma concentration (Cmax) of ecopipam within 2.5 hours of administration and provides a plasma concentration of ecopipam 12 hours after administration of about 35% to about 50% of Cmax.

In another aspect, the invention features a pharmaceutical dosage form that can include a controlled release component coated with a layer of an immediate release component wherein: (a) the immediate release component including from about 5% to about 50% of ecopipam free base or a pharmaceutically acceptable salt thereof, by weight, based on a total weight of the pellet; (b) the controlled release component including from about 40% to about 80% of ecopipam free base or a pharmaceutically acceptable salt thereof, by weight, based on a total weight of the pellet; and (c) the dosage form is formulated as a pellet. In some embodiments, the immediate release component can include about 26%, by weight, of the total weight of the pellet, and the immediate release component can include about 61%, by weight, of the total weight of the pellet. The pellet can include from about 10% to about 50%, by weight, of one or more excipients. The one or more excipients can be selected from those described above (microcrystalline cellulose … or stearic acid and salts thereof) or elsewhere herein.

In another aspect, the invention features an osmotic pump composition including, by weight, based on the total weight of the osmotic pump composition: (a) from about 20% to about 50% of ecopipam free base or a pharmaceutically acceptable salt thereof; (b) from about 35% to about 65% of sodium chloride or other osmotic agent; and (c) up to about 20% of one or more excipients. The one or more excipients can be selected from those described above (microcrystalline cellulose … or stearic acid and salts thereof) or elsewhere herein.

In another aspect, the invention features a process for the preparation of the pharmaceutical dosage form described herein. The process can include the steps of: (a) blending ecopipam free base or a pharmaceutically acceptable salt thereof, with one or more excipients to generate a first mixture; (b) adding water to the first mixture and mixing in a planetary mixer to form a paste; (c) feeding the paste into an extruder to produce a first extrudate; (d) spheronizing the first extrudate to produce spheronized beads; and (e) drying the spheronized beads in a fluid bed dryer to obtain an immediate release component; (f) blending ecopipam free base or a pharmaceutically acceptable salt thereof, with one or more excipients to generate a second mixture; (g) adding water to the second mixture and mixing in a planetary mixer to form a second paste; (h) feeding the second paste into an extruder to generate a second extrudate; (i) spheronizing the second extrudate to produce a second population of spheronized beads; (j) drying the second population of spheronized beads in a fluid bed dryer to generate dried, spheronized bead; (k) applying a clear coating of a mixture of hydroxypropyl methylcellulose and hydroxypropyl cellulose to the dried,

spheronized beads to generate coated spheronized beads; (l) applying an enteric coating to the coated spheronized beads; and (m) applying a second clear coating of a mixture of hydroxypropyl methylcellulose and hydroxypropyl cellulose to the spheronized beads from step l) to obtain the controlled release component; (n) blending the spheronized beads from step (e) and step (m); and (o) filling the spheronized beads of step (n) into capsules.

Any of the pharmaceutical compositions of the invention can be formulated for use in the preparation of a medicament, and particular uses are indicated below in the context of treatment.In another aspect, the invention features use of a composition as described herein in the preparation of a medicament and use in the preparation of a medicament for treating a central nervous system disorder. The central nervous system disorder can be Lesch-Nyhan disease, pathological gambling, Tourette's syndrome, or Parkinson's disease.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows microcrystalline cellulose (MCC)/active pharmaceutical ingredient (API) pellets density versus API loading (%) and water content (%).

Figure 2 illustrates the dissolution profile of 225 mg ecopipam HCl capsules having pellet sizes of 850-1400 μm at a pH of 1.0.

Figure 3 illustrates a comparison of the dissolution profile of 225 mg ecopipam HCl capsules having pellet sizes of 850-1400 μm with those having pellet sizes of less than 500 μm.

Figure 4 shows the dissolution profile of 225 mg ecopipam HCl capsules having pellet sizes of 850-1400 μm at a pH of 6.8.

Figure 5 shows the dissolution profiles of 25 and 225 mg ecopipam capsules having pellets sizes of 850-1400 μm at a pH of 1.0.

Figure 6 shows the dissolution profile of 25 mg ecopipam HCl capsules in various dissolution media.

Figure 7 shows the effect of the total dose on the dissolution profile for the immediate release (IR) pellets in 0.1 N HCl.

Figure 8 shows the effect of the total dose on the dissolution profile for the sustained release (SR) pellets in 0.1 N HCl.

Figure 9 shows the effect of the total dose on the dissolution profile for the SR pellets in 0.1% sodium dodecyl sulfate (SDS) in sodium phosphate buffer at a pH of 6.8.

Figure 10 represents 25 and 100 mg capsules dissolution profiles of lot 003 ecopipam HCl, uncoated and coated pellets in a pH 6.8 in 0.1% SDS medium.

Figure 11 represents dissolution profiles for ecopipam HCl 100 mg coated capsules from lot 003 and uncoated pellets from lot 014 at a pH of 6.8 in 0.1% SDS medium.

Figure 12 shows the dissolution profiles for lot L107-03015 corresponding to 25 and 100 mg ecopipam HCl capsules.

Figure 13 shows the dissolution profiles for lots 008, 009, and 015 corresponding to 25 mg ecopipam HCl capsules.

Figure 14 shows the dissolution profiles for lots 008, 009, 015, and 016 corresponding to 25 mg ecopipam HCl capsules in 0.1 N HCl.

Figure 15 shows the dissolution profiles for lots 008, 015, and 016 corresponding to 100 mg ecopipam HCl capsules in 0.1 N HCl.

Figure 16 illustrates the dissolution profiles for lots 001, 003, and 019 corresponding to 100 mg ecopipam HCl uncoated pellets at a pH of 6.8 in 0.1% SDS medium.

Figure 17 illustrates the dissolution profiles for 90 and 100 mg ecopipam HCl capsules in 0.1 N HCl for 2 hours followed by a pH of 6.8 in 0.1% SDS.

Figure 18 shows the dissolution profiles for 90 mg ecopipam HCl capsules corresponding to lots L107-03021 and L107-03003-5O20A5O-017-90MG in 0.1 N HCl for 2 hours followed by a pH of 6.8 in 0.1% SDS.

Figure 19 shows the dissolution profiles for ecopipam HCl CR pellets used in lot L107-03003-5O20A5O-017 at a pH of 6.8 in 0.1% SDS and after 12 weeks at 25 °C at 60% relative humidity (RH).

Figure 20 shows the stability dissolution profiles for 100 mg ecopipam HCl capsules with enteric coating corresponding to lot L107-03-003-5O20A.

Figure 21 shows the stability dissolution profiles for 100 mg ecopipam HCl capsules with 5% Opadry® coating corresponding to lot L107-03-009-5O.

Figure 22 shows the stability dissolution profiles for 100 mg ecopipam HCl capsules corresponding to lot L107-03-003-5O20A-009 at 40 °C at 75% relative humidity.

Figure 23 shows the dissolution profiles for 100 mg ecopipam HCl capsules with enteric coating and Opadry® coating corresponding to lot L107-03-003-5O20A5O.

Figure 24 shows the dissolution profile for 100 mg ecopipam HCl capsules corresponding to lot L107-03017.

Figure 25 shows the dissolution profile for 100 mg ecopipam HCl capsules corresponding to lot L107-03-003-5O20A5O-017.

Figure 26 shows data from a study comparing plasma levels of ecopipam given on day 1 and day 13 after repeated daily oral dosing.

Figure 27 shows the results of a human pharmacokinetic study in which an IR/CR dosage form of ecopipam was compared to existing immediate release tablets.

DETAILED DESCRIPTION OF THE INVENTION

Typical drug release from standard controlled release dosage forms, such as matrix tablets, osmotic pumps, and coated beads, can be approximated as having first order kinetics, zero order kinetics, or something in between. However, these dosage forms lack the ability to provide patients with both rapid relief and sustained, effective doses. That is, their release profile does not allow for an immediate release of the pharmaceutical agent that effects a rapid onset of action as well as a controlled release that subsequently maintains an effective plasma level of the agent over a long period of time.

In one aspect, the present invention features sustained release pharmaceutical dosage forms that also effect immediate release of ecopipam in a free base form or a pharmaceutically acceptable salt thereof. Although we often refer to "ecopipam in a free base form or a pharmaceutically acceptable salt thereof," we may not mention salts at every possible opportunity. Unless the text clearly indicates otherwise, it is to be understood that wherever an ecopipam free base can be incorporated in the present compositions, a pharmaceutically acceptable salt thereof can be incorporated in addition to, or instead of, the free base and vice versa. We may also refer to ecopipam in a free base form or a pharmaceutically acceptable salt thereof more generally and simply as an active pharmaceutical ingredient (API) or "active agent." In other aspects, the invention features dosage forms having only an immediate release or only a sustained release component; processes for preparing the dosage forms described herein; and their use in the treatment of various central nervous system disorders.

More specifically, the invention features pharmaceutical dosage forms that include an immediate release component (IRC) having from about 20% to about 60% ecopipam free base or a

pharmaceutically acceptable salt thereof, by weight, based on the total weight of the immediate release component, and a controlled release component (CRC) having from about 30% to about 90% ecopipam free base or its pharmaceutically acceptable salt, by weight, based on the total weight of the controlled release component. For example, the IRC can include about 25% to about 50% by weight of ecopipam free base or its pharmaceutically acceptable salt, based on a total weight of the immediate release component (*e.g.*, about 25%, 30%, 40%, or 50% of the IRC, by weight), and the CRC can include about 50% to about 80% by weight of ecopipam free base or a pharmaceutically acceptable salt thereof (*e.g.*, about 63% (*e.g.*, 63.5%), 65%, 68% (*e.g.*, 68.5%), or 70% of the CRC, by weight. For example, the CRC can include from about 65% to about 95%, by weight, of ecopipam free base or a pharmaceutically acceptable salt thereof. In other embodiments, the amount of API in the CRC can be less. We often state that amounts and percentages are "about" a certain numerical value. Other than in the operating examples, or where otherwise indicated, all numbers expressing quantities of ingredients or reaction conditions used herein should be understood as modified in all instances by the term "about."

With respect to absolute amounts, the IRC can include from about 12 mg to about 300 mg of ecopipam free base or a pharmaceutically acceptable salt thereof (*e.g.*, about 20 mg, 22 mg, 30 mg, 31 mg, 32 mg, 33 mg, 34 mg, 35 mg, 36 mg, or 40 mg and up to about 200 mg, 210 mg, 225 mg, 250 mg (*e.g.*, about 245-255 mg), 275 mg, or 290 mg), and the CRC can include from about 30 mg to about 400 mg of ecopipam free base or its pharmaceutically acceptable salt (*e.g.*, about 31 mg, 40 mg, 45 mg, 48 mg, 50 mg, 53 mg, 54 mg, 55 mg, 60 mg, or 70 mg and up to about 275 mg, 280 mg, about 300 mg (*e.g.*, about 290-310 mg), or about 335 mg (*e.g.*, about 330-340 mg).

In one embodiment, the IRC contains about 30 mg to about 210 mg of ecopipam free base or a pharmaceutically acceptable salt thereof, and the CRC contains about 48 mg to about 290 mg of ecopipam free base or a pharmaceutically acceptable salt thereof. In another embodiment, the IRC contains about 22 mg to about 290 mg of ecopipam free base or a pharmaceutically acceptable salt thereof, and the CRC contains about 31 mg to about 335 mg of ecopipam free base or a pharmaceutically acceptable salt thereof. In another embodiment, the IRC contains about 31 mg to about 245 mg of ecopipam free base or a pharmaceutically acceptable salt thereof, and the CRC contains about 40 mg to about 290 mg of ecopipam free base or a pharmaceutically acceptable salt thereof.

In total, the dosage form can include about 40 mg to about 1,000 mg (*e.g.*, 800 mg). For example, the dosage form can include, in total, about 80 mg to about 110 mg (*e.g.*, about 90 mg) of ecopipam free base or its pharmaceutically acceptable salt. Table A summarizes the amounts of ecopipam or a pharmaceutically acceptable salt thereof in each component of the dosage form.

TABLE A	% by Weight of Ecopipam or its Pharmaceutically Acceptable Salt	Amount (mg) of Ecopipam or its Pharmaceutically Acceptable Salt
IRC	About 20% to about 60%	About 12 mg to about 300 mg
CRC	About 30% to about 90%	About 30 mg to about 400 mg

The amount of each release component (*i.e.*, the amount of the IRC relative to the CRC) can vary in order to generate dosage forms with varied pharmacokinetics. The immediate release component can constitute about 15% to about 85% of the total weight of the pharmaceutical dosage form (*e.g.*, about 40%, 45%, 50%, 55%, or 60%), and the controlled release component can constitute from about 15% to about 85% (*e.g.*, 25% to about 85%) of the total weight of the pharmaceutical dosage form (*e.g.*, about 40%, 45%, 50%, 55%, or 60%). In one embodiment, the IRC can constitute about 40% of the total weight of the pharmaceutical dosage form, and the CRC can constitute the remaining 60%. In one embodiment, the IRC can constitute about 50% of the total weight of the pharmaceutical dosage form, and the CRC can constitute the remaining 50%.

In Table B, we present suitable ratios of the IRC to the CRC based upon the ratio of API in the IRC to API in the CRC. Our current expectation is that the shaded ranges will be preferable.

TABLE B			
By % of ecopipam dose		By mass	
% in IRC	% in CRC	%IRC	%CRC
20%	80%	43%	57%
30%	70%	56%	44%
40%	60%	67%	33%
50%	50%	75%	25%
60%	40%	82%	18%
70%	30%	88%	13%
80%	20%	92%	8%
90%	10%	96%	4%

Within a pharmaceutical dosage form, the IRC can include from about 40% to about 80% (*e.g.*, about 70%) of one or more excipients, by weight, based on the total weight of the immediate release component, and the CRC can include from about 10% to about 70% of one or

more excipients, by weight, based on a total weight of the controlled release component. For example, in one embodiment, the IRC can include about 70% of one or more excipients and about 30% of an API, and the CRC can include about 35-40% of one or more excipients (*e.g.*, about 36.5%) and about 60%-65% of an API. These percentage values are weight % based on the total weight of the component (the IRC or the CRC) in which the excipients are found.

Excipients are considered to have no therapeutic activity in the body (*see* HANDBOOK OF PHARMACEUTICAL EXCIPIENTS (Am. Pharm. Association 1986)). One of ordinary skill in the art will recognize that many different excipients can be used in formulations according to the present invention. For example, the excipient can be any one or more of the following: microcrystalline cellulose, hydroxyalkyl alkylcellulose, hydroxyalkyl cellulose, a surfactant, glycol, sodium lauryl sulfate, a starch or a derivative thereof, a cellulose ether, a cellulose ester, a copolymer of esters of at least one of acrylic acid and methacrylic acid, a sugar or sugar alcohol, an alginate, gelatin, a food coloring, polyvinylalcohol, polyvinylpyrrolidone, and stearic acid and salts thereof. Other excipients include, but are not limited to, saline, buffered saline, dextrose, water, ethanol, sugars, such as lactose, and combinations thereof. The excipient(s) can be non-sterile or sterile.

Ecopipam may be included in the present dosage forms, in either the immediate-release or the controlled-release component (or both, where both are present), in the form of any pharmaceutically acceptable salt known in the literature. One of ordinary skill in the art can readily refer to sources such REMINGTON'S PHARMACEUTICAL SCIENCES, Arthur Osol, ed., 1553-93 (1980), which is incorporated herein by reference. Preferably, the pharmaceutically acceptable salt is ecopipam hydrochloride. “HCl” as defined herein may have different non-limiting meanings. When used, for example, as ecopipam HCl, “HCl” means the hydrochloride salt of ecopipam. When used, for example, as 0.1 N HCl, “HCl” means an aqueous hydrochloric acid solution.

Other useful salts include, but are not limited to, the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic,

salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluensulfonic, methanesulfonic, ethane dislfonic, oxalic, isethionic, and the like.

The IRC, the CRC, or both of these components can be formulated to include discrete units selected from, but not limited to, beads, granules, particles, tablets, pellets, or mixtures thereof. For example, the immediate release component can include beads, and the beads can be encapsulated. Examples of dosage forms of the present invention may be, but are not limited to, capsules, tablets, pH-independent matrix tablets, pH-dependent matrix tablets, pellets, and osmotic pumps. Methods of making the dosage forms of the present invention are described further below, and methods of producing dosage forms are generally well known in the art. For example, techniques and compositions for making tablets (compressed and molded), capsules (hard and soft gelatin), and pills are described in REMINGTON'S PHARMACEUTICAL SCIENCES, Arthur Osol, ed., 1553-93 (1980).

The controlled release component of a dosage form must provide for both a delay before API is released and for sustained release over time. The initial delay can be brought about with, for example, a pH-sensitive coating, an erodible coating, or a non-erodible porous membrane in which pores are blocked by a material that erodes away or otherwise clears over time. A pH-sensitive coating (*e.g.*, a polymer layer) and/or an enteric coating may include one or more of the following: cellulose acetate succinate, hydroxy propyl methyl cellulose phthalate, hydroxy propyl methyl cellulose acetate succinate, polyvinyl acetate phthalate, copolymers of esters of at least one of acrylic acid and methacrylic acid, alginates, and stearic acid and salts thereof.

The foregoing notwithstanding, our work to date indicates that sustained release of the API from the controlled release component in a neutral pH milieu can be achieved in the absence of conventional release modifiers, such as matrix formers and porous membrane coatings. In fact, as is detailed in the Examples section, uncoated beads containing only about 20% microcrystalline cellulose (MCC) as an excipient were found to exhibit slow and sustained release of ecopipam. Thus, in one aspect, the present dosage forms exclude release modifiers, such as matrix formers and porous membrane coatings.

As will be understood by those skilled in the art, sustained release formulations of pharmaceutical agents typically require the use of substantial quantities of release modifying agents, such as high molecular weight swellable polymers or semi-permeable coatings. A surprising aspect of one embodiment of the invention is that sustained release of ecopipam at

neutral pH can be obtained in the absence of any such agents. For example, beads composed of as much as about 80% ecopipam with about 20% microcrystalline cellulose were found to provide sustained release over the course of about 12 hours to about 24 hours in neutral pH buffer despite the absence of a typical sustained release agent in the formulation. Typical sustained release agents include swellable polymers such as hydroxyalkyl celluloses, hydroxyalkyl alkylcelluloses, polyethylene glycols. Achieving sustained release in the absence of excipients typically used for that purpose allows higher drug loads to be obtained, thereby reducing the size of the dosage form for a given dose level. Thus, the invention encompasses formulations that are free of sustained release agents yet are still able to deliver the active agent in a sustained or controlled manner.

Another pharmaceutical dosage form of the present invention may be a tablet comprising an immediate release component and a controlled release component.

An elegant means of combining IR and CR components is to start with CR beads and to coat them with a layer of drug formulated for immediate release. The concept of a multilayer IR/CR pellet was evaluated by coating CR beads with a suspension of ecopipam in Opadry® clear coating. Thus, yet another pharmaceutical dosage form of the present invention is a pellet having a controlled release component that is then coated with a layer of an immediate release component. The controlled release component comprises from about 40% to about 80% (*e.g.*, about 61%) by weight of ecopipam free base or its pharmaceutically acceptable salt, based on the total weight of the pellet. The immediate release component comprises from about 5% to about 50% (*e.g.*, about 26%) by weight of ecopipam free base or its pharmaceutically acceptable salt, based on the total weight of the pellet. The pellet also comprises from about 10% to about 50% by weight of one or more excipients, based on a total weight of the pellet.

The invention also features pH-independent and pH-dependent matrix tablets as pharmaceutical dosage forms. In addition to the API (ecopipam free base or a pharmaceutically acceptable salt thereof), these tablets include one or more high molecular weight polymers, and the API and polymeric material(s) can be essentially uniformly distributed throughout the tablet. Thus, matrix tablets constitute relatively simple controlled release dosage forms. Upon administration, the polymer hydrates and swells, and it may do so in response to pH or without regard to pH. Upon swelling, the tablet forms a gel from which the API is released by diffusion and as the polymer erodes away. The polymers included in pH-independent matrix tablets do not respond differently at different pH levels, while those that are pH-dependent do. pH-dependent

matrix tablets include polymers that are uncharged and/or insoluble at low pH. These polymers become charged and swell with increasing pH. Suitable polymers for inclusion in a pH-dependent matrix tablet of the invention include cross-linked acrylic acid homopolymers (such as Carbopol®), cellulose acetate phthalate (CAP), hydroxypropylmethyl cellulose phthalate (HPMCP), methacrylic acid and methacrylic esters, and polyvinyl acetate phthalate. The idea of using a pH-sensitive/pH-dependent polymer to modulate release of ecopipam is that drug release is inhibited at low pH, where the polymer is insoluble, and promoted at higher pH, where the polymer responds by swelling, permitting drug release.

Polymers that swell in a pH-independent manner are uncharged and/or non-ionic and include hydrophilic polymers such as hydroxypropylmethyl cellulose (HPMC), hydroxypropyl cellulose, and polyethylene glycol (PEG).

Drug release from matrix tablets is inherently non-linear, and early release is typically even more substantial than predicted by diffusion theory. As such, a matrix tablet could be used as a standalone (as formulated) to provide an early, immediate release burst followed by a prolonged (but not delayed) release. As discussed further below, matrix tables can also be further modified to include an immediate release component or formulated as one layer of a bilayer or trilayer tablet that includes an immediate release layer. The matrix tablet, the matrix portion of a layered tablet, or the layered tablet, can be coated with an enteric polymer.

Whether pH-dependent or pH-independent, the matrix tablets of the present invention can include about 25% to about 75%, by weight, of ecopipam free base or its pharmaceutically acceptable salt (*e.g.*, about 30%, 40%, 50%, 55%, 60%, or 65%) and about 25% to about 75%, by weight, of one or more excipients (*e.g.*, about 30%, 40%, 50%, 60%, or 70%).

As noted above, matrix tablets can be administered as such or in combination with an immediate release tablet or as one layer of a bilayer or trilayer tablet that includes an immediate release layer. Alternatively, the pharmaceutical dosage form of the present invention can be a matrix tablet coated with an immediate release component. The matrix tablet portion of such formulations can include from about 40% to about 90%, by weight, of ecopipam free base or its pharmaceutically acceptable salt (*e.g.*, about 50%, 60%, 70%, 75%, 80% or 85%). The immediate release component can include from about 25% to about 50%, by weight, of ecopipam free base or its pharmaceutically acceptable salt, based on a total weight of the immediate release component (*e.g.*, about 30%, 35%, 40% or 45% ecopipam free base or a pharmaceutically acceptable salt

thereof). For example, the immediate release component can include from about 25% to about 35%, by weight, (*e.g.*, about 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33% or 34%) based on the total weight of the tablet. The matrix tablet portion of the formulation can also include from about 5% to about 35%, by weight, of one or more excipients (*e.g.*, about 10%, 20%, 25%, or 30%).

Osmotic pumps are complex dosage forms that utilize osmotic pressure generated across a semi-permeable membrane to drive the API out from the dosage form. Although there are many variations, a typical osmotic pump tablet consists of one or more reservoirs containing drug substance and an osmotic agent surrounded by a semipermeable membrane which contains a small orifice through which drug can permeate. After the tablet is ingested, water is drawn in across the semipermeable membrane by the osmotic agent, creating a pressure gradient across the membrane. This pressure inside the tablet pushes drug solution or suspension out through the orifice. Typically these dosages are designed such that the osmotic pressure remains relatively constant and the rate of drug release is therefore nearly constant. Since zero order release is desirable for the controlled release portion of the ecopipam dosage, an osmotic pump might be a good option if adequate solubility of the drug could be maintained inside the semi-permeable membrane and if the size of the dosage form could be kept reasonable.

Another pharmaceutical dosage form of the present invention may be an osmotic pump composition. The pump comprises from about 20% to about 50% by weight of ecopipam free base or its pharmaceutically acceptable salt, based on the total weight of the osmotic pump composition, from about 35% to about 65% by weight of sodium chloride or another osmotic agent known by those skilled in the art, based on the total weight of the osmotic pump composition, and up to about 20% by weight of one or more excipients, based on the total weight of the osmotic pump composition.

Another pharmaceutical dosage form of the present invention may be an osmotic pump composition coated with an immediate release component, and optionally a coating of a controlled release component between the osmotic pump composition and the immediate release component. The pump comprises from about 20% to about 50% by weight of ecopipam free base or its pharmaceutically acceptable salt, based on the total weight of the osmotic pump composition and from about 35% to about 65% by weight of sodium chloride or another osmotic agent known by those skilled in the art, based on the total weight of the osmotic pump composition.

The immediate release component comprises from about 25% to about 75% by weight of ecopipam free base or its pharmaceutically acceptable salt, based on a total weight of the immediate release component. The controlled release component comprises from about 20% to about 50% by weight of ecopipam free base or its pharmaceutically acceptable salt, based on a total weight of the controlled release component. The immediate release component comprises from about 5% to about 50% by weight of ecopipam free base or its pharmaceutically acceptable salt, based on a total weight of the osmotic pump composition. The controlled release component comprises from about 5% to about 50% by weight of ecopipam free base or its pharmaceutically acceptable salt, based on a total weight of the osmotic pump composition. The osmotic pump composition comprises up to about 40% by weight of one or more excipients, based on the total weight of the osmotic pump composition.

The controlled release formulations and the CRCs of the dosage forms of the present invention can be formulated to produce varying profiles of plasma concentrations versus time. Where both an IRC and a CRC are present, the dosage form can be configured to release ecopipam in such a way that as plasma concentrations provided by the IRC begin to wane, ecopipam becomes available from the CRC to sustain the total plasma concentration of ecopipam. The controlled release component can therefore be formulated to provide a delay of about 1 to about 3 hours before significant drug release followed by a relatively constant release of drug for a period of about 6 to about 12 hours.

As will be understood by one of ordinary skill in the art, a weak base drug such as ecopipam has limited solubility and will therefore be poorly absorbed in the distal regions of the gastrointestinal tract, where the pH is higher than in the stomach and duodenum. Such a drug is expected to have an "absorption window" in the upper GI tract and to be poorly absorbed beyond this window. Since dosage forms move down the GI tract over time, this is a consideration in the formulation of oral sustained release dosage forms of poorly soluble weak base drugs such as ecopipam. Thus, in the present dosage forms, the CRC is formulated in such a way as to allow release over a sustained period of time despite the solubility limits of the GI tract. Accordingly, the CRC can be formulated as discrete beads, granules or other particles to facilitate dissolution in unfavorable conditions. For example, the beads, granules or other particles of the CRC can be enteric-coated, with the beads, granules or other particles including a core of ecopipam free base or its pharmaceutically acceptable salt. The API can then be coated with an inner pH-insensitive

polymer layer, a middle pH-sensitive enteric coating, and an outer pH-insensitive polymer layer. The inner pH-insensitive polymer layer adheres to and substantially envelopes the core. The middle pH-sensitive enteric coating adheres to the inner pH-insensitive polymer layer and substantially envelopes both the core and the inner pH-insensitive polymer layer. The outer pH-insensitive polymer layer adheres to the middle pH-sensitive enteric coating and substantially envelopes the core, the inner pH-insensitive polymer layer, and the middle pH-sensitive enteric coating. The dissolution profiles of the present dosage forms can be tailored by adjusting the thickness and composition of the enteric coated layers, the composition of the core, and/or the slow release coating over the core. Only the enteric coating is pH-sensitive.

Any coating can be measured and characterized by various means well known in the art. For example, one can determine, for example, the percentage of the coating's weight with respect to the controlled release bead, the thickness of the coating(s), and/or the weight percent of the coating with respect to the pharmaceutical dosage form. *In vitro* dissolution tests are also well known in the art and may be performed at about 20 °C to about 45 °C in different dissolution media using any USP (United States Pharmacopeia) Apparatus known in the art, such as USP Apparatus 1, 40-mesh wire basket. The basket may be rotated at speeds of about 50 rpm (revolutions per minute) to about 150 rpm for up to 24 hours. The dissolution media may be basic, neutral, or acidic with pH levels up to 14.

Where the dosage form comprises both an IRC and a CRC, the ratio of the two components can be modified to yield different pharmacokinetic outcomes. For example, the components can be combined such that the dosage form yields a lower C_{max} and more sustained plasma concentration following administration to human subjects when compared to an intermediate release dosage form of ecopipam. On average, among a group of human subjects, administration of the dosage form can result in a 12 hour plasma concentration (C_{12h}) that is more than 20% of the maximal plasma concentration (C_{max}). Preferably, C_{12h} obtained after oral administration of the dosage form to human subjects is, on average, about 30% to about 60% of C_{max}. Most preferably C_{12h} is about 40% to about 50% of C_{max}. In some embodiments, C_{12h} is about 35%, about 40%, about 45%, about 50%, about 55% of C_{max}. Furthermore, upon administration to a human subject, the dosage forms allow for a rapid peak in plasma concentration. Preferably, the time to maximum plasma concentration (T_{max}) (taken as a mean value among a group of subjects) is less than 2.5 hours (*e.g.*, less than 2.0 hours or less than 1.5 hours).

Preferably, the *in vitro* dissolution rates for the immediate release component of the present invention in acidic media are from about 80% to about 100% (*e.g.*, about 90% to about 100%) after about 2 hours. Preferably, the *in vitro* dissolution rates for the controlled release component of the present invention in acidic media are less than about 5% (*e.g.*, less than about 1%) after about 2 hours, and in aqueous buffer of approximately neutral pH are about 50% to about 100% (*e.g.*, about 60% to about 90%) after about 24 hours.

Another aspect of the invention is that the dosage form is formulated in such a way that the time to maximal plasma concentration (T_{max}) following oral administration of the dosage form is not substantially prolonged relative to that obtained following oral administration of an IR formulation of ecopipam. Preferably, T_{max} is less than about 2.5 hours and more preferably it is less than about 2.0 hours. Most preferably, T_{max} is less than about 1.5 hours.

The optimal pharmacokinetic profile to be provided by the dosage form may vary from one disease state to another. The dosage form can be adjusted through modification of each component (immediate release and controlled release) and through modification of the ratio of the two components in the dosage form to yield an optimal pharmacokinetic profile for the specific disease state to be treated. For example, for certain conditions the primary side effect of somnolescence may be unacceptable. In this case, it would be necessary to minimize the peak plasma concentration of ecopipam (Cmax) while maintaining prolonged exposure. A dosage form intended for such an indication would comprise a reduced percentage of the IR component and an increased percentage of the CR component. In other instances, rapid onset may be more critical and somnolescence less critical. In this case, a dosage form would comprise a higher percentage of the IR component and a lower percentage of the CR component. Generally, the speed to onset and the peak plasma concentration will both increase as the ratio of the IRC to the CRC increases, and the dosage form can be tuned to the disease state in this manner.

Another aspect of the present invention provides processes for the preparation of a capsule or other dosage form that includes ecopipam free base or a pharmaceutically acceptable salt thereof; methods for preparing an IRC; and methods for preparing a CRC.

Methods of preparing the immediate release component can include the following steps: (1) blending ecopipam free base or its pharmaceutically acceptable salt, and excipients; (2) adding water to ecopipam free base or its pharmaceutically acceptable salt, and excipients from step 1 with mixing in a planetary mixer to form a paste; (3) feeding the paste from step 2 into an extruder;

(4) spheronizing the extrudate from step 3; and (5) drying the spheronized beads from step 4 in a fluid bed dryer to obtain the immediate release component.

Methods of preparing a controlled release component can include at least the following steps: (1) blending ecopipam free base or its pharmaceutically acceptable salt, and excipients; (2) adding water to ecopipam free base or its pharmaceutically acceptable salt, and excipients from step 1 with mixing in a planetary mixer to form a paste; (3) feeding the paste from step 2 into an extruder; (4) spheronizing the extrudate from step 3; (5) drying the spheronized beads from step 4 in a fluid bed dryer; (6) applying a clear coating of a mixture of hydroxypropyl methylcellulose and hydroxypropyl cellulose to the spheronized beads from step 5; (7) applying an enteric coating to the spheronized beads from step 6; and (8) applying a second clear coating of a mixture of hydroxypropyl methylcellulose and hydroxypropyl cellulose to the spheronized beads from step 7 to obtain the controlled release component.

The methods can further include the steps of blending the immediate release component with the controlled released component; and filling appropriate amounts of the blended components into an appropriate dosage unit.

It should be noted that the preparation of the pharmaceutical dosage forms of the present invention is not limited to the process disclosed herein. Any process may be used as deemed appropriate by one of ordinary skill in the art to prepare a desired dosage form having the desired constituents, amounts, and exhibiting the desired effect.

Another aspect of the present invention provides methods for the treatment of a central nervous system disorder with a composition as described herein. The methods provide for the treatment of Lesch-Nyhan disease (LND), gambling addiction, Tourette's syndrome (TS), and Parkinson's disease (PD) by administering, to a host (which we may also refer to as a "patient" or "subject"), an effective amount of a pharmaceutical dosage form described herein (*i.e.*, a dosage form that includes ecopipam free base or a pharmaceutically acceptable salt thereof). Considerable research has been directed at effectively treating such conditions, as they can be debilitating for the patient and their cost to society is very high. While the host, patient, or subject can certainly be a human, the invention is not so limited. Veterinary use, including administration to any mammal, is within the scope of the invention. In any of the treatments described herein, and with regard to the use of the present compositions in the preparation of a medicament, the API can be administered in, or included in, an "effective amount" (*i.e.*, an amount that produces a desired therapeutic effect).

Lesch-Nyhan disease is an ultra-rare neurogenetic disorder caused by a mutation of the HPRT gene (Nyhan, *Environmental Health Perspectives* 108:409-411, 2000). It is characterized by uric acid accumulation, intellectual impairment, movement disorders and self-injurious behaviors (SIB) (Jinnah *et al.*, *J. Neurosci.* 14(3):1164-1175, 1994). Post-mortem and human PET studies have shown that LND patients have significant dysfunction of their brain dopamine systems. Animal models suggest that SIB is mediated by the dopamine D_1 receptor family (D_1/D_5) and that D_1 receptor supersensitivity may be a mechanism for the repetitive and compulsive SIB (Jinnah, *Disease Models and Mechanisms* 2:116-121, 2001). Lesch-Nyhan patients are typically minimally functional, so our treatment design is attractive, even though it may have side effects such as somnolence.

Gambling addictions can have devastating impacts on victims and their families. While most people are able to gamble without any appreciable effect on their lives, a small percentage (~2.5%) suffers from "problem gambling" and an even smaller percentage (~0.6%) suffers from "pathological gambling." Based on the scientific literature, there is substantial evidence that pathological gambling has dopamine agonist involvement (Comings *et al.*, *Prog. Brain Res.* 126:325-341, 2000; Blum *et al.*, *Theoretical Biology and Medical Modelling* 5(24):1-16, 2008; Blum *et al.*, *Current Pharm. Design* 17:1158-1167, 2011; Potenza, *Semin. Clin. Neuropsychiatry* 6:217-226, 2001; Bowirrat *et al. Am. J. Med. Genet. B Neuropsychiatr. Genet.* 132:29-37, 2005; Di Chiara *Physiol. Behav.* 86:9-10, 2005; Wang *et al.*, *J. Addict Dis.* 23:39-53, 2004; Aamodt, *Nature Med.* 4:660, 1998; Grant *et al.*, *Minn. Med.* 89(9):44-48, 2006; Grant *et al.*, *British J. Psychiatry* 197:330-331, 2010; Goudriaan *et al.*, *Neuroscience and Biobehavioral Reviews* 28:123-141, 2004; Steeves *et al.*, *Brain* 132:1376-1385, 2009; Zack *et al.*, *Current Drug Abuse Reviews* 2:11-25, 2009; and Koepp *et al.*, *Nature* 393:266-268, 1998). We aimed to design our ecopipam-containing formulations for gambling addicts so that a rapid onset of action would provide relief at the critical time when the urge to gamble starts to become uncontrollable, and to include sustained release for continued relief over time.

Tourette's syndrome is a neurological disease characterized by verbal and motor tics. Although its causes are unknown, many researchers believe that changes in neurotransmitters, including dopamine, are critically involved (Jankovic, *N. Engl. J. Med.* 345(16):1184-1192, 2001). It has been suggested that the symptoms of Tourette's syndrome are due to an overactivity at D_1/D_5 receptors (Singer *et al.*, *Am. J. Psychiatry* 159(8):1329-1336, 2002). Preferably, a treatment for

Tourette's syndrome will minimize side effects such as somnolescence, as patients need to have control over their symptoms at times when they need to function without the distraction of tics. Therefore, formulations that deliver a sustained release profile over time are desirable. Any of the conditions amenable to treatment may be treated with only the controlled release component of a pharmaceutical dosage form described herein, and this may be especially desirable for patients suffering from TS.

The primary symptoms of Parkinson's disease are related to excessive muscle contraction. Dopamine affects muscle contraction via all five dopamine receptors (D_1, D_2, D_3, D_4, and D_5). Activation of the D_2, D_3 and D_4 receptors has an inhibitory effect while activation of D_1 and D_5 receptors is stimulatory. The combined inhibitory effect of D_2, D_3 and D_4 is more powerful in total than the combined stimulatory effect of D_1 and D_5 so that the overall effect of dopamine is normally to inhibit muscle contraction. As such, the disease is conventionally treated by increasing dopamine levels (Seeman *et al.*, *FASEB J.* 4:2737-2744, 1990). However, adding a D_1/D_5 antagonist to the therapeutic regimen could have obvious benefits (Factor, *Neurotherapeutics: The J. of the Amer. Soc. for Exp. Neurotherapeutics* 5:164-180, 2008). Like the treatment for Tourette's syndrome, a treatment for Parkinson's disease should also have a sustained release profile over time as patients need to have control over their symptoms at times when they need to be functional.

The compounds and compositions disclosed herein are generally and variously useful for treatment of tic disorders, including Tourette's Syndrome, as described above, which is also variously referred to as Tourette Syndrome, Tourette's Disorder, Gilles de la Tourette syndrome (GTS), or simply Tourette's or TS. The tic disorder may also be a pediatric autoimmune disorder associated with streptococcal infection (PANDAS), a transient tic disorder, a chronic tic disorder, or a Tic Disorder Not Otherwise Specified (NOS). Transient tic disorders are generally characterized by multiple motor and/or phonic tics that occur for at least four weeks but less than 12 months. Chronic tic disorders are generally characterized by either single or multiple motor or phonic tics, but not both, which are present for more than a year; Tourette's Syndrome is diagnosed when both motor and phonic tics are present (although not necessarily concurrently) for more than one year. Tic Disorder NOS is diagnosed when tics are present but do not meet the criteria for any specific tic disorder. The present compounds and compositions can also be administered for the treatment of tics induced as a side effect of a medication; tics associated

with autism; and Tourettism (the presence of Tourette-like symptoms in the absence of Tourette's Syndrome (*e.g.*, as a result of another disease or condition, such as a sporadic, genetic, or neurodegenerative disorder)).

The compounds and compositions disclosed herein are also useful for the treatment of movement disorders generally. These disorders include akinetic-rigid syndrome, chorea (*e.g.*, as occurs in Huntington's Disease), myoclonus and/or dystonia of any etiology, tremor, or Parkinson's Disease. The movement disorder may also be one induced by a medication or other stimulus to which a patient has been exposed. For example, the compounds and compositions disclosed herein can be used to alleviate dyskinesias induced by dopamine agonists (*e.g.*, including but not limited to levodopa, levodopa and carbidopa combinations, ropinirole, pramipexole, or pergolide) and tardive dyskinesias induced by anti-psychotic drugs (*e.g.*, including but not limited haloperidol, risperidone, olanzapine, quetiapine, aripiprazole, ziprasidone, paliperidone, iloperiodone, perphenazine, metoclopramide, and chlorpromazine).

As noted, the methods described herein are useful for the treatment of tics. Tics can take many forms, but typically consist of simple, repetitive or sequential movements, gestures, and utterances that mimic fragments of normal behavior. Simple motor tics involve only a single muscle or a group of muscles, and often cause a brief, jerking movement (clonic tics); they may also be slower, causing a briefly sustained abnormal posture (dystonic tics) or an isometric contraction (tonic tics). Examples of simple clonic motor tics include blinking, nose twitching, and head and limb jerking. Dystonic tics include sustained eye closure (blepharospasm), ocular deviations, bruxism, mouth opening, torticollis, sustained jaw opening, and shoulder rotation. Tonic tics are typically manifested by abdominal contraction, limb extension or limb flexion. Examples of complex motor tics include head shaking, trunk bending or gyrating, brushing hair, touching, throwing, hitting, jumping, kicking, making rude gestures, burping, vomiting, retching, smelling objects, grabbing one's genitalia and making other lewd or obscene gestures (copropraxia), and imitating others' gestures (echopraxia).

Simple phonic tics typically include sniffing, throat clearing, grunting, squeaking, screaming, coughing, barking, blowing, throat clearing, and making sucking sounds. Complex phonic tics include linguistically meaningful utterances and verbalizations, such as the shouting of obscenities, profanities, or otherwise socially inappropriate words or phrases (coprolalia), the

repetition of someone else's words or phrases (echolalia), and the repetition of one's own utterances, particularly the last syllable, word, or phrase in a sentence (palilalia).

The methods disclosed herein can be applied to both pediatric and adult subjects.

While we expect the favored route of administration will be oral, the invention is not so limited, and the dosage forms described herein may formulated for administration by topical, transmucosal (*e.g.*, anal, vaginal, sublingual or intranasal), intravenous, intraperitoneal, intramuscular, subcutaneous, transdermal or intradermal routes of administration.

It will be understood that the specific dose level for any particular patient will depend upon a variety of factors including body weight, general health, gender, diet, time and route of administration, rates of absorption and excretion, combination with other drugs, and the severity of the particular disease being treated. Actual dosage levels of ecopipam free base or its pharmaceutically acceptable salt in the compositions of the present invention may be varied so as to obtain an amount of ecopipam free base or its pharmaceutically acceptable salt that is effective to obtain a desired therapeutic response for a particular composition and method of administration.

It may be necessary to administer more than one dosage unit at a time to reach target plasma concentrations.

For indications such as Lesch-Nyhan and pathological gambling, quick onset is important and the side effect of somnolence can be tolerated. The ideal plasma concentration profile for a dosage form for these indication would provide for a rapid peak in plasma concentration (Cmax) to about 40 ng/mL to about 80 ng/mL of active agent within about two hours. Suitable C_{max} values provided by one or more units taken as a dose of a dosage form of the present invention designed for these indications can be from about 50 ng/mL to about 70 ng/mL of active agent in the patient's plasma within about two hours. Following this peak in plasma concentration, such a dosage form might provide sustained plasma concentrations for about 12 hours after administration that are in the range of about 10 to about 50 ng/mL, and the plasma level would ideally be sufficiently consistent that on average, the plasma concentrations in patients 12 hours after dosing will be about 10% to about 50% of Cmax. An oral dose comprising one or more units of a dosage form of the present invention for these indications can comprise from about 195 to about 454 mg of ecopipam incorporated into an IR component and from about 195 to about 454 mg of ecopipam incorporated into a CR component. When such a dosage form is tested in a USP dissolution apparatus under appropriate conditions with 2 hours in an appropriate low pH solution, such as

simulated gastric fluid followed by 22 hours in an appropriate neutral pH solution, such as simulated intestinal fluid, about 35% to about 60% of the total amount of ecopipam in the dosage form will dissolve quickly within the first two hours and an additional about 25% to about 55% of the total ecopipam will dissolve gradually over the course of the remaining 22 hours.

For indications such as Tourette's and Parkinson's, reduction of side effects associated with high peak plasma concentrations is more important than rapid onset. For such indications a desirable plasma concentration profile might consist of a rapid increase to a Cmax of about 30 to about 50 ng/mL and a sustained plasma concentration of about 10 to about 50 ng/mL at least until about 12 hours after dosing will be about . The plasma concentration 12 hours administration of such a dosage form will be about 25% to about 65% of Cmax. An oral dose comprising one or more units of a dosage form of the present invention can comprise from about 130 to about 302 mg of ecopipam incorporated into an IR component and from about 195 to about 454 mg of ecopipam incorporated into a CR component. When such a dosage form is tested in a USP dissolution apparatus under appropriate conditions with 2 hours in an appropriate low pH solution, such as simulated gastric fluid followed by 22 hours in an appropriate neutral pH solution, such as simulated intestinal fluid, about 45% to about 70% of the total amount of ecopipam in the dosage form will dissolve quickly within the first two hours and an additional about 15% to about 45% of the total ecopipam will dissolve gradually over the course of the remaining 22 hours.

While the present invention has been described in conjunction with specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

EXAMPLES

The following formulations were prepared by extrusion spheronization (Tables 2 to 24). The preparation of pellets with high drug loading (55, 70 and 80%) was investigated for controlled drug delivery (CR) component. 20, 30 and 35% drug loading were evaluated for immediate release (IR) component. The 2 pellet types will then mixed at different ratio to be able to modulate the drug release. Influence of formulation (drug load, excipients and pelletization variables) on the pellet properties was examined. Controlled and immediate release pellets formulations were chosen on the basis of degree of sphericity and *in vitro* dissolution rates.

Example 1: Dissolution at High Drug Loading

The first set of experiments was intended to evaluate the intrinsic expected slow dissolution of the insoluble API at high drug loadings of 55% to 80% (Tables 1-3) and API suitability for extrusion-spheronization. Indeed, ecopipam HCl possesses binding properties allowing proper extrusion spheronization with a small amount of microcrytalline cellulose (MCC) as spheronization aid/filler. Furthermore, the poor solubility of the drug allowed a slow release in simulated physiological media.

Table 1. CR Formulation Lot L107-03001 with API Loading of 70%

Raw Materials	% w/w	mg/capsules (salt)	g/batch
Ecopipam-HCl	70.0	253.0	70.0
Microcrystalline Cellulose Avicel PH-101	30.0	108.4	30.0
Total	**100.0**	**361.4**	**100.0**

Table 2. CR Formulation Lot L107-03002 with API Loading of 55%

Raw Materials	% w/w	mg/capsules (salt)	g/batch
Ecopipam-HCl	55.0	253.0	55.0
Microcrystalline Cellulose Avicel PH-101	45.0	207.0	45.0
Total	**100.0**	**460.0**	**100.0**

Table 3. CR Formulation Lot L107-03003 with API Loading of 80%

Raw Materials	% w/w	mg/capsules (salt)	g/batch
Ecopipam-HCl	80.0	253.0	80.0
Microcrystalline Cellulose Avicel PH-101	20.0	63.2	20.0
Total	**100.0**	**316.2**	**100.0**

Example 2: Evaluation of Various Combinations of Excipients

The second set of experiments was intended to evaluate various combinations of excipients in order to speed up the release of the insoluble API and reach a typical immediate release profile (*i.e.*, more than 75% release within 1 hour). The use of high drug loading ranging from 55 to 80% and hydrophilic filler (Lactose monohydrate, disintegrants (sodium starch glycolate, starch and Crospovidone®) and surfactant (sodium lauryl sulfate) were evaluated (Tables 4-7).

Table 4. IR Formulation Lot L107-03004 with API Loading of 55% - Use of Hydrophilic Filler and Surfactant (SLS)

Raw Materials	% w/w	mg/capsules (salt)	g/batch
Ecopipam-HCl	55.0	253.0	55.0
Lactose monohydrate (Tabletose-80)	44.0	202.4	44.0
Sodium Lauryl Sulfate (SLS)	1.0	4.6	1.0
Total	**100.0**	**460.0**	**100.0**

Table 5. IR Formulation Lot L107-03005 with API Loading of 55% - Use of Hydrophilic Filler and Disintegrant (sodium starch glycolate (SSG))

Raw Materials	% w/w	mg/capsules (salt)	g/batch
Ecopipam-HCl	55.0	253.0	55.0
Lactose monohydrate Tabletose-80	41.0	188.6	41.0
Sodium Starch glycolate (SSG)	4.0	18.4	4.0
Total	**100.0**	**460.0**	**100.0**

Table 6. IR Formulation Lot L107-03006 with API Loading of 55% - Use of Hydrophilic Filler, Surfactant (SLS) and Disintegrants (SSG and starch)

Raw Materials	% w/w	mg/capsules (salt)	g/batch
Ecopipam-HCl	55.0	253.0	55.0
Lactose monohydrate Tabletose-80	35.0	161.0	35.0
Starch 1500	5.0	23.0	5.0
SSG	4.0	18.4	4.0
SLS	1.0	4.6	1.0
Total	**100.0**	**460.0**	**100.0**

Table 7. IR Formulation Lot L107-03007 with API Loading of 80% - Use of Hydrophilic Filler and Disintegrant (SSG)

Raw Materials	% w/w	mg/capsules (salt)	g/batch
Ecopipam-HCl	80.0	253.0	80.0
Lactose monohydrate Tabletose-80	16.0	50.6	16.0
SSG	4.0	12.6	4.0
Total	**100.0**	**316.2**	**100.0**

Example 3: Lower Drug Loading

In the third set of experiments, the same immediate release formulation strategy was applied but with lower drug loading ranging from 20 to 35% to further speed up the release (Tables 8-12). This strategy was found to be successful to obtain a full API release in less than 2 hours in simulated gastric fluid.

Table 8. IR Formulation Lot L107-03008 with API Loading of 30% - Use of Hydrophilic and Hydrophobic Fillers and Disintegrant (Crospovidone®)

Raw Materials	% w/w	mg/capsules (salt)	mg/capsules (salt)	g/batch
Ecopipam-HCl	30.0	28.5	126.8	30.0
Lactose monohydrate Tabletose-80	50.0	47.5	211.3	50.0
Microcrystalline Cellulose Tabulose-101	15.0	14.3	63.4	15.0
Crospovidone CL	5.0	4.8	21.1	5.0
Total	**100.0**	**95.0**	**422.5**	**100.0**

Table 9. IR Formulation Lot L107-03009 with API Loading of 20% - Use of Hydrophilic and Hydrophobic Fillers and Disintegrant (Crospovidone®)

Raw Materials	% w/w	mg/capsules (salt)	g/batch
Ecopipam-HCl	20.0	28.0	20.0
Lactose monohydrate Tabletose-80	50.0	70.0	50.0
Microcrystalline Cellulose Tabulose-101	25.0	35.0	25.0
Crospovidone CL	5.0	7.0	5.0
Total	**100.0**	**140.0**	**100.0**

Table 10. IR Formulation Lot L107-03010 with API Loading of 30% - Use of Hydrophilic and Hydrophobic Fillers and Disintegrant (Crospovidone®)

Raw Materials	% w/w	g/batch
Ecopipam-HCl	30.0	60.0
Lactose monohydrate (fine grade)	50.0	100.0
Microcrystalline Cellulose Tabulose-101	15.0	30.0
Crospovidone CL	5.0	10.0
Total	**100.0**	**200.0**

Table 11. IR Formulation Lot L107-03011 with API Loading of 30% - Use of Hydrophilic and Hydrophobic Fillers and Disintegrants (Crospovidone® and starch)

Raw Materials	% w/w	g/batch
Ecopipam-HCl	30.0	30.0
Lactose monohydrate (fine grade)	30.0	30.0
Starch 1500	20.0	20.0
Microcrystalline Cellulose Tabulose-101	15.0	15.0
Crospovidone CL	5.0	5.0
Total	**100.0**	**100.0**

Table 12. IR Formulation Lot L107-03012 with API Loading of 35% - Use of Hydrophilic and Hydrophobic Fillers and Disintegrants (Polyplasdone® and starch)

Raw Materials	% w/w	g/batch
Ecopipam-HCl	35.0	175.0
Microcrystalline Cellulose Tabulose-101	25.0	125.0
Lactose monohydrate (fine grade)	22.5	112.5
Starch 1500	10.0	50.0
Polyplasdone XL	7.5	37.5
Total	**100.0**	**500.0**

Example 4: Extrusion Spheronization Process Parameters

CR formulation was selected at 80% drug loading using MCC as only filler (Tables 13 and 14). The following lots were manufactured to confirm extrusion spheronization process parameters.

Table 13. CR Formulation Lot L107-03013 with API Loading of 80%

Raw Materials	% w/w	g/batch
Ecopipam-HCl	80.0	400.0
Microcrystalline Cellulose Tabulose -101	20.0	100.0
Total	**100.0**	**500.0**

Table 14. CR Formulation Lot L107-03014 with API Loading of 80%

Raw Materials	% w/w	mg/capsules (salt)	g/batch
Ecopipam-HCl	80.0	112.6	80.0
Microcrystalline Cellulose Tabulose -101	20.0	28.2	20.0
Total	**100.0**	**140.8**	**100.0**

Example 5: Evaluation of New Immediate Release Formulations Comprising Crospovidone

A new immediate release formulation strategy was evaluated. It consisted of using crospovidone (Polyplasdone®) know as a disintegrant as main filler and spheronization aid in order to accommodate higher drug loadings of 70% and 80% (Tables 15 and 16). Adequate spheres were obtained in terms of shape and size but exhibited slow dissolution.

Table 15. IR Formulation Lot L107-03015 with API Loading of 70% - Use of Disintegrant as Spheronization Aid.

Raw Materials	% w/w	mg/capsules (salt)	g/batch
Ecopipam-HCl	70.0	112.7	70.0
Polyplasdone XL-10	30.0	48.3	30.0
Total	**100.0**	**161.0**	**100.0**

Table 16. IR Formulation Lot L107-03016 with API Loading of 80% - Use of Disintegrant as Filler.

Raw Materials	% w/w	mg/capsules (salt)	g/batch
Ecopipam-HCl	80.0	112.6	80.0
Polyplasdone XL-10	20.0	28.2	20.0
Total	**100.0**	**140.8**	**100.0**

Example 6: Preparation of Final Immediate and Controlled Release Formulations

Final immediate and controlled release formulations with API loadings of 30% and 80% were prepared based on process robustness and dissolution profiles (Tables 17 and 18).

Table 17. IR Formulation Lot L107-03017 with API Loading of 30%

Raw Materials	% w/w	mg/capsules	g/batch
Ecopipam-HCl	30.0	112.7	75.0
Lactose monohydrate Tabletose-80	50.0	187.8	125.0
Microcrystalline cellulose Tabulos	15.0	56.3	37.5
Polyplasdone XL-10	5.0	18.8	12.5
Total	**100.0**	**375.6**	**100.0**

Table 18. CR Formulation Lot L107-03018 with API Loading of 80%

Raw Materials	% w/w	mg/capsules (salt)	g/batch
Ecopipam-HCl	80.0	112.6	200.0
Microcrystalline cellulose Tabulose -101	20.0	28.2	50.0
Total	**100.0**	**140.8**	**250.0**

Example 7: Controlled Release Formulation with Lower Drug Loading

A CR formulation with a slightly lower drug loading of 75% was prepared (Table 19). No major impact on product performance was observed.

Table 19. CR Formulation Lot L107-03019 with API Loading of 75%

Raw Materials	% w/w	mg/capsules (salt)	g/batch
Ecopipam-HCl	75.0	112.6	150.0
Microcrystalline cellulose Tabulose -101	25.0	37.5.2	50.0
Total	**100.0**	**150.2**	**200.0**

Example 8: 100 mg Strength Ecopipam Formulations

100 mg strength ecopipam formulations were prepared for an informal stability study (Tables 20-23). Lot L107-03003-5O20A (Table 20) was prepared from lot L107-03003 (Table 3) by coating with Opadry Clear® followed of Acryl-Eze® enteric coating. Opadry Clear® is a nonfunctional coating used as barrier component to avoid API-enteric coating interactions. For lot L107-03009-5O (Table 21) only a film of Opadry Clear® was applied. Lot L107-03003-5O20A-009-5O consisted of a mixture of CR lot L107-03003-5O20A (85.2 mg of pellets) with IR lot L107-03009-5O (291 mg of pellets), equivalent to 50 mg of ecopipam free base from each lot per capsule. Lot L107-03003-5O20A5O pellets (Table 22) were prepared from L107-03003-5O20A pellets. The pellets were spray-coated with 5% theoretical weight gain using Opadry Clear® containing Yellow No.6 Aluminum Lake as colorant. Lot L107-03003-5O20A5O-017-100mg (Table 23A) was prepared by mixing for 10 minutes in V-blender pellets from lot L107-03003-5O20A5O (CR pellets formulation) and L107-03017 (IR pellets formulation), equivalent to 50 mg of ecopipam free base from each lot per capsule. 90 mg ecopipam capsules containing a different ratio of 40% IR pellets and 60% CR pellets were prepared from samples of lots L107-03017 and L107-03003-5O20A5O stored at 25 °C and 60% RH for 5 months (Table 23B).

Table 20. Ecopipam-HCl Formulation Lot L107-03003-5O20A, CR Pellets

Raw Materials	% w/w	mg/capsule (salt)
Ecopipam-HCl	66.1	112.7
Microcrystalline cellulose Avicel PH-101	12.9	22.0
Opadry® 20A19301 clear (sub-coat)	5.0*	8.5
Acryl-EZE MP93018508 white (enteric coat)	16.0	27.3
Size 1 white opaque Gelatin capsule (Lot No.: 70292091)	-	-
Total	**100.0**	**170.5**

*Theoretical

Table 21. Ecopipam-HCl Formulation Lot L107-03009-5O, IR Pellets

Raw Materials	% w/w	mg/capsule (salt)
Ecopipam-HCl	19.4	112.7
Lactose monohydrate Tabletosse-80	48.4	281.7
Microcrystalline cellulose Tabulose-101	24.2	140.9
Crospovidone CL (disintegrant)	4.9	28.3
Opadry® 20A19301 clear (sub-coat)	3.2	18.6
Size 00 white opaque Gelatin capsule (Lot No.: 90085321)	-	-
Total	**100.0**	**582.1**

Table 22. Ecopipam-HCl Formulation Lot L107-03003-5O20A5O, CR Pellets

Raw Materials	% w/w	mg/capsule (salt)
Ecopipam-HCl	63.5	112.7
Microcrystalline Cellulose (Avicel PH-101)	10.5	18.6
Opadry® 20A19301 clear (sub-coat)	10.0*	17.8
Acryl-EZE MP93018508 white (enteric coat)	16.0	28.4
FD&C (Yellow No.6 Al. Lake)	NMT 0.004	0.01
Size 1 white opaque Gelatin capsule (Lot No.: 70187731)	-	-
Total	**100.0**	**177.6**

*Theoretical

Table 23A. 100 mg Ecopipam-HCl Formulation Lot L107-03003-5O20A5O-017-100MG, Controlled Release

Materials	mg pellets /cap	% w/w	g/lot
Ecopipam-HCl (63.5%) CR Coated pellets Corealis Lot No.: L107-03003-5O20A5O	88.8	32.4	7.83
Ecopipam-HCl (30.0%) IR Uncoated pellets Corealis Lot No.: L107-03017	187.8	67.6	16.36
Size 1 white opaque Gelatin capsule (Lot No.: 70187731)	Capsule shell is full	-	-
Total	**276.6**	**100.0**	**24.19**

Table 23B. 90 mg -Ecopipam-HCl Formulation Lot L107-03003-5O20A5O-017-90MG, Controlled Release

Materials	mg pellets /cap	% w/w	g/lot
Ecopipam-HCl (63.5%) CR Coated pellets Corealis Lot No.: L107-03003-5O20A5O	100.0	43.6	0.70
Ecopipam-HCl (30.0%) IR Uncoated pellets Corealis Lot No.: L107-03017	132.0	57.4	0.92
Size 1 white opaque Gelatin capsule (Lot No.: 70187731)	Capsule shell is close to full	-	-
Total	**232.0**	**100.0**	**1.62**

Example 9: Extrusion/Spheronization and Coating Process Development

The manufacture of pellets using the extrusion/spheronization technique includes the following stages: (1) blending of the dry powders, (2) wet granulation (wet massing), (3) extrusion of the wet mass, (4) spheronization, (5) drying and (6) coating. The parameters used during the pelletization and spheronization process of each formulation are shown in Tables 24-1 to 24-5.

Blending and Wet Massing: The dry ingredients were pre-mixed in a Hobart low shear mixer/granulator (model N-50) at 60 rpm. The premixed material was wetted using a Cole Parmer

Masterflex L/S Peristaltic Pump Model 7521-50 to form a homogeneous wet mass suitable for the extrusion. Purified USP water was used as wetting liquid.

Extrusion: In order to obtain extrudates, the wet mass was placed into a LCI Multi Granulator MG-55 and extruded through the screen (dome configuration). The screw speed was varied depending on the formulations.

Spheronization: The extrudates were spheronized in batches of 100 to 200 g using a LCI Marumerizer (spheronizer) QJ-230T equipped with 2.0 mm friction plate. Spheronizer friction plate speed and spheronization time was varied according to the formulations.

Drying: Pellets were dried on trays in an Isotemp Oven, Model 655F, Fisher Scientific at 50°C. The residual moisture measurements was achieved by gravimetric LOD (loss-on-drying) (Sartorius Thermo Control, YTC 01L) of 3 g samples heated at 100 °C until the rate of weight loss dropped to less than 0.1 % in 50 s. Pellets from lot 012 and 'onward' were dried in a Glatt GPCG-1 fluid bed system at an inlet temperature of 50-55 °C for 15-30 minutes.

Screening: The pellets were screened (hand-sieving) using 8 inches standard sieves. After screening, the pellets with diameters between 500 to 850 and 850 to 1400 μm and those with diameters lower than 500 μm were retained for analyses.

Coating Process: Pellets from lot L107-03003 were coated in a fluid bed coating apparatus (GPCG 1, Glatt, Binzen, Germany) equipped with a Wurster column. Enteric coating was done using Opadry® 20A19301 clear (Hydroxypropyl methylcellulose /Hydroxypropylcellulose mixture) as protective sub-coating and an aqueous coating dispersion of Acryl-Eze®.

Preparation of Opadry® solution: Opadry® solution was prepared by weighing 5 g of Opadry® powder and 95 g of purified water. The powder was added gradually to the vortex, avoiding powder flotation on the liquid surface. This mixture was thoroughly mixed for 40-45 minutes in order to obtain a clear solution.

Preparation of Acryl-Eze® dispersion: 80 g of purified water was weighed into a mixing vessel and stirred to form a vortex. 20 g Acryl-Eze® MP93018508 powder was weighed and added to the center of the liquid vortex in a slow steady stream, avoiding clumping and maintaining a vortex. Stirring was continued for 30 minutes. Acryl-Eze® dispersion was passed through a 250 μm sieve prior to the coating process. Dispersion was continuously stirred during the coating process.

Process parameters: Lot L107-03003-5O20A: 50 g of pellets having a diameter between 850-1400 μm were pre-heated between 52-62 °C (inlet temperature) for 5 minutes. During the subcoating process, the atomizing air pressure was 1.4 bar, the air exhaust air flap was 50% (0.6 bar) and the liquid feed rate (spray rate) 3.7 g/min. The product temperature was between 43-46 °C.

During the enteric coating process, the temperature was decreased to 33 °C (product temperature) and the spray rate to 1.7 g/min, the height of the partition above the orifice plate (Wurster column height) was 10 mm. After enteric coating, the heating was maintained for an additional 5 minutes as a final drying phase. The pellets gained about 5% weight during Opadry® sub coating step and about 16% weight after Acryl-Eze® coating (lot # L107-03003-5O20A).

For lot L107-03009-5O Opadry® coating was carried out as for lot 003. For lot L107-03003-5O20A5O an additional Opadry® coating was applied to 24.5 grams of L107-03003-5O20A pellets. Yellow No.6 Aluminium Lake colorant was added to Opadry® solution in order to be able to visually differentiate the CR versus the IR pellets. The pellets were coated to a 5% theoretical weight gain using same parameters as for lot L107-03003 Opadry® sub coating.

Enteric coated pellets were subjected to enteric integrity and dissolution tests by placing in 0.1 M hydrochloric acid for 2 h and in phosphate buffer with a pH of 6.8 respectively.

Encapsulation: Pellets (coated or not) were encapsulated in white opaque hard gelatin capsules for an equivalent of 25, 100 or 225 mg of ecopipam/capsule.

Table 24.1. MCC Based Formulations Extrusion/Spheronization Parameters

Lot No. (API loading) / Parameters	L107-03001 (70% API, 30% MCC-101)	L107-03002 (55% API, 45% MCC-101)	L107-03003 (80% API, 20% MCC-101)
Pre-mixing			
Mixer speed (rpm)	60	60	60
Pre-mix time (min)	2:00	2:00	2:00
Wet Granulation			
Dose time (min:sec)	2:15	2:15	1:58
Mixer speed (rpm)	60	60	60
Total granulation time (min:sec)	2:15	3:15	3:32
Mixer speed (rpm)	60	60	60
Water (g)	53	60	45
Liquid rate (g/min)	23	23	23
Amount of water on wet basis (% w/w)	35	38	31
Amount of water on dry basis (% w/w)	53	60	45
Observations:	over-wetted mass	-	slightly over-wetted mass
Extrusion			
Shaft speed (rpm)	30	30	30
Die diameter (mm)	1.2	1.2	1.2
Observations:	good extrudates, sticking on screw and on extruder walls	good extrudates, slightly dry at the end	good extrudates, no sticking
Spheronization			
Plate speed (rpm)	750	750	750
Spheronization time (min:sec)	3:00	5:00	2:47
Observations:	Acceptable spheronization	Dumbbell shape pellets, presence of rods	Acceptable spheronization but pellets-pellets agglomeration, sticking on spheronizer walls
Drying			
Temperature (°C)	50	50	50
Drying time (h)	5/72	22	20.5
LOD (%)	13.8/1.1	1.1	1.0

Table 24.2. Lactose Based Formulations Extrusion/Spheronization Parameters

Lot No. (API loading) / Parameters	L107-03004 (55% API, 44% Lactose, 1% SLS)	L107-03005 (55% API, 41% Lactose, 4% SSG)	L107-03006 (55% API, 35% Lactose, 5.0% Starch, 4% SSG, 1% SLS)	L107-03007 (80% API, 16% Lactose, 4% SSG)
Pre-mixing				
Mixer speed (rpm)	60	60	60	60
Pre-mix time (min)	3:00	3:00	4:00	3:00
Wet Granulation				
Dose time (min:sec)	1:57	1:06	1:19	1:04
Mixer speed (rpm)	60	60	60	60
Total granulation time (min:sec)	3:57	3:06	3:19	3:04
Mixer speed (rpm)	60 for 1 min 124 for 1min	60 for 1 min 124 for 1min	60 for 1 min 124 for 1min	60 for 1 min 124 for 1min
Water (g)	45	25	30	25
Liquid rate (g/min)	23	23	23	23
Amount of water on wet basis (% w/w)	31 (23)	20	23	20
Amount of water on dry basis (% w/w)	45 (30)	25	30	25
Observations:	over-wetted mass	presence of fines	-	presence of fines
Extrusion				
Shaft speed (rpm)	50 (50)	50	50	50
Die diameter (mm)	1.2 (1.0)	1.0	1.0	1.0
Observations:	good extrudates, sticking (good extrudates, not sticking)	good extrudates, not sticking	good extrudates, not sticking	good extrudates, not sticking
Spheronization				
Plate speed (rpm)	750 (750)	750/1250/1500	750	750/1750
Spheronization time (min:sec)	less than 30 sec (1:00)	4:00/1:00/1:00	5:00	5:00/1:00
Observations:	Agglomeration of extrudates forming wet mass (spheres and rods formed)	Dumbbell shape pellets, presence of rods	Dumbbell shape pellets, presence of rods	no spheres formed/granules fracturing presence of extrudates
Drying				
Temperature (°C)	50	50	50	50
Drying time (h)	22	20	21	22
LOD (%)	1.0	0.9	1.5	1.2

Note: after drying 1-2 h in the oven at 50°C, LOD = 23 %

Table 24.3. Lactose/MCC Based Formulations Extrusion/Spheronization Parameters

Lot No. (API loading) / Parameters	L107-03008 (30% API, 50% Lact., 15% MCC, 5.0% Crosp.	L107-03009 (20% API, 50% Lact., 25% MCC, 5.0% Crosp.	L107-03010 (30% API, 50% Lact., 15% MCC, 5.0% Crosp.	L107-03011 (30% API, 30% Lact., 20% Star., 15% MCC, 5.0% Crosp.	L107-03012 (35% API, 22.5% Lact., 10% Star., 25% MCC, 7.5% PP-XL.
Pre-mixing					
Mixer speed (rpm)	60	60	60	60	60
Pre-mix time (min)	4:00	4:00	5:00	5:00	3:00
Wet Granulation					
Dose time (min:sec)	1:39	2:22	3:23	1:54	8:20
Mixer speed (rpm)	60	60	60	60	60
Total granulation time (min:sec)	2:39	3:22	4:23	3:54	9:20
Mixer speed (rpm)	60 /1 min	60 /1 min	60 /1 min	60 /30 sec 124 /1:30	60 /1 min
Water (g)	35	50	70	40	192
Liquid rate (g/min)	21	21	21	21	23
Amount of water on wet basis (% w/w)	26	33	26	29	28
Amount of water on dry basis (% w/w)	35	50	35	40	38
Observations:	-	-	-	-	-
Extrusion					
Shaft speed (rpm)	50	50	50	50	30
Die diameter (mm)	1.0	1.0	1.0	1.0	1.0
Observations:	-	-	-	Spaghettis formed	Spaghettis formed
Spheronization					
Plate speed (rpm)	500	750/500	750	750 (1750)	1250/1500
Spheronization time (min:sec)	5	1:00/4:00	20:00	0:15 (8:00)	7/3
Observations:	Better than only Lactose based formulations but not well rounded spheres presence of rods	Acceptable	Pulverization (dumbbell shape pellets presence of rods)	Extrudates did not break (dumbbell shape pellets presence of rods)	Dumbbell shape pellets
Drying					
Temperature (°C)	50	50	50	50	50
Drying time (h)	21	20	70	70	0.5
LOD (%)	1.0	2.0	1.6	1.7	ND

Table 24.4. High Drug Load/MCC-101 and HDL/ Polyplasdone® XL-10 (PP-XL10) Based Formulations Extrusion/Spheronization Parameters

Lot No. (Composition / Parameters	L107-03013 (80% API, 20% MCC)	L107-03014 (80% API, 20% MCC)	L107-03015 (70% API, 30% PP-XL10)	L107-03016 (80% API, 20% PP-XL10)
Pre-mixing				
Mixer speed (rpm)	60	60	60	60
Pre-mix time (min)	3:00	2:00	2:00	2:00
Wet Granulation				
Dose time (min:sec)	8:00	1:49	2:51	2:49
Mixer speed (rpm)	60	60	60	60
Total granulation time (min:sec)	9:00	2:40	3:51	3:19
Mixer speed (rpm)	60 for 1 min	60 for 1 min	60 for 1 min	60 for 30 sec
Water (g)	187	36	60	60
Liquid rate (g/min)	23	21	21	21
Amount of water on wet basis (% w/w)	27	27	38	38
Amount of water on dry basis (% w/w)	37	36[2]	60	60
Observations:	-	-	-	-
Extrusion				
Shaft speed (rpm)	30	30	30	30
Die diameter (mm)	0.7 and 0.8/1.2	1.0	1.2	1.2
Observations:	Jamming/good extrusion	Slightly dry	Very good	Very good
Spheronization				
Plate speed (rpm)	500/1250	750	1000/750	1000/750
Spheronization time (min:sec)	1-2/2-3	2-3	2:30/2:30	1:00/1:30
Observations:	Pulverization and sticking/ acceptable spheronization but formation agglomerates	Acceptable spheronization, wide pellets size distribution, presence of fines	Acceptable Spheronization	Acceptable Spheronization
Drying				
Temperature (°C)	50	50	50	50
Drying time (min)	30	30	30	20
LOD (%)	2.1	ND	ND	2.2

Table 24.5. Formulations for Stability/Optimization Study Extrusion/Spheronization Parameters

Lot No. (API loading) / Parameters	L107-03017 (30% API, 50% Lact., 15% MCC, 5.0% PP-XL10	L107-03018 (80% API, 20% MCC)	L107-03019 (75% API, 25% MCC)Sub lot-1/Sub lot-2
Pre-mixing			
Mixer speed (rpm)	60	60	60
Pre-mix time (min)	5:00	3:00	3:00/2:00
Wet Granulation			
Dose time (min:sec)	4:00	4:09	4:00/3:35
Mixer speed (rpm)	60	60	60
Total granulation time (min:sec)	5:00	5:09	5:00/4:00
Mixer speed (rpm)	60 for 30 sec 120 for 30 sec	60 for 30 sec 120 for 30 sec	-
Water (g)	88	90	90/80
Liquid rate (g/min)	22	22	21
Amount of water on wet basis (% w/w)	26	26	31/29
Amount of water on dry basis (% w/w)	35	36	45/40
Observations:	Small agglomerates	Small agglomerates	Agglomerates/ Small agglomerates
Extrusion			
Shaft speed (rpm)	50	50/30	30
Die diameter (mm)	1.2	1.0/1.0	1.2
Observations:	Very good	Solidification of mass in the extrusion area / extrudable	Good
Spheronization			
Plate speed (rpm)	750	750	Sub lot-1: speed; time; results 750; 1:19; oversized pellets After re-extrusion 1000; 1:00; some agglomerates 500; 1:00; big agglomerates Sub lot-2: 750; 2:00; some agglomerates after its break-down and successive spheronization to complete 3 minutes, acceptable, small agglomerates
Spheronization time (min:sec)	7:00	0:45	
Observations:	Acceptable Spheronization	Inferior spheronization than lot 014 and 013 and 003	
Drying			
Temperature (°C)	55	55	55
Drying time (min)	20	20	25/25
LOD (%)	1.2	1.1	ND/ND

Results: The bulk densities of the pellets are shown in Table 25. Pellets from MCC-based formulations showed a decreased bulk density with the increase of API drug loading and the decrease in the amount of water as liquid binder. Lot 002 (highest water content: 60% w/w)

showed the highest density (Figure 1 and Table 25). For pellets from lactose-based formulations, no correlation was found. Pellets from Polyplasdone® XL-10 based formulations showed lower bulk densities than MCC-based formulations having the same drug loading.

The largest pellets were obtained from the formulation containing 80% ecopipam/20% MCC (Lot 003). Only 1.7 % of total amount of pellets had a diameter below 850 μm.

Table 25. Density of 850-1400 μm Pellets and Yields

Lot No. (API %)	Water (%)	Bulk Density (g/cm^3)	Yield $_{II}$ (%) Load 850-1400 μm	Yield $_{II}$ (%) Load < 850 μm
L107-03001 (70%)	53	0.642	77	18.9
L107-03002 (55%)	60	0.782	78	20.7
L107-03003 (80%)	45	0.595	77	1.7
L107-03004 (55%)	30	0.625	88	10.1
L107-03005 (55%)	25	0.646	94	2.8
L107-03006 (55%)	30	0.641	94	5.1
L107-03007 (80%)	25	0.618	85	13.5
L107-03008 (30%)	35	0.684	77	22.3
L107-03009 (20%)	50	0.715	80	19.1
L107-03010 (30%)	35	0.712	89	6.2
L107-03011 (30%)	40	0.712	93	4.1
L107-03012 (35%)	38	ND	ND	ND
L107-03013 (80%)	37	ND	51	11.9
L107-03014 (80%)	36	0.605	66	28.5
L107-03015 (70%)	60	0.503	86	15.1
L107-03016 (80%)	60	0.510	88	8.6
L107-03017 (30%)	35	0.632	85	9.0
L107-03018 (80%)	36	0.587	68	13.5
L107-03019 (75%) sub lot-2	40	0.595	75	8.6

ND: Not determined

Yield$_{II}$ Calculated as pellets load fraction/amount total of pellets

Example 10: Dissolution Trials

Dissolution profiles of 225 mg ecopipam capsules, pellets from lots 001 to 007, are presented in Figures 2 to 4. For lots 001A, 002A and 003A the baskets were rotated at 50 rpm for 120 min and at 150 rpm from 120 min to 135 min. For lots 004 to 007 the baskets were rotated at 50 rpm for 240 min in both media, with an additional 150 rpm from 240 min to 255 min the samples in buffer at pH 6.8. For lots 001B and 002B and 003C to 019, the rotation speed was 50 rpm.

The comparison of dissolution profile of ecopipam capsules in acidic medium (900 mL pH 1.0) of the pellets having diameters between 850-1400 μm and for those with less than 500 μm can be found in Figures 2 and 3, respectively. Figure 4 depicts the dissolution profiles at pH 6.8 phosphate buffer (900 mL) of the capsules containing 850-1400 μm pellets. Dissolution results can be also found in Tables 26 to 30.

Ecopipam pellets dissolved faster in acidic (pH 1.0) than in pH 6.8 buffer, regardless of filler type and drug load. Concentration of 225 mg dose strength in 900 mL was 0.25 mg/mL. Poor dissolution results may be due to the poor solubility of this API at pH 6.5-6.8. Solubility results from client indicate the following solubility values: Solubility 1.28 mg/mL at pH 1.46, 0.10 mg/mL at pH 6.50, 0.02 mg/mL at pH 6.60 and 0.02 mg/mL at pH 6.83.

As shown in Figure 2, for MCC based formulations, drug release increased with the increase in drug loading. One of the reasons may be the fact that increasing drug loading required less water as granulation liquid (liquid binder). The amount of granulation liquid affects directly hardness, density, size, morphology and porosity of the pellets. Drug release rates depend on all these parameters. In general, by increasing amount of granulation liquid, slower release rates are obtained. As well, smaller pellets (higher exposed surface area) dissolved faster.

Similar dissolution rates were observed for 80% API loading formulations (lots 003 with MCC and 007 with Lactose).

55% API loading lactose based formulations (lots 004 to 006) dissolved faster than 55% MCC based formulation (lot 002). These lots contained the lactose that is hydrophilic filler and much less water. The fastest release was obtained for the formulation 006 containing higher proportion of disintegrant (Starch 1500 and SSG).

25 mg dose strength capsules from lots 008 (API 30%) and 009 (API 20%) and 225 mg capsules from lot 008 (lot 008A, two capsules containing 112.5 mg of ecopipam each) dissolution profiles are presented in Figure 5. A dissolution rate typical of immediate-release dosage forms was obtained from lot 008 25 mg capsules. 225 mg capsules from same formulation (lot 008A) dissolved less quickly. Decreasing the API load from 30 to 20% with an increasing fraction of MCC and subsequently more water required, led to a complete release of the drug in more than 30 minutes. Tables 26-29 show the results of dissolution testing for various lots of ecopipam HCl with varying pellet sizes.

Table 26. Results of Dissolution Testing for Ecopipam-HCl Capsules (Pellets: 850-1400 μm)

Lot No. (API %)	L107-03001A (70%)		L107-03002A (55%)		L107-03003A (80%)	
Dissolution medium	0.1 N HCl pH 1.0	USP Phosphate buffer, pH 6.8	0.1 N HCl pH 1.0	USP Phosphate buffer, pH 6.8	0.1 N HCl pH 1.0	USP Phosphate buffer, pH 6.8
Capsule weight (mg)	1: 459.37 2: 462.86 3: 456.65	1: 457.15 2: 461.51 3: 459.45	1: 558.41 2: 557.80 3: 558.86	1: 554.61 2: 556.09 3: 555.54	1: 414.37 2: 416.21 3: 412.38	1: 413.16 2: 415.62 3: 413.66
Dissolution (%) (To report @120 min)	Mean: 45.4 (n=3: 45.8, 46.0, 44.3)	Mean: 6.1 (n=3: 6.5, 5.0, 6.8)	Mean: 29.6 (n=3: 30.4, 28.9, 29.6)	Mean: 6.9 (n=3: 6.5, 6.4, 7.8)	Mean: 60.8 (n=3: 60.4, 60.0, 62.0)	Mean: 5.8 (n=3: 6.2, 5.7, 5.6)
Dissolution (%) (To report @ 135 min)	Mean: 49.8 (n=3: 50.6, 50.2, 48.7)	Mean: 7.1 (n=3: 7.5, 6.1, 7.8)	Mean:32.3 (n=3: 33.4, 31.7, 32.0)	Mean: 7.9 (n=3: 7.7, 7.0, 9.0)	Mean: 66.3 (n=3: 65.2, 65.4, 68.4)	Mean: 6.2 (n=3: 6.7, 6.0, 5.9)
Dissolution (%) (To report @ 18 hrs)	Not tested	Not tested	Not tested	Not tested	99.5 (n=1)	8.0 (n=1)

Table 27. Results of Dissolution Testing for Ecopipam-HCl Capsules (Pellets: < 500μm)

Sample	L107-03001B	L107-03002B
Dissolution medium	0.1 N HCl (pH 1.0)	0.1 N HCl (pH 1.0)
Capsule weight (mg)	1: 460.54/ 2: 459.38	1: 562.22/ 2: 560.27
Dissolution (%) (To report @ 6 hrs)	Mean: 97.6 (n=2: 96.7, 98.5)	Mean: 94.0 (n=3: 95.7, 92.3)

Table 28. Results of Dissolution Testing for Ecopipam-HCl Capsules (Pellets: 850-1400 μm)

Sample	L107-03004		L107-03005		L107-03006		L107-03007	
Dissolution medium	0.1 N HCl pH 1	USP Phosphate buffer, pH 6.8	0.1 N HCl pH 1	USP Phosphate buffer, pH 6.8	0.1 N HCl pH 1	USP Phosphate buffer, pH 6.8	0.1 N HCl pH 1	USP Phosphate buffer, pH 6.8
Capsule weight (mg)	1: 557.07 2: 558.11 3: 555.53	1: 555.60 2: 554.53 3: 559.17	1: 559.11 2: 557.49 3: 556.87	1: 559.05 2: 560.28 3: 557.96	1: 556.63 2: 557.92 3: 552.85	1: 558.19 2: 558.51 3: 556.34	1: 414.79 2: 414.71 3: 410.85	1: 414.59 2: 413.63 3: 415.64
Dissolution (%) (To report @ 240 min)	Mean:93.1 (n=3: 94.4, 93.0, 92.0)	Mean:8.6 (n=3: 8.5, 8.8, 8.6)	Mean:76.3 (n=3: 76.4, 75.6, 76.8)	Mean: 9.9 (n=3: 9.5, 9.8, 10.2)	Mean:94.7 (n=3: 95.2, 94.7, 94.2)	Mean:11.2 (n=3: 11.5, 10.9, 11.4)	Mean:81.5 (n=3: 82.1, 81.7, 80.6)	Mean: 9.3 (n=3: 8.6, 10.1, 9.1)
Dissolution (%) (To report @ 255 min)	Not tested	Mean: 8.5 (n=3: 8.4, 8.7, 8.5)	Not tested	Mean: 9.9 (n=3: 9.6, 9.9, 10.3)	Not tested	Mean:11.0 (n=3: 11.2, 10.6, 11.1)	Not tested	Mean: 9.3 (n=3: 8.6, 10.0, 9.2)

Table 29. Results of Dissolution Testing for Ecopipam-HCl Capsules (Pellets: 850-1400 μm)

Lot No. (API %)		L107-03008 (30%)	L107-03009 (20%)	L107-03008A
Dissolution medium		0.1 N HCl	0.1 N HCl	0.1 N HCl
Dose strength (mg)		25	25	225
Capsule weight (mg)		1: 133.56 2: 132.31 3: 134.42	1: 176.38 2: 177.45 3: 177.07	1: 1040.08 2: 1040.95 3: 1041.15
Dissolution (%)*		Mean: 101.7 (n=3: 100.8, 101.2, 102.9)	Mean: 99.8 (n=3: 99.9, 99.8, 99.6)	Mean: 95.9 (n=3: 95.0, 96.4, 96.3)
Dissolution (%)	10 min	46.7	24.5	14.4
	20 min	75.6	42.1	32.8
	30 min	90.9	55.6	48.3
	45 min	98.9	70.7	67.3
	60 min	100.8	81.1	79.3
	90 min	101.2	89.6	91.6
	120 min	101.6	96.5	95.9
	240 min	101.7	99.8	ND

*To report @ 240 min for lots 008 and 009, @ 120 min for lots 008A
ND: not determined

Example 11: Verification of Ecopipam-HCl Pellet Capsule Dissolution Profile

Ecopipam-HCl pellets capsules (dose 25 mg) dissolutions profiles were verified in various dissolution media (Figure 6). The results demonstrated that approximately 67% of the drug was released in a sustained manner in the pH 6.8 phosphate buffer (with 0.1% SDS) within 6 hours and 95% within 24 hours for 25 mg capsule dissolution profile from lot 008 and 003C. Detailed information on dissolution results can be found in Table 30.

The effect of the total dose on the dissolution profile for the immediate release (IR) pellets (Lot 107-03 008 (30%)) and for the controlled release (CR) pellets (Lot 107-03 003 (80%)) was investigated by comparison of the dissolution profiles in 0.1N HCl (pH 1.0) (Figures 24 and 25).

The results obtained for IR 25, 100 and 225 mg capsule (2x 112.5 mg capsules) at pH 1 showed that the dissolution rate decreases with increasing total dose (Figure 8). For lot 003 (CR pellets), no significant difference in dissolution profiles between 25 and 100 mg were found at pH 1(Figure 8). However, when the experiment was carried at pH 6.8, slower dissolution profile with increasing total dose was obtained (Figure 9).

The dissolution profiles of the enteric coated pellets for lot L107-03003-5O20A-25 and lot L107-03003-5O20A-100 capsules are shown in Figure 10. Dissolution was carried out in acid stage (0.1N HCl) for 2 hours, transferred to sodium phosphate buffer pH 6.8 with 0.1% SDS and sampled out to 18 hours.

Less than 1% of the drug was released in the acid stage, confirming the efficacy of the enteric coat. The profile in pH 6.8 buffer was similar for the 25 and 100 mg dose strengths of the same enteric coated pellets and for the uncoated pellets having a similar pellet size (more than 850 μm). A faster profile was obtained for the uncoated pellets between 500- 850 μm.

Table 30. Results of Dissolution Testing for Ecopipam-HCl Capsules (Pellets: 850-1400 μm)

Lot No. (API %)		L107-03008 (30%)		L107-03003C (80%)	
Dose strength		25 mg		25 mg	
Dissolution medium		0.1N HCl	0.1% SDS in Na Phosphate pH 6.8	0.1N HCl	0.1% SDS in Na Phosphate pH 6.8
Capsule weight (mg)		1: 133.56 2: 132.31 3: 134.42	1: 132.68 2: 133.19	1: 72.53 2: 72.46	1: 73.93 2: 72.90
Dissolution n= 2 capsules (%)	10	46.7	8.5	7.8	2.3
	20	75.6	13.9	17.3	5.1
	30	90.9	17.9	23.2	7.3
	45	98.9	23.1	32.5	10.6
	60	100.8	28.6	38.8	14.4
	90	101.2	41.6	51.0	22.0
	120	101.6	55.0	58.5	29.4
	240	101.7	77.3	81.0	53.5
	360	NA	85.5	92.3	66.9
	1440	NA	97.6	101.3	95.2

Method: Apparatus 1, 40 mesh basket, 50 rpm to 240 min.

Example 12: Comparison of Dissolution Profiles of Uncoated Pellets with Coated Pellets

The dissolution profile of uncoated pellets from lot 014 was compared with that of coated pellets from lot 003 (Figure 11). Drug release was slightly faster from lot 014 (36% of water on dry basis) compared to lot 003 (45% of water on dry basis). The capsules were filled with pellets having between 850-1400 μm. Lot 014 was extruded with a 1.0 mm die while lot 003 were formed with a 1.2 mm die. Small die extruders produce smaller and more compacted "compact" pellets. Depending on the type of drug and/or on the formulation, slower drug release resulted from more "compact" pellets.

In formulations 015 and 016, MCC was substituted by Crospovidone® (Polyplasdone®XL-10) in order to provide a faster rate of dissolution. The dissolution profiles of the uncoated pellets for lot L107-03015 (70% drug loading (DL) and 016 (80% DL) capsules 'IR' were carried out in 0.1N HCl for 2 hours. The dissolution profiles for lot 015 25 mg and 100 mg capsules are shown

in Figure 12. The dissolution profile of the L107-03015-25 mg was compared to L107-03008 – 25 mg and the L107-03009 -25 mg in Figure 13.

No difference between 25 and 100 mg capsules were found for lot 015 (70% DL) in acid media, similar to results obtained for 25 mg and 100 mg capsules for lot 003 (80% DL), showed in Figure 8. Thus it was established that for high drug load, the dose strength did not affect the dissolution profiles. Compared to lots 008 (30% DL) and 009 (20% DL), MCC/Lactose based formulations, slower drug release could be achieved from lot 015 (70% DL) and 016 (70% DL), Crospovidone® based formulation, for both. 25 and 100 mg capsule (Figure 14 and 15).

Example 13: Controlled Release Pellets Formulation Comparative Study

Promising CR formulations (acceptable spheronization) at 70, 75 and 80% drug loading were compared by recovery (Table 31) and dissolution profiles (Figure 16). In terms of recovery, lot L107-03001 (70% drug loading) showed the highest yield while lowest but acceptable recovery was given by the lot L107-03003 (80% drug loading). During spheronization lots L107-03003 followed by lot L107-030019 (75% drug loading) showed some pellets-pellets agglomeration or fusion into a solid mass. In terms of disssolution the results were inverted (Figure 16). Indeed, lot L107-03003 (80%), followed by L107-03019 (75%) dissolved more rapidly than lot L107-03001 (70%). All 3 lots showed similar assay values ranging from 97-103.3 %.

Table 31. 850-1400 μm Pellets and Yields

Lot No. (API %)	Yield $_{Tot}$ (%)	Yield $_{Fr}$ (%) Load 850-1400 μm
L107-03001 (70%)	87.3	67.5
L107-03019 (75%) sub lot-2	82.3	61.4
L107-03003 (80%)	75.6	58.0

Yield $_{Tot}$ calculated as amount total of pellets /amount total of blend
Yield $_{Fr}$ calculated as pellets load fraction/amount total of blend

Example 14: 90 mg Ecopipam Capsule

A final dosage of 90 mg ecopipam consisting of 40% 'IR' component (132 mg of pellets equivalent to 36 mg of ecopipam) and 60% 'CR' component (100 mg of pellets equivalent to 54 mg of ecopipam) was selected for clinical and long term stability evaluation. Demo batch lot L107-03003-5O20A5O-017-90mg (IR40/CR60) was manufactured for R&D purposes with available pellets and lot L107-03021 (CTM batch) was manufactured under cGMP conditions for clinical trial purposes. "Clinical trial material" is abbreviated as CTM.

As shown in Figure 17, 90 mg ecopipam capsule CTM batch (IR40/CR60) dissolved slower than 100 mg ecopipam capsule lot L107-03003-5O20A5O-017-100 mg (IR50/CR50). The slower dissolution rate was attributed principally to an increase in CR component. As obtained in previous dissolution testing at pH 6.8, CR pellets dose increasing results in a slower dissolution rate of the drug (Figure 9). Figure 18 compares 90 mg ecopipam capsule CTM batch (IR40/CR60) and equivalent demo batch for 2 stages dissolution profiles at both 50 and 100 RPM. For both lots, no major differences were found between profiles obtained at 50 and 100 RPM. For initial testing CTM capsules showed similar dissolution profiles between 0 and 540 minutes. After 540 minutes, CTM lot showed a slower release. That could be explained by the curing/stabilization time of the enteric coating layer on the pellets used for the demo batch. Indeed, stability testing on CR pellets showed an increase of the drug release after 12 weeks at 25 °C/60% RH, notably after 360 minutes (Figure 19 and Table 32).

Table 32. Dissolution Results at T=0 and 12 Weeks for L107-03003-5O20A5O CR Pellets

Dissolution / Time (min)/Conditions	60	120	240	360	540	720	840	1080	1440
T=0	0	0	12	22	34	44	51	61	74
T=12wks/25°C/60%RH	0	0	13	26	43	56	64	75	84

Results: Extrusion/spheronization process was evaluated for ecopipam-HCl up to 225 mg dosage per unit in order to obtain immediate and controlled release pellets combined in hard shell capsule in order to reach an immediate release dose dumping within 1 hour followed by a zero-order type sustained release up to 24 hours.

Immediate release ecopipam-HCl formulations could be only achieved from low drug loading (30%) pellet formulations containing Lactose monohydrate as hydrophilic filler and Polyplasdone® XL-10 as disintegrant with more than 75% of API released within 1 hour in acidic media. Acceptable extrusion-spheronization process produced 850-1400 um average size pellets. Immediate release pellets were not further coated.

Ecopipam-HCl at high drug loading (80%) combined with microcrystalline cellulose as spheronization aid agent and hydrophobic filler produced acceptable pellets in terms of yield and shape with a size fraction between 850-1400 μm. Easier spheronization with higher recovery but too slow dissolution profiles were obtained at lower drug loading of 70 and 75%. The selected 80% drug loading formulation led to a sustained release over 24 hours in simulated intestinal fluid

phosphate buffer pH 6.8 with 0.1% sodium lauryl sulfate. In general, all lots containing lower drug loading and microcrystalline cellulose as single filler resulted in rods or dumbbell shaped pellets. MCC/ecopipam-HCl pellets dissolved faster in acidic than in pH 6.8 media. As well, formulations containing higher drug loading dissolved faster, justifying the use of an enteric coating on the controlled release pellets. The use of this functional coating required sub- and over-coating layers in order to avoid potential interactions with the API from the immediate and controlled release pellets. For the 25 and 100 mg dose strengths of the same enteric coated pellets, the profile in buffer pH 6.8 was similar with a 76% of drug released in 18 hours. For these pellets, less than 1% of the drug was released in the acid stage, confirming the efficacy of the enteric coat. CR formulation lots at 70, 75 and 80% drug loading were compared.

Lot L107-03003-5O20A5O (coated CR pellets) and L107-03017 (uncoated IR pellets) were selected as final formulations based on dissolution profiles and combined as IR-CR pellets mixture to a theoretical ratio to obtain 50 mg of each pellets type per capsule unit in lot L107-03003-5O20A5O-017. Similar bulk densities and pellets sizes were observed for both final formulations. V-Blending process was found to be suitable in order to obtain adequate blend uniformity of combined immediate and controlled release pellets as confirmed by image analysis performed on final pellets mixture. This formulation was selected for long term stability

A 90 mg ecopipam capsule (IR40%/CR60%) was selected as final dosage and IR/CR final formulation pellets ratio for clinical purposes.

Example 15: Prototype Formulation of 100 mg Ecopipam-HCl Capsule

Stability studies were conducted on 100 mg ecopipam-HCl hard gelatin shell capsules containing pellet formulations presented in Tables 33-38.

Table 33. 100 mg (Strength) - Ecopipam-HCl Formulation Lot L107-03003-5O20A, Controlled Release (CR) Pellets

Raw Materials	Lot No.	% w/w	mg/capsule (salt)
Ecopipam-HCl	IRQ-39166-00-X-2	66.1	112.7
Microcrystalline Cellulose Avicel PH-101	P105815404	12.9	22.0
Opadry® 20A19301 clear	TS054021	5.0*	8.5
Acryl-EZE MP93018508 white	TS058598	16.0	27.3
Size 1** white opaque Gelatin capsule	70292091	-	-
Total		**100.0**	**170.5**

*Theoretical

**Capsules filled to approximately 40 percent of its volume

Table 34. 100 mg (Strength) - Ecopipam-HCl Formulation Lot L107-03009-5O, Immediate Release (IR) Pellets

Raw Materials	Lot No.	% w/w	mg/capsule (salt)
Ecopipam-HCl	IRQ-39166-00-X-2	19.4	112.7
Lactose Monohydrate (Tabletose-80)	L0918A4003	48.4	281.7
Microcrystalline Cellulose (Tabulose-101)	038/07	24.2	140.9
Crospovidone CL	18682656PO	4.9	28.3
Opadry® 20A19301 clear	TS054021	3.2	18.6
Size 00 white opaque Gelatin capsule	90085321	-	-
Total		**100.0**	**582.1**

Table 35. 100 mg (Strength) - Ecopipam-HCl Formulation Lot L107-03003-5O20A-009-5O, Controlled Release

Raw Materials	Lot No.	% w/w	mg/capsule (salt)
Ecopipam-HCl (66.1%) CR Coated pellets	L107-03003-5O20A	77.4	85.0
Ecopipam-HCl (19.4%) IR Opadry-coated pellets	L107-03009-5O	22.6	291.0
Size 0 white opaque Gelatin capsule	90083661	-	-
Total		**100.0**	**376.0**

Table 36. 100 mg (Strength) - Ecopipam-HCl Formulation Lot L107-03003-5O20A5O, Controlled Release (CR) Pellets

Raw Materials	Lot No.	% w/w	mg/capsule (salt)
Ecopipam-HCl	IRQ-39166-00-X-2	63.5	112.7
Microcrystalline Cellulose (Avicel PH-101)	P105815404	10.5	18.6
Opadry® 20A19301 clear	TS054021	10.0*	17.8
Acryl-EZE MP93018508 white	TS058598	16.0	28.4
FD&C (Yellow No.6 Al. Lake)	AM6882	NMT 0.004	0.01
Size 1** white opaque Gelatin capsule	70187731	-	-
Total		**100.0**	**177.6**

*Theoretical, 5% sub-coat and 5% over coat

**Capsules filled to approximately 60 percent of its volume

Table 37. 100 mg(Strength) - Ecopipam-HCl Formulation Lot L107-03017, Immediate Release (IR) Pellets

Raw Materials	Lot No.	% w/w	mg/capsule (salt)
Ecopipam-HCl	IRQ-39166-00-X-2	30.0	112.7
Lactose Monohydrate (Tabletose-80)	L0918A4003	50.0	187.8
Microcrystalline Cellulose (Tabulose-101)	038/07	15.0	56.3
Crospovidone (Polyplasdone XL-10)	03000241672	5.0	18.8
Size 0** white opaque Gelatin capsule	90083661	-	-
Total		**100.0**	**375.6**

**Capsule filled to about 90 percent of its volume

Table 38. 100 mg (Strength) -Ecopipam-HCl Formulation Lot L107-03003-5O20A5O-017, Controlled Release

Materials	Lot No.	mg pellets /cap	% w/w	g/lot
Ecopipam-HCl (63.5%) CR Coated pellets	L107-03003-5O20A5O	88.8	32.4	7.83
Ecopipam-HCl (30.0%) IR Uncoated pellets	L107-03017	187.8	67.6	16.36
Size 1 white opaque Gelatin capsule	70187731	-	-	-
Total		**276.6**	**100.0**	**24.19**

Example 16: Short Term Stability Study on 100 mg Ecopipam Free Base

A short term stability study was initiated for 100 mg (free base) ecopipam hard gelatin shell capsules containing coated pellets from initial promising formulations:

• Lot L107-03003 5O20A - 100 mg capsules 'CR' (pellets from lot 003 subcoated with Opadry® and entericaly coated with Acryl-eze®);

• L107-03009 5O - 100 mg capsules 'IR' (pellets from lot 009 coated with Opadry®) and

• L107-03003 5O20A + L107-03009 5O (L107-03003-5O20A -009-5O) - 100 mg capsules 'SR' (50 mg from each lot/capsule).

Capsules were incubated in HDPE bottles with PP caps as per the stability protocol of Table 39. To perform a short term stress study, the caps were not induction sealed and samples were incubated only under accelerated conditions. The placebo was incubated in powder form.

Table 39. Drug Product Stability Protocol for 100 mg Ecopipam HCl Capsules (Study #1).

Stability Protocol Ecopipam-HCl 100 mg Capsules

Project	Lot (Strenght)	Packaging	Temperature (°C)			Humidity (% RH)			TTmepoints (Months)					
			25	30	40	60	65	75	0	0.5	1	2	3	6
107-03	L107-03003-5020A (100 mg)	HOPE Bottles with PP caps			√			√	2010 AU 31	2310 SE 14	2010 SE 28	2010 OC 29	2010 NO 30	2011 FE 28
	L107-03009-50 (100 mg)				√			√	2010 AU 31	2310 SE 14	2010 SE 28	2010 OC 29	2010 NO 30	2011 FE 28
	L107-03003-502GA-009-5Q (100 mg)				√			√	2010 AU 31	231C SE 14	2010 SE 28	2010 OC 29	2010 NO 30	2011 FE 28

Sample to be analyzed for:

Test: Appearance Method: Visual

Test: Water Content Method: USP < 921 > method 1c (Karl-Fisher Titration)

Test: Dissoluton Method: Corealis-10703-B

Test: Assay and Related Substances. Method Corealis-10703-A&D

Example 17: Second Stability Study on 100 mg Ecopipam Free Base

A second stability program was conducted on 100 mg (free base) ecopipam hard gelatin shell capsules containing pellets from the final formulations:

• Lot L107-03003 5O20A5O -100 mg capsules 'CR' (pellets from lot 003-5O20A, coated with Opadry-containing colorant solution to a 5% theoretical weight gain);

• L107-030017 -100 mg capsules 'IR' and

• L107-03003 5O20A5O + L107-03017 (L107-030035O20A5O -017)-100 mg capsules 'SR' (50 mg from each lot).

Capsules were incubated in induction sealed HDPE bottles as per the stability protocol shown in Table 40. The Placebo was incubated in powder form.

Table 40. Drug Product Stability Protocol for 100 mg Ecopipam HCl Capsules (Study #2).

Stability Protocol Ecopipam-HCI 100 mg Capsules

Project	Lot (Strenght)	Packaging	Temperature (°C)				Humidity (% RH)				Timepoints (Months)				
			4	25	30	40	Amb.	60	65	75	0	1	2	3	6
107-03	L107-03003-5O20A5O (100 mg)	Gelatin capsules into induction sealed HDPE bottles	√				√				2010 OC 14	2010 NO 15	2010 DE 14	2011 JA 13	2011 AL 14
				√				√				2010 NO 15	2010 DE 14	2011 JA 13	2011 AL 14
						√				√		2010 NO 15	2010 DE 14	2011 JA 13	2011 AL 14
	L107-03017 (100 mg)		√				√				2010 OC 14	2010 NO 15	2010 DE 14	2011 JA 13	2011 AL 14
				√				√				2010 NO 15	2010 DE 14	2011 JA 13	2011 AL 14
						√				√		2010 NO 15	2010 DC 14	2011 JA 13	2011 AL 14
	L107-03003-5O20A5O-017 (100 mg)		√				√				2010 OC 14	2010 NO 15	2010 DE 14	2011 JA 13	2011 AL 14
				√				√				2010 NO 15	2010 DE 14	2011 JA 13	2011 AL 14
						√				√		2010 NO 15	2010 DC 14	2011 JA 13	2011 AL 14
	L107-03003-5O20A5OP PLACEBO	Powder into closed cap HOPE bottles									2010 OC 14	2010 NO 15	2010 DE 14	2011 JA 13	2011 AL 14
				√				√				2010 NO 15	2010 DE 14	2011 JA 13	2011 AL 14
						√				√		2010 NO 15	2010 DE 14	2011 JA 13	2011 AL 14
	L107-03017P PLACEBO										2010 OC 14	2010 NO 15	2010 DE 14	2011 JA 13	2011 AL 14
				√				√				2010 NO 15	2010 DE 14	2011 JA 13	2011 AL 14
						√				√		2010 NO 15	2010 DE 14	2011 JA 13	2011 AL 14
	L107-03003-5020A50-017P PLACEBO										2010 OC 14	2010 NO 15	2010 DE 14	2011 JA 13	2011 AL 14
				√				√				2010 NO 15	2010 DE 14	2011 JA 13	2011 AL 14
						√				√		2010 NO 15	2010 DE 14	2011 JA 13	2011 AL 14

Three prototypes to be analyzed for:

Test: Appearance. Method: Visual

Test: Water Content. Method: USP < 921 > method 1c (Karl Fisher Titration).

Test: Dissolution. Method: Corealis-10703-B

Test: Assay and Related Substances. Method: Corealis-10703 A&D

One prototype to be analyzed

Sample analyzed only at the request of Client.

Used as analytical baseline information.

Results for Stability Study 1:

The samples stored at 40 °C/75% RH for 2, 4, 8, 12 and 26 weeks (6 months) were analyzed for dissolution, assay and water content (Tables 39 to 41). The results were compared to those at T=0.

L107-03003-5O20A-100 mg capsules 'CR'

As shown in Table 41, the assay values were between 97 and 103 % of label claimed (100 mg free base) throughout the duration of the study. No related substances above the reporting threshold were found in those samples. The moisture content was low (2.1%) and did not vary between 2 and 4 weeks of exposition at 40 °C and 75% RH.

The dissolution profiles of the enteric coated pellets for lot L107-03003-5O20A-100 mg capsules controlled release (CR) (850-1400 μm) was carried out in acid stage (0.1N HCl) for 2 hours, transferred to sodium phosphate buffer pH 6.8 with 0.1% SDS and sampled out to 24 hours (Figure 22).

Table 41. Tabulated Assay Values and Dissolution Profiles L107-03003 5O20A

Lot No.:		L10703003 5O20A CR Formulation					
Dose strength		100 mg					
Stability conditions		40°C/75%RH					
Stability Time Point		T = 0	2 weeks	4 weeks	8 weeks	12 weeks	26 weeks
Assay (% Label Claim)		97.0	97.0	100.1	100.9	102.7	99.5
Moisture by KF (% water)		Not tested	2.1	2.1	Not tested	Not tested	Not tested
Dissolution medium		0.1N HCl + 0.1% SDS in Na Phosphate pH 6.8					
Dissolution (%) n= 2	10	<1	<1	<1	<1	<1	<1
	30	<1	<1	<1	<1	<1	<1
	60	<1	<1	<1	<1	<1	<1
	90	<1	<1	<1	<1	<1	<1
	120	<1	<1	<1	<1	<1	<1
	150	3	3	3	2	3	3
	240	15	12	12	10	11	11
	360	28	23	23	20	21	21
	540	45	37	36	34	34	34
	720	59	48	48	45	45	45
	840	67	55	54	51	51	51
	1080	78	65	64	60	63	62
	1440	NA	77	76	69	73	71

Less than 1% was released in the acid stage, confirming the efficacy of the enteric coat upon storage. At the 2 week time point, the dissolution profile was slightly slower that that at time

zero. No significant changes in dissolution profiles at 4 wks compared to 2 wks were observed. The dissolution profiles at 2, 4, 8, 12 and 26 weeks were superimposable.

L107-03009-5O-100 capsules 'IR'

Assay values were found to be stable over 26 weeks at values between 97 and 101% (Table 42). Water content values were between 4.6 and 4.9%, most probably due to the higher proportion of microcrystalline cellulose, excipient that contains typically 5% of water.

The dissolution profiles of the pellets for lot L107-03009-5O-100 capsules 'IR', pellets coated with non-functional coating (Opadry®) is shown in Figure 23. Dissolution was carried out in acid stage (0.1N HCl) for 2 hours. Approximately 80% was released in 2 hours. No dissolution profile is available of the capsules at time zero, thus the dissolution was compared to the uncoated pellet of lot L107-03009. The coated pellets showed a slower dissolution profile compared to time zero. However, there was no difference in the dissolution profiles between 2, 4, 8 and 26 weeks. Although at the 12 week time point only, a very slight decrease in dissolution was observed.

Table 42. Tabulated Assay Values and Dissolution Profiles L107-03009 5O

Lot No. :		L10703009 5O IR Formulation					
Dose strength		100 mg					
Stability conditions		40°C/75%RH					
Stability Time Point		T = 0	2 weeks	4 weeks	8 weeks	12 weeks	26 weeks
Assay (% Label Claim)		96.9	96.7	97.8	97.7	100.7	97.9
Moisture by KF (% water)		Not tested	4.9	4.6	Not tested	Not tested	Not tested
Dissolution medium		0.1N HCl					
Dissolution (%) n= 2	10	24	6	7	6	5	6
	30	56	30	32	33	27	30
	60	81	53	55	58	50	54
	90	90	69	70	72	65	69
	120	97	78	80	81	75	78

L107-03003-5O20A + L107-03009 5O-100 capsules 'SR' (IR+CR)

The dissolution profiles of the enteric coated pellets for lot L107-03003-5O20A + L107-030095O-100 capsules 'IR+CR' is presented in Figure 24. Dissolution was carried out in acid stage (0.1N HCl) for 2 hours, transferred to sodium phosphate buffer pH 6.8 with 0.1% SDS and sampled out to 24 hours (Table 43). In the acid stage, approximately 40% was released, which corresponds well with the release profile of L107-03009 5O 'IR' (*i.e.*, 80% of 50 mg of the 'IR' formulation). In the buffer stage, at 18 hours the amount release is higher by approximate 10% as compared to the 'CR' formulation alone. This difference is accounted for by the amount of the

'IR' formulation not dissolved in the acid stage. No changes were observed in the dissolution profile after 2, 4, 8, 12 and 26 weeks of storage at 40 °C and 75% of relative humidity. Assay and water content values were also stable with time.

Table 43. Tabulated Assay Values and Dissolution Profiles L107-03003 5O20A-009 5O

Lot No.:		L10703003 5O20A-009 5° SR Formulation					
Dose strength		100 mg					
Stability conditions		40°C/75%RH					
Stability Time Point		T = 0	2 weeks	4 weeks	8 weeks	12 weeks	26 weeks
Assay (% Label Claim)		Not tested	98.2	99.4	100.7	102.1	99.0
Moisture by KF (% water)			4.0	4.4	Not tested	Not tested	Not tested
Dissolution medium			0.1N HCl + 0.1% SDS in Na Phosphate pH 6.8				
Dissolution (%) n= 2	10		3	4	4	8	6
	30		16	18	16	18	17
	60		27	28	32	27	30
	90		34	35	36	33	35
	120		39	40	38	38	38
	150		42	43	40	41	41
	240		49	49	45	47	47
	360		56	57	52	54	54
	540		65	65	62	64	64
	720		72	72	69	71	71
	840		75	76	72	75	75
	1080		81	82	78	83	83
	1440		89	89	84	89	89

Results for Stability Study 2:

Final formulations of CR, IR and SR (mixture) pellets at T=0 and samples into induction sealed HDPE bottles, stored under ICH controlled temperature/moisture conditions, were analyzed for dissolution and composite assay (Table 44 to 46).

The stability study results for L107-03003 5O20A5O, L107-03017 and L107-03003 5O20A5O +L107-03017 100 mg capsules are reported in Tables 44 to 46 and Figures 25 to 27. The samples stored at 40 °C/75% RH were analyzed for dissolution and composite assay. The samples stored at 25 °C/60% RH were analyzed for dissolution only.

L107-03003-5O20A5O-100 mg capsules 'CR'

The dissolution profiles of the enteric coated pellets for lot L107-03003-5O20A5O-100 capsules 'CR'. Dissolution was carried out in acid stage (0.1N HCl) for 2 hours, transferred to sodium phosphate buffer pH 6.8 with 0.1% SDS and sampled out to 24 hours (Figure 25).

Assay values of about 105% observed at T=0 for samples containing pellets from lot L107-03003-5O20A5O were elevated indicating that gain weight after last Opadry® film coating was less than the theoretical weight gain value of 5%. For these samples, less than 1% was released in the acid stage, confirming the efficacy of the enteric coat upon storage. Compared to lot L107-03003-5O20A, pellets from L107-03003-5O20A5O dissolved slightly slower, 61 % at 1080 min (Table 44) vs. 78 % at 1080 min for lot pellets from lot L107-03003-5O20A (Table 41), most probably due to the additional coating level.

The assay value remained similar and stable over 4, 8 and 12 weeks with no detectable amount of related substances. The dissolution profiles slightly decreased after 4 weeks of storage under both conditions of 25 °C/60% RH and 40 °C/75% RH. After 8 and then 12 weeks of storage at 40 °C/75% RH, a slight increase in dissolution was observed in relation to initial results. Less than 1% of drug was found in acid media confirming the stability of the enteric coat upon storage.

Table 44. Tabulated Assay Values and Dissolution Profiles L107-03003 5O20A5O

Lot No.:		L10703003 5O20A5O CR Formulation					
Dose strength		100 mg					
Time Point		T = 0	4 weeks		8 weeks	12 weeks	
Stability conditions		N/A	25°C/60 %RH	40°C/75 %RH	40°C/75 %RH	25°C/60 %RH	40°C/75 %RH
Assay (% Label Claim)		104.5	Not tested	105.7	107.9	106.2	105.9
Dissolution medium		0- 2 hours: 0.1N HCl 2- 24 hours: 0.1% SDS in Na Phosphate pH 6.8					
Dissolution (%) n= 2	10	<1	<1	<1	<1	<1	<1
	30	<1	<1	<1	<1	<1	<1
	60	<1	<1	<1	<1	<1	<1
	90	<1	<1	<1	<1	<1	<1
	120	<1	<1	<1	<1	<1	<1
	150	2	1	2	3	3	3
	240	12	10	10	12	13	14
	360	22	19	19	23	26	27
	540	34	30	29	38	43	43
	720	44	40	38	51	56	57
	840	51	45	44	57	64	65
	1080	61	54	53	68	75	76
	1440	74	66	64	79	84	85

L107-03017-100 capsules 'IR'

Dissolution profile of 'IR' pellets (uncoated pellets) from lot L107-03017 (100 mg capsules) was carried out in acid stage (0.1N HCl) for 2 hours. Approximately 100% was released in 2 hours (Table 45 and Figure 26). The 4, 8 and 12 week time point results for lot L107-03017 indicated stable assay with no detectable amount of related substances but the dissolution profiles slightly decreased upon storage.

Table 45. Tabulated Assay Values and Dissolution Profiles L107-03017

Lot No.:		L10703017 IR Formulation					
Dose strength		100 mg					
Stability conditions		T = 0	4 weeks		8 weeks	12 weeks	
Time Point		N/A	25°C/60 %RH	40°C/75 %RH	40°C/75 %RH	25°C/60 %RH	40°C/75 %RH
Assay (% Label Claim)		100.0	Not tested	99.5	103.1	101.0	101.6
Dissolution medium		0.1 N HCl					
Dissolution (%) n= 2	10	21	13	6	14	17	14
	30	61	41	48	43	54	44
	60	87	70	77	70	83	72
	90	97	86	92	85	94	88
	120	99	93	97	91	98	95

L107-03003-5O20A5O + L107-03017-100 capsules 'SR' (IR+CR)

The dissolution profiles of the enteric coated pellets for lot L107-03003-5O20A5O + L107-03017-100 capsules 'IR+CR' was carried out in acid stage (0.1N HCl) for 2 hours, transferred to sodium phosphate buffer pH 6.8 with 0.1% SDS and sampled out to 24 hours.

At T=0, L107-03003-5O20A5O-017 SR pellets formulation showed similar dissolution profile than previous SR pellets formulation (L107-03003-5O20A-009-5O), 89-90 % in 1440 minutes (Tables 43 and 46).

4, 8 and 12 week time points assay values remained similar. No degradation products were reported. The dissolution profile remained stable after 4 and 8 weeks of storage but was slightly faster after 12 weeks. No significant differences were found between 25 °C/60% RH and 40 °C/75% RH storage conditions. No drug was found in acid media confirming the stability of the enteric coat upon storage.

Table 46. Tabulated Assay Values and Dissolution Profiles L107-03003 5O20A5O-017

Lot No.:		L10703003 5O20A5O-017 SR Formulation					
Dose strength		100 mg					
Time Point		T = 0	4 weeks		8 weeks	12weeks	
Stability conditions		N/A	25°C/60 %RH	40°C/75 %RH	40°C/75 %RH	25°C/60 %RH	40°C/75 %RH
Assay (% Label Claim)		105.2	Not tested	103.6	103.2	103.9	101.2
Dissolution medium		0- 2 hours: 0.1N HCl 2- 24 hours: 0.1% SDS in Na Phosphate pH 6.8					
Dissolution (%) n= 2	10	11	8	6	10	9	7
	30	34	27	20	24	25	19
	60	50	43	35	40	40	34
	90	53	47	43	48	46	42
	120	53	48	45	50	48	46
	150	54	49	46	52	50	49
	240	59	54	51	57	55	55
	360	64	59	57	62	62	63
	540	71	66	63	69	72	72
	720	76	72	69	75	79	79
	840	79	75	72	78	84	83
	1080	85	80	78	84	91	89
	1440	90	87	86	87	95	94

Stability study results for lots L107-03003 5O20A, L107-03009-5O and L107-03003 5O20A + L107-03009-5O 100 mg capsules showed stable assay and water content values over 26 weeks of storage at 40 °C and 75 % of relative humidity. As well, no related substances above the reporting threshold were found in the samples evaluated. Dissolution profiles of lot L107-03003-5O20A (enteric coated CR pellets) stored for 2 weeks at 40 °C/75% RH (closed cap), were slightly slower than that at time zero but remained unchanged on further storage up to 26 weeks. IR coated pellets (lot L107-03009-5O) showed a slower dissolution profile compared to uncoated pellets at time zero but as for CR coated pellets, there was no difference in the dissolution profiles between 2 and 26 weeks. SR (CR + IR) pellets dissolution profiles at 2, 4, 8, 12 and 26 weeks were super-imposable showing no significant difference in the rate and release of the drug after 6 months of storage at 40 °C/75% RH (as the worst-case scenario).

Stability study results for final formulations lots L107-03003 5O20A5O, L107-03017 and L107-03003 5O20A5O + L107-03017 100 mg capsules showed stable assay, related substances and dissolution profiles for the formulations after 4 weeks at 25 °C/60% RH and 40 °C/75% RH

and after 8 weeks at 40 °C/75% RH. 12 weeks time point stability samples stored at 25 °C/60% RH and 40 °C/75% RH were evaluated by assay composite and dissolutions profiles. Assay values remained stable and compared with previous time points at about 100%. Dissolutions profiles of samples stored under both storage conditions were comparable and similar or slightly faster when compared to previous time points. For enteric coated pellets, less than 1% was released in the acid stage, confirming the efficacy and stability of the enteric coat upon storage. It was found that more than 94% of the drug was released within 24 hours from sustained release 100 mg ecopipam-HCl pellets in capsule formulation. No degradation products were reported under all conditions. The results confirm stability after 3 months of storage at 40 °C/75% RH for both, enteric coated and uncoated ecopipam-HCl pellets.

Example 18: Human Pharmacokinetic Study of Ecopipam Dosage Form

Healthy volunteers were administered either ecopipam 100 mg immediate release tablets or 1, 2, or 3 capsules of a dosage form comprising ecopipam immediate release and controlled release components with a total ecopipam dose per capsule of 90 mg. Mean data from this study are provided in Table 47 (*see also* Figure 27). As expected, the dose adjusted AUC was lower for the IR/CR capsules than for the IR tablets, but a good dose response curve was obtained for the IR/CR capsules, and the shape of the pharmacokinetic profile fit the target of reduced C_{max} and sustained plasma levels over about 12 hours. For subjects receiving the IR tablets C_{12hr} averaged about 12% of C_{max}. In contrast C_{12hr} averaged 44%, 43%, and 45% of C_{max} for subjects receiving 90 mg, 180 mg, and 270 mg, respectively, in the form of the IR/CR dosage form described herein. Furthermore, the average values for T_{max} for the 3 groups given IR/CR capsules did not differ substantially from the average value of T_{max} for the group given the IR tablets.

Dose	100 mg	90 mg	180 mg	270 mg
Type	IR tablet	IR/CR capsule	IR/CR capsule	IR/CR capsule
AUC_{0-12h} (ng/mL × hr)	215	66	117	177
AUC_{0-24h} (ng/mL × hr)	292	107	201	308
AUC_{0-48h} (ng/mL × hr)	382	161	310	478
C_{max} (ng/mL)	78	9.5	20	28
T_{max} (hr)	1.3	1.4	1.3	1.4
C_{6hr} (ng/mL)	11.9	6.4	10.9	16.3
C_{12hr} (ng/mL)	6.7	3.3	6.7	10.6
C_{24hr} (ng/mL)	6.0	3.5	7.2	11.3
C_{12hr}/C_{max}	0.12	0.44	0.43	0.45

WHAT IS CLAIMED IS:

1. A pharmaceutical dosage form comprising:

an immediate release component comprising from about 20% to about 60% ecopipam free base or its pharmaceutically acceptable salt, by weight, based on the total weight of the immediate release component; and

a controlled release component comprising from about 30% to about 90% ecopipam free base or its pharmaceutically acceptable salt, by weight, based on the total weight of the controlled release component.

2. The pharmaceutical dosage form of claim 1, wherein the immediate release component comprises from about 12 mg to about 300 mg of ecopipam free base or its pharmaceutically acceptable salt, and the controlled release component comprises from about 30 mg to about 400 mg of ecopipam free base or its pharmaceutically acceptable salt.

3. The pharmaceutical dosage form of claim 1, wherein the immediate release component comprises about 30% ecopipam free base or its pharmaceutically acceptable salt, by weight, based on the total weight of the immediate release component; and the controlled release component comprises about 63.5% ecopipam free base or its pharmaceutically acceptable salt, by weight, based on a total weight of the controlled release component.

4. The pharmaceutical dosage form of claim 3, wherein the immediate release component comprises about 36 mg of ecopipam free base or its pharmaceutically acceptable salt, and the controlled release component comprises about 54 mg of ecopipam free base or its pharmaceutically acceptable salt.

5. The pharmaceutical dosage form of claim 1, wherein the immediate release component comprises from about 15% to about 85% of the total weight of the pharmaceutical dosage form, and the controlled release component comprises from about 15% to about 85% of the total weight of the pharmaceutical dosage form.

6. The pharmaceutical dosage form of claim 1, wherein the immediate release component comprises about 40% of the total weight of the pharmaceutical dosage form and the controlled release component comprises about 60% of the total weight of the pharmaceutical dosage form, or, wherein ecopipam or a pharmaceutically acceptable salt thereof comprises about 40% of the total weight of the IRC and about 60% of the weight of the CRC.

7. The pharmaceutical dosage form of claim 1, wherein the immediate release component comprises about 50% of the total weight of the pharmaceutical dosage form and the controlled release component comprises about 50% of the total weight of the pharmaceutical dosage form, or, wherein ecopipam or a pharmaceutically acceptable salt thereof comprises about 50% of the IRC and about 50% of the CRC.

8. The pharmaceutical dosage form of claim 1, wherein the dosage form comprises from about 80 mg to about 110 mg of ecopipam free base or its pharmaceutically acceptable salt.

9. The pharmaceutical dosage form of claim 8, wherein the dosage form comprises about 90 mg of ecopipam free base or its pharmaceutically acceptable salt.

10. The pharmaceutical dosage form of claim 1, wherein the immediate release component comprises from about 40% to about 80% of one or more excipients, by weight, based on the total weight of the immediate release component, and the controlled release component comprises from about 10% to about 70% of one or more excipients, by weight, based on a total weight of the controlled release component.

11. The pharmaceutical dosage form of claim 10, wherein the immediate release component comprises about 70% of one or more excipients, by weight, based on the total weight of the immediate release component, and the controlled release component comprises about 36.5% of one or more excipients, by weight, based on the total weight of the controlled release component.

12. The pharmaceutical dosage form of claim 10 or claim 11, wherein the one or more excipients are one or more of: microcrystalline cellulose, hydroxyalkyl alkylcellulose, hydroxyalkyl cellulose, a glycol, sodium lauryl sulfate, a starch or a derivative thereof, a cellulose ether, a cellulose ester, a copolymer of esters of at least one of acrylic acid and methacrylic acid, a sugar or sugar alcohol, an alginate, gelatin, a food coloring, polyvinylalcohol, polyvinylpyrrolidone, and stearic acid and salts thereof.

13. The pharmaceutical dosage form of claim 1, wherein the pharmaceutically acceptable salt of ecopipam is hydrochloride.

14. The pharmaceutical dosage form of any one of claims 1-13, wherein the immediate release component and/or the controlled release component comprises beads.

15. The pharmaceutical dosage form of claim 14, wherein the dosage form further comprises a capsule.

16. The pharmaceutical dosage form of any one of claims 1-15 which, when administered to a human subject, provides a maximum plasma concentration (Cmax) of ecopipam within about 2.5 hours of administration and a plasma concentration of ecopipam of about 35% to about 50% of Cmax within about 12 hours after administration.

17. A method of treating a central nervous system disorder in a patient, the method comprising administering to the patient an effective amount of a pharmaceutical dosage form of any of claims 1-16.

18. The method of claim 17, wherein the central nervous system disorder is Lesch-Nyhan disease, pathological gambling, Tourette's syndrome, or Parkinson's disease.

19. A method of treating a central nervous system disorder in a patient, the method comprising administering to the patient an effective amount of the pharmaceutical dosage form of claim 14.

20. The method of claim 19, wherein the central nervous system disorder is Lesch-Nyhan disease, pathological gambling, Tourette's syndrome, or Parkinson's disease.

21. A matrix tablet comprising about 40% to about 90%, by weight, of ecopipam free base or a pharmaceutically acceptable salt thereof, and a pH-dependent or pH-independent polymer.

22. The matrix tablet of claim 21, wherein the tablet comprises a pH-dependent polymer.

23. The matrix tablet of claim 22, wherein the pH-dependent polymer is a cross-linked acrylic acid homopolymer, cellulose acetate phthalate (CAP), hydroxypropylmethyl cellulose phthalate (HPMCP), methacrylic acid, a methacrylic ester, or polyvinyl acetate phthalate.

24. The matrix tablet of claim 21, wherein the tablet comprises a pH-independent polymer.

25. The matrix tablet of claim 24, wherein the pH-independent polymer is hydroxypropylmethyl cellulose (HPMC), hydroxypropyl cellulose, or polyethylene glycol (PEG).

26. The matrix tablet of claim 21, wherein the tablet comprises about 5% to about 60% of the polymer and, optionally, a further excipient.

27. The matrix tablet of claim 26, wherein the polymer or the further excipient is microcrystalline cellulose, hydroxyalkyl alkylcellulose, sodium chloride, hydroxyalkyl cellulose, a glycol, sodium lauryl sulfate, a starch or a derivative thereof, a cellulose ether, a cellulose ester, a copolymer of an ester of at least one of acrylic acid and at least one methacrylic acid, a sugar or sugar alcohol, an alginate, gelatin, a food coloring, polyvinylalcohol, polyvinylpyrrolidone, or stearic acid or a salt thereof.

28. A pharmaceutical dosage form comprising the matrix tablet of claim 21 and an immediate release component.

29. The pharmaceutical dosage form of claim 28, wherein the matrix tablet is encapsulated by the immediate release component or is formulated as a layer adjacent to a layer of the immediate release component.

30. The pharmaceutical dosage form of any one of claims 21-29 which, when administered to a human subject, provides a maximum plasma concentration (Cmax) of ecopipam within about 2.5 hours of administration and a plasma concentration of ecopipam of about 35% to about 50% of Cmax within about 12 hours after administration.

31. A method of treating a central nervous system disorder in a patient, the method comprising administering to the patient an effective amount of the matrix tablet of any of claims 21-27 or the pharmaceutical dosage form of claim 28 or claim 29.

32. The method of claim 31, wherein the central nervous system disorder is Lesch-Nyhan disease, pathological gambling, Tourette's syndrome, or Parkinson's disease.

33. A pharmaceutical dosage form comprising:

(a) an immediate release component comprising from about 25% to about 50% ecopipam free base or a pharmaceutically acceptable salt thereof, by weight, based on the total weight of the immediate release component; and

(b) a controlled release component comprising from about 65% to about 95% ecopipam free base or a pharmaceutically acceptable salt thereof, by weight, based on the total weight of the controlled release component;

wherein the dosage form is formulated as a tablet.

34. The pharmaceutical dosage form of claim 33, wherein the immediate release component comprises from about 25% to about 35%, by weight, of the total weight of the tablet, and the controlled release component comprises from about 37% to about 47%, by weight, of the total weight of the tablet.

35. The pharmaceutical dosage form of claim 33, wherein the tablet comprises from about 12% to about 42% of one or more excipients, by weight, based on a total weight of the tablet.

36. The pharmaceutical dosage form of claim 35, wherein the one or more excipients are microcrystalline cellulose, hydroxyalkyl alkylcellulose, hydroxyalkyl cellulose, glycols, sodium lauryl sulfate, starch and derivatives thereof, cellulose ethers, sodium chloride, cellulose esters, copolymers of esters of at least one of acrylic acid and methacrylic acid, sugars and sugar alcohols, alginates, gelatin, food coloring, polyvinylalcohol, polyvinylpyrrolidone, or stearic acid and salts thereof.

37. The pharmaceutical dosage form of any one of claims 33-36 which, when administered to a human subject, provides a maximum plasma concentration (Cmax) of ecopipam within about 2.5 hours of administration and a plasma concentration of ecopipam of about 35% to about 50% of Cmax within about 12 hours after administration.

38. A method of treating a central nervous system disorder in a patient, the method comprising administering to the patient an effective amount of the pharmaceutical dosage form of any of claims 33-37.

39. The method of claim 38, wherein the central nervous system disorder is Lesch-Nyhan disease, pathological gambling, Tourette's syndrome, or Parkinson's disease.

40. A pharmaceutical dosage form comprising a controlled release component coated with a layer of an immediate release component wherein:

(a) the immediate release component comprises from about 5% to about 50% of ecopipam free base or a pharmaceutically acceptable salt thereof, by weight, based on a total weight of the pellet;

(b) the controlled release component comprises from about 40% to about 80% of ecopipam free base or a pharmaceutically acceptable salt thereof, by weight, based on a total weight of the pellet; and

(c) the dosage form is formulated as a pellet.

41. The pharmaceutical dosage form of claim 40, wherein the immediate release component comprises about 26%, by weight, of the total weight of the pellet, and the immediate release component comprises about 61%, by weight, of the total weight of the pellet.

42. The pharmaceutical dosage form of claim 41, wherein the pellet comprises from about 10% to about 50%, by weight, of one or more excipients.

43. The pharmaceutical dosage form of claim 42, wherein the one or more excipients are microcrystalline cellulose, hydroxyalkyl alkylcellulose, hydroxyalkyl cellulose, glycols, sodium lauryl sulfate, starch and derivatives thereof, cellulose ethers, sodium chloride, cellulose esters, copolymers of esters of at least one of acrylic acid and methacrylic acid, sugars and sugar alcohols, alginates, gelatin, food coloring, polyvinylalcohol, polyvinylpyrrolidone, or stearic acid and salts thereof.

44. The pharmaceutical dosage form of any one of claims 40-43 which, when administered to a human subject, provides a maximum plasma concentration (Cmax) of ecopipam within about 2.5 hours of administration and a plasma concentration of ecopipam of about 35% to about 50% of Cmax within about 12 hours after administration.

45. A method of treating a central nervous system disorder in a patient, the method comprising administering to the patient an effective amount of the pharmaceutical dosage form of any of claims 40-44.

46. The method of claim 45, wherein the central nervous system disorder is Lesch-Nyhan disease, pathological gambling, Tourette's syndrome, or Parkinson's disease.

47. An osmotic pump composition comprising, by weight, based on the total weight of the osmotic pump composition:

(a) from about 20% to about 50% of ecopipam free base or a pharmaceutically acceptable salt thereof;

(b) from about 35% to about 65% of sodium chloride or other osmotic agent; and

(c) up to about 20% of one or more excipients.

48. The osmotic pump composition of claim 47, wherein the one or more excipients are microcrystalline cellulose, hydroxyalkyl alkylcellulose, talc, polyethylene glycol, sodium chloride, hydroxyalkyl cellulose, starch and derivatives thereof, cellulose ethers, cellulose esters, copolymers of esters of at least one of acrylic acid and methacrylic acid, sugars and sugar alcohols, alginates, gelatin, food coloring, polyvinylalcohol, polyvinylpyrrolidone, or stearic acid and salts thereof.

49. The osmotic pump composition of claims 47-48 which, when administered to a human subject, provides a maximum plasma concentration (Cmax) of ecopipam within about 2.5 hours of administration and a plasma concentration of ecopipam of about 35% to about 50% of Cmax within about 12 hours after administration.

50. A process for the preparation of the pharmaceutical dosage form of any of claims 1-13, comprising the steps:

(a) blending ecopipam free base or a pharmaceutically acceptable salt thereof, with one or more excipients to generate a first mixture;

(b) adding water to the first mixture and mixing in a planetary mixer to form a paste;

(c) feeding the paste into an extruder to produce a first extrudate;

(d) spheronizing the first extrudate to produce spheronized beads; and

(e) drying the spheronized beads in a fluid bed dryer to obtain an immediate release component;

(f) blending ecopipam free base or a pharmaceutically acceptable salt thereof, with one or more excipients to generate a second mixture;

(g) adding water to the second mixture and mixing in a planetary mixer to form a second paste;

(h) feeding the second paste into an extruder to generate a second extrudate;

(i) spheronizing the second extrudate to produce a second population of spheronized beads;

(j) drying the second population of spheronized beads in a fluid bed dryer to generate dried, spheronized bead;

(k) applying a clear coating of a mixture of hydroxypropyl methylcellulose and hydroxypropyl cellulose to the dried, spheronized beads to generate coated spheronized beads;

(l) applying an enteric coating to the coated spheronized beads; and

(m) applying a second clear coating of a mixture of hydroxypropyl methylcellulose and hydroxypropyl cellulose to the spheronized beads from step l) to obtain the controlled release component;

(n) blending the spheronized beads from step (e) and step (m); and

(o) filling the spheronized beads of step (n) into capsules.

Figure 1

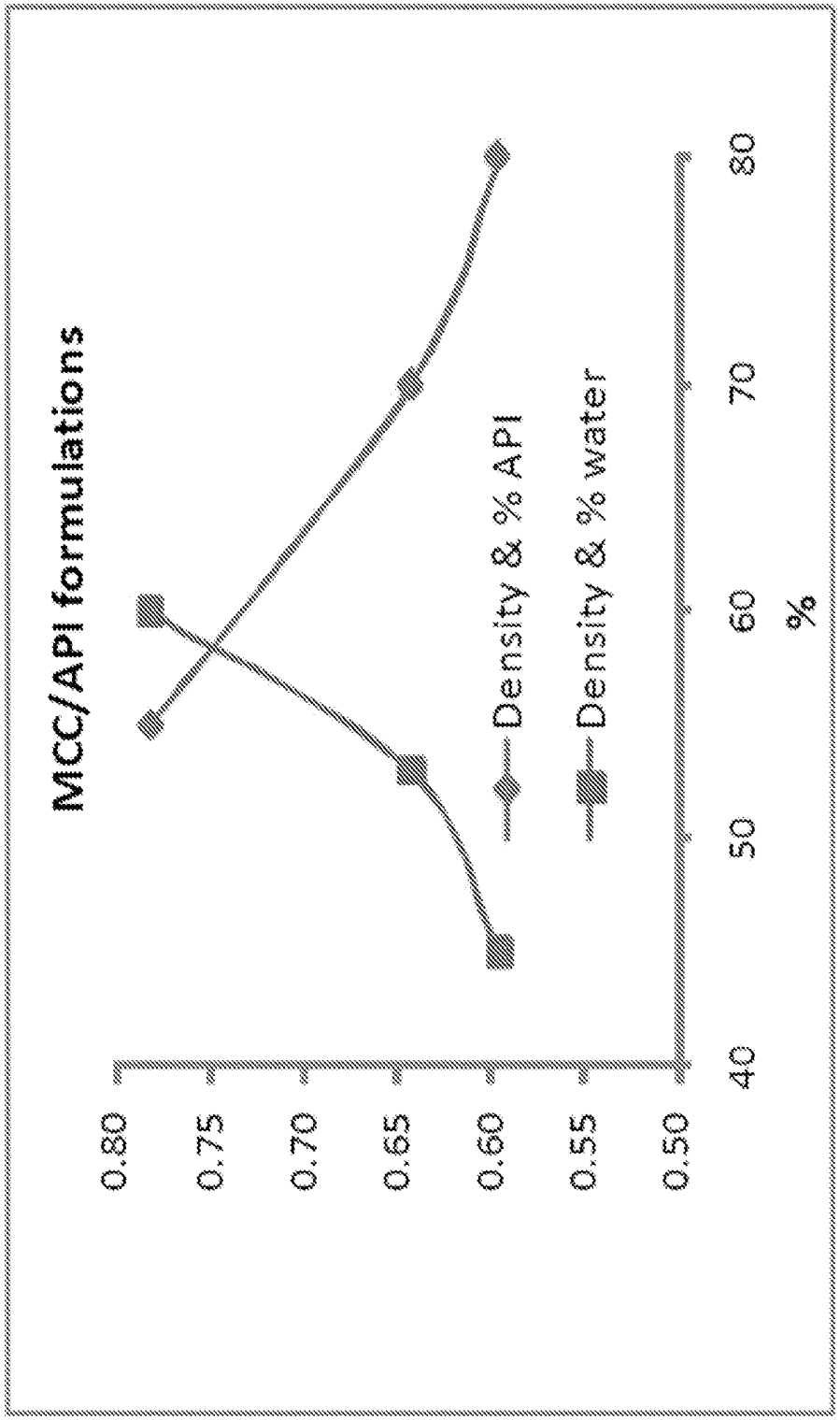

MCC/API formulations
0.80
0.75
0.70
0.65
0.60
0.55
0.50
40
50
60
70
80
%
Density & % API
Density & % water

Figure 2

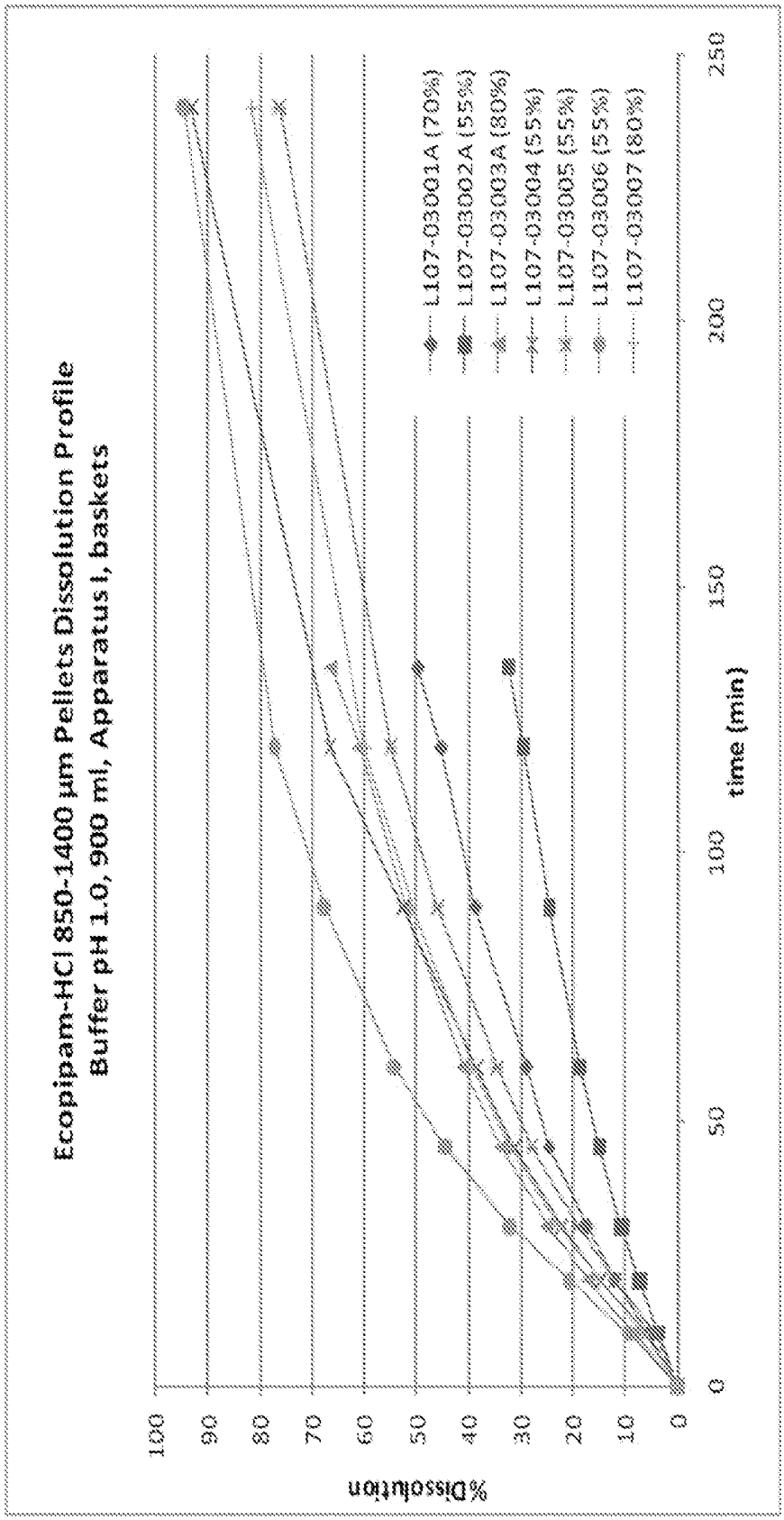

Ecopipam-HCl 850-1400 µm Pellets Dissolution Profile
Buffer pH 1.0, 900 ml, Apparatus I, baskets
% Dissolution
100
90
80
70
60
50
40
30
20
10
0
0
50
100
150
200
250
time (min)
L107-03001A (70%)
L107-03002A (55%)
L107-03003A (80%)
L107-03004 (55%)
L107-03005 (55%)
L107-03006 (55%)
L107-03007 (80%)

Figure 3

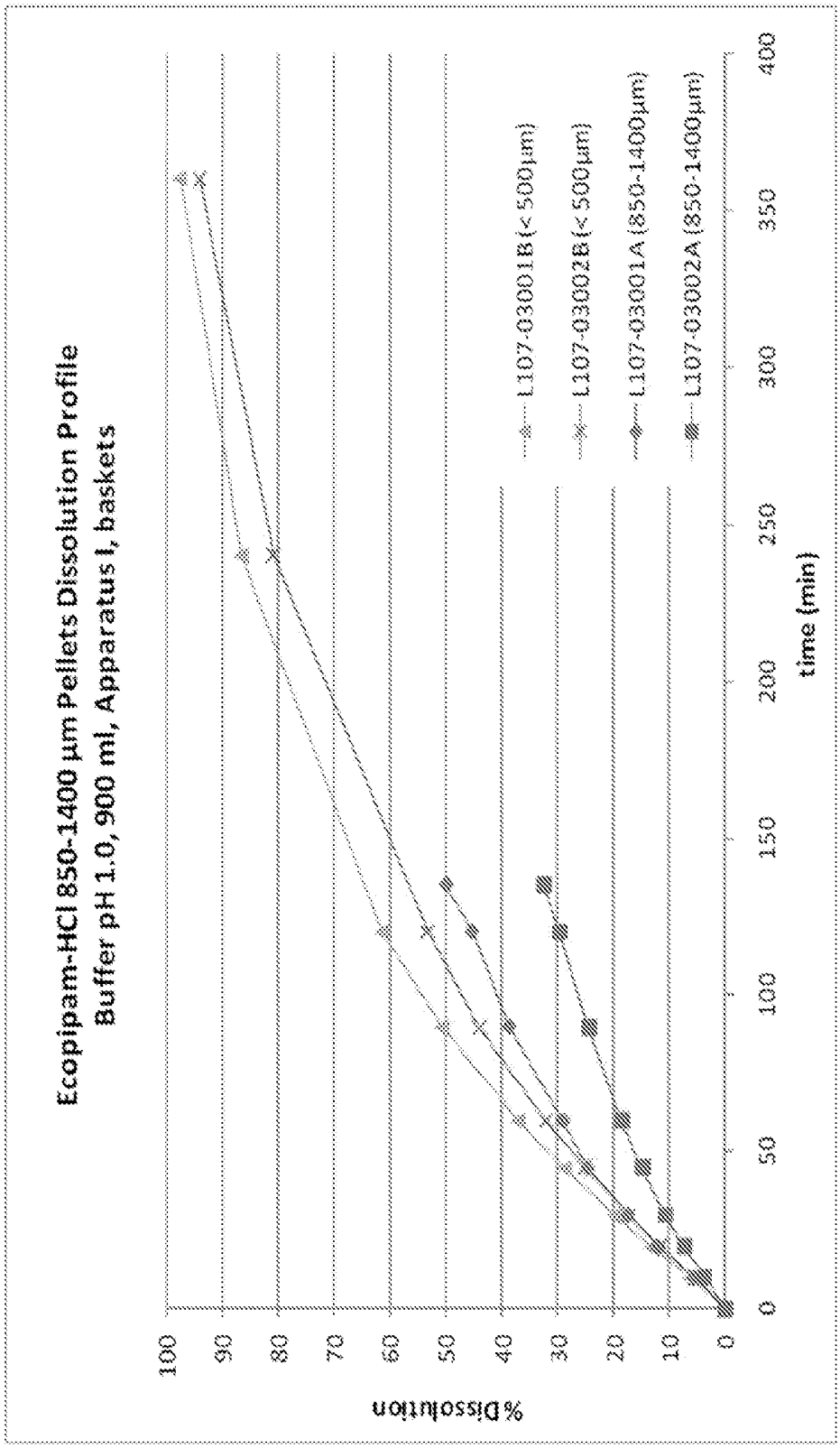

Ecopipam-HCl 850-1400 µm Pellets Dissolution Profile
Buffer pH 1.0, 900 ml, Apparatus I, baskets
% Dissolution
100
90
80
70
60
50
40
30
20
10
0
0
50
100
150
200
250
300
350
400
time (min)
L107-03001B (< 500µm)
L107-03002B (< 500µm)
L107-03001A (850-1400µm)
L107-03002A (850-1400µm)

Figure 4

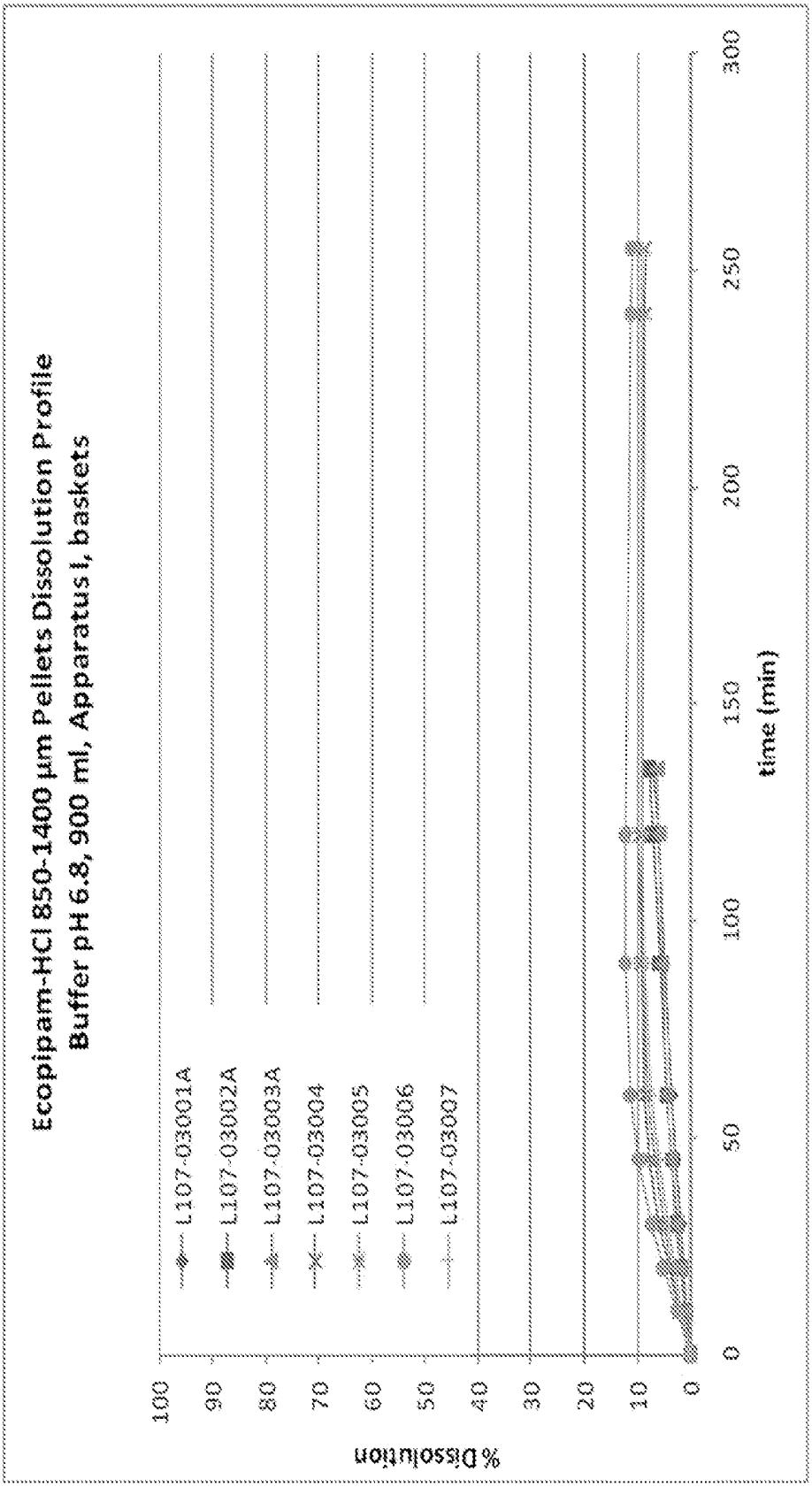

Ecopipam-HCl 850-1400 µm Pellets Dissolution Profile
Buffer pH 6.8, 900 ml, Apparatus I, baskets
L107-03001A
L107-03002A
L107-03003A
L107-03004
L107-03005
L107-03006
L107-03007
% Dissolution
100
90
80
70
60
50
40
30
20
10
0
0
50
100
150
200
250
300
time (min)

Figure 5

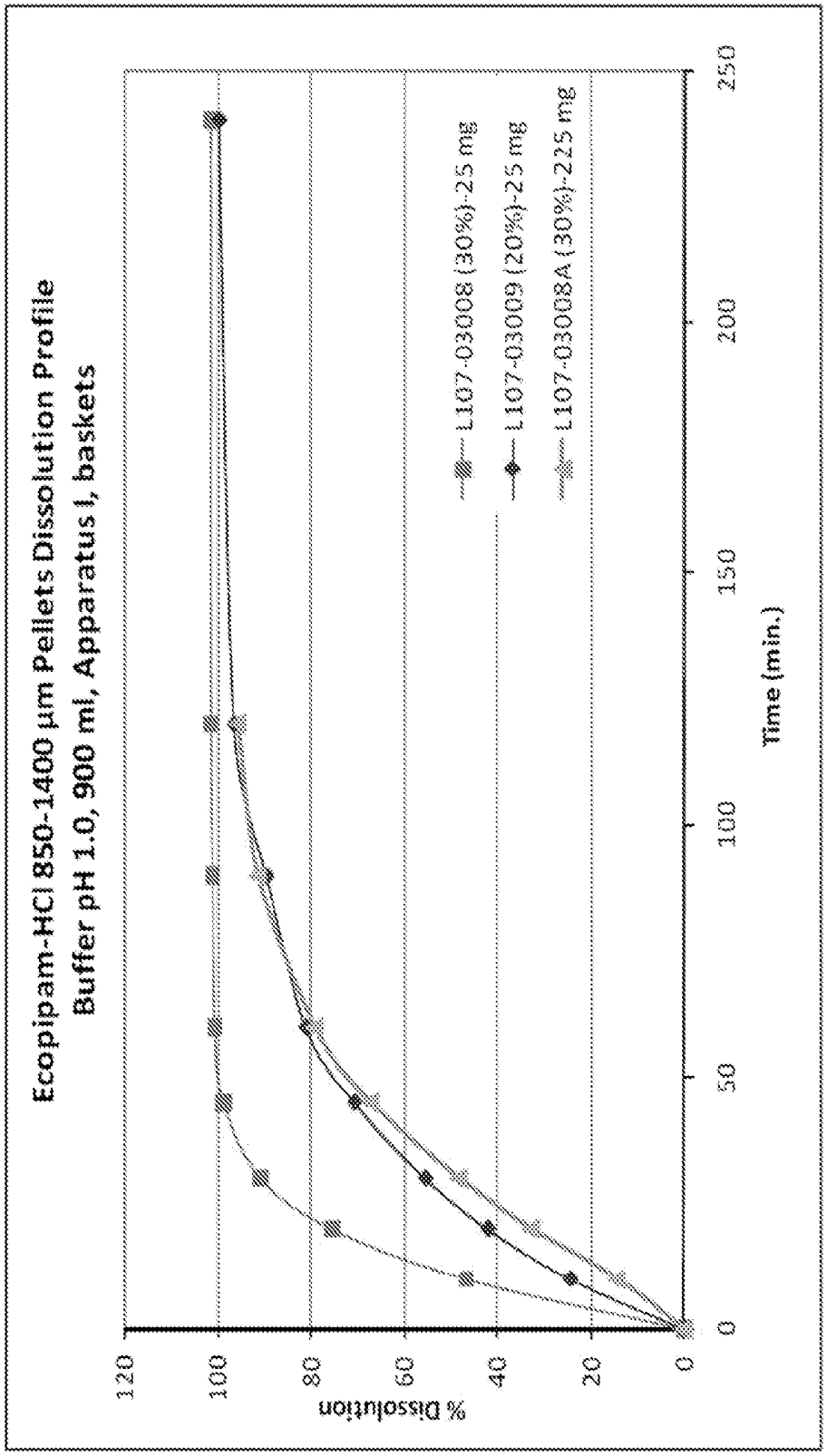

Ecopipam-HCl 850-1400 µm Pellets Dissolution Profile
Buffer pH 1.0, 900 ml, Apparatus I, baskets
% Dissolution
120
100
80
60
40
20
0
0
50
100
150
200
250
Time (min.)
L107-03008 (30%)-25 mg
L107-03009 (20%)-25 mg
L107-03008A (30%)-225 mg

Figure 6

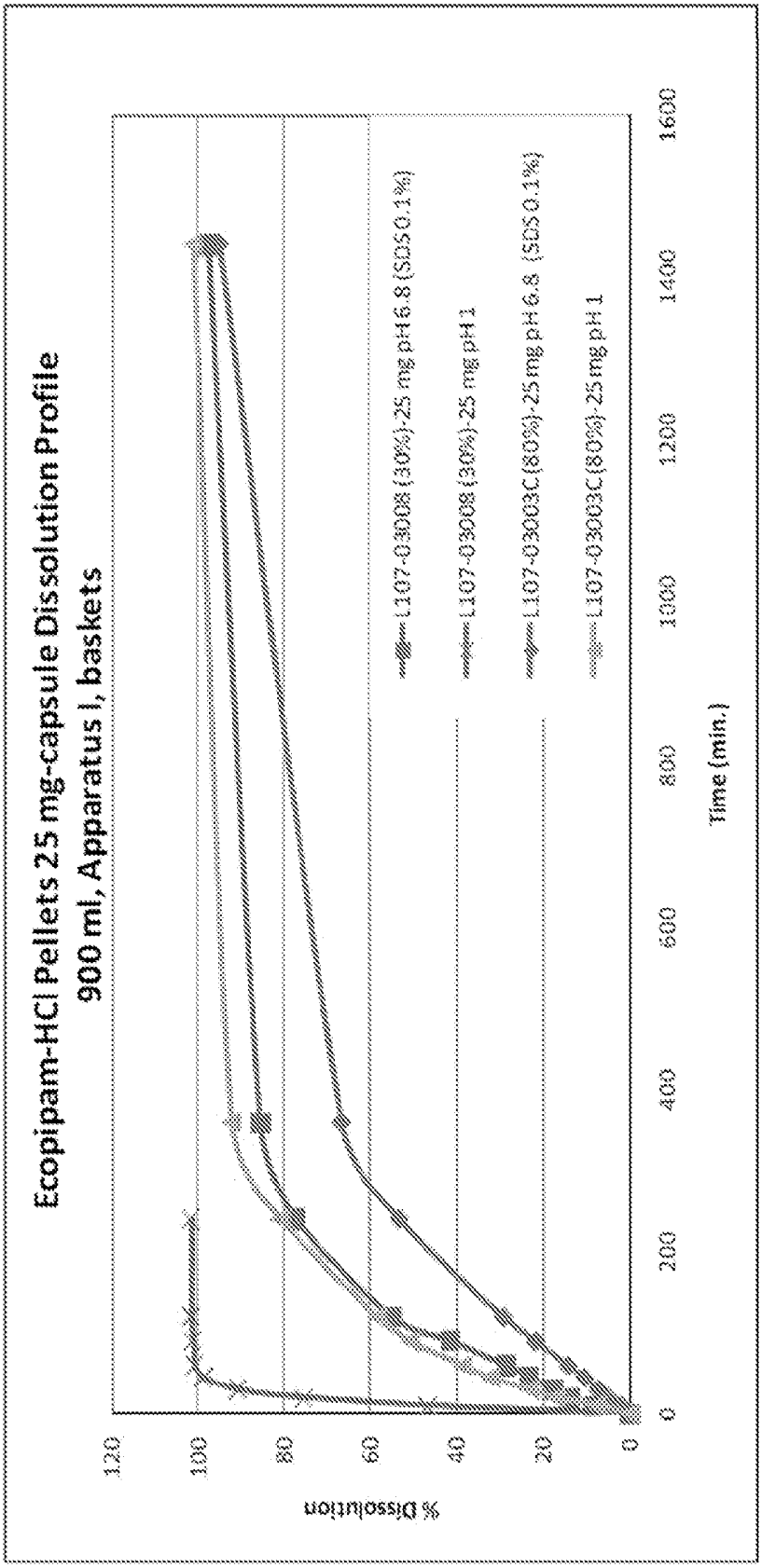

Ecopipam-HCl Pellets 25 mg-capsule Dissolution Profile
900 ml, Apparatus I, baskets
% Dissolution
120
100
80
60
40
20
0
0
200
400
600
800
1000
1200
1400
1600
Time (min.)
L107-03008 (30%)-25 mg pH 6.8 (SDS 0.1%)
L107-03008 (30%)-25 mg pH 1
L107-03003C (80%)-25 mg pH 6.8 (SDS 0.1%)
L107-03003C (80%)-25 mg pH 1

Figure 7

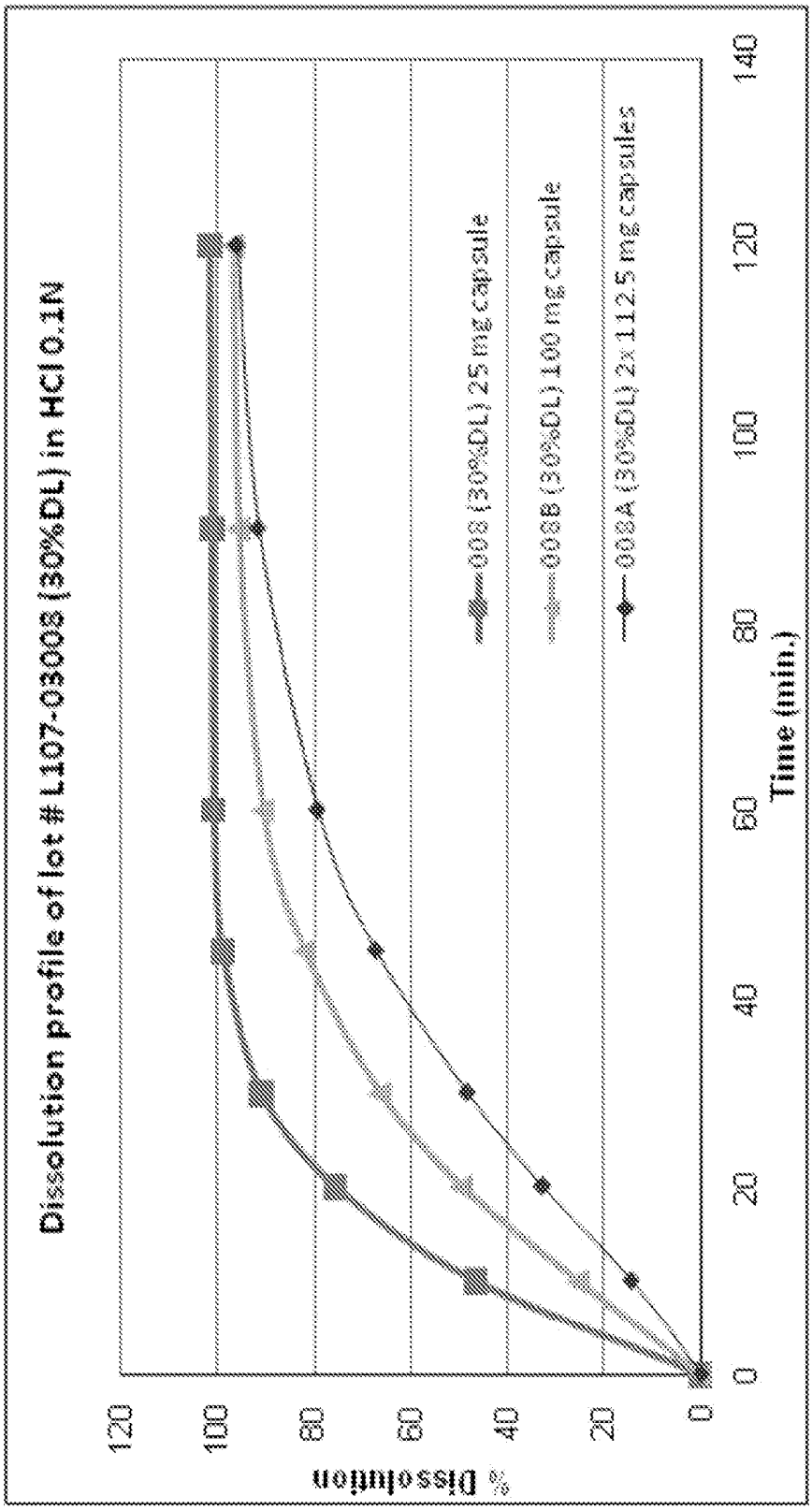

Dissolution profile of lot # L107-03008 (30%DL) in HCl 0.1N
% Dissolution
120
100
80
60
40
20
0
0
20
40
60
80
100
120
140
Time (min.)
008 (30%DL) 25 mg capsule
008B (30%DL) 100 mg capsule
008A (30%DL) 2x 112.5 mg capsules

Figure 8

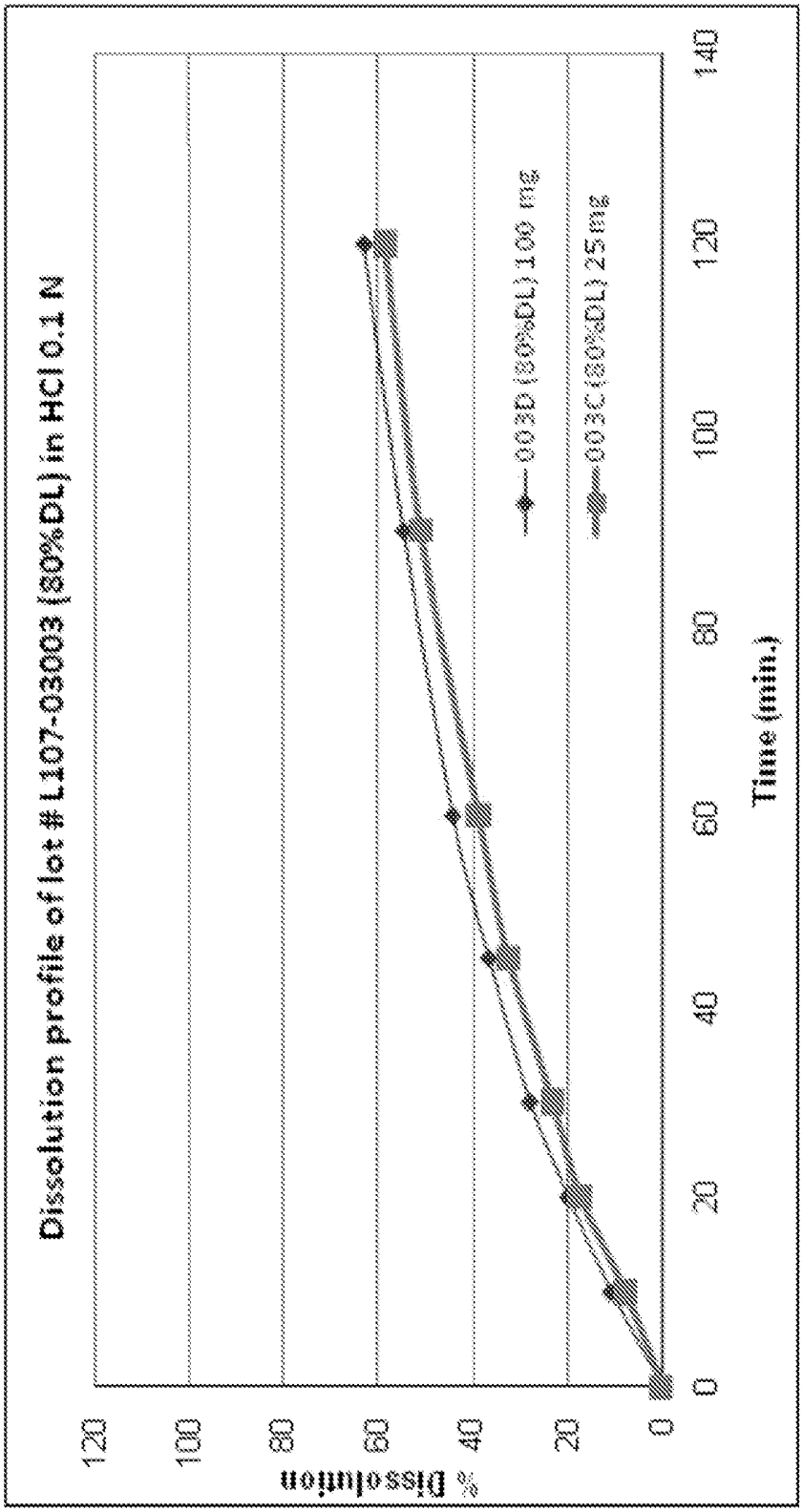

Dissolution profile of lot # L107-03003 (80%DL) in HCl 0.1 N
% Dissolution
120
100
80
60
40
20
0
0
20
40
60
80
100
120
140
Time (min.)
003D (80%DL) 100 mg
003C (80%DL) 25 mg

Figure 9

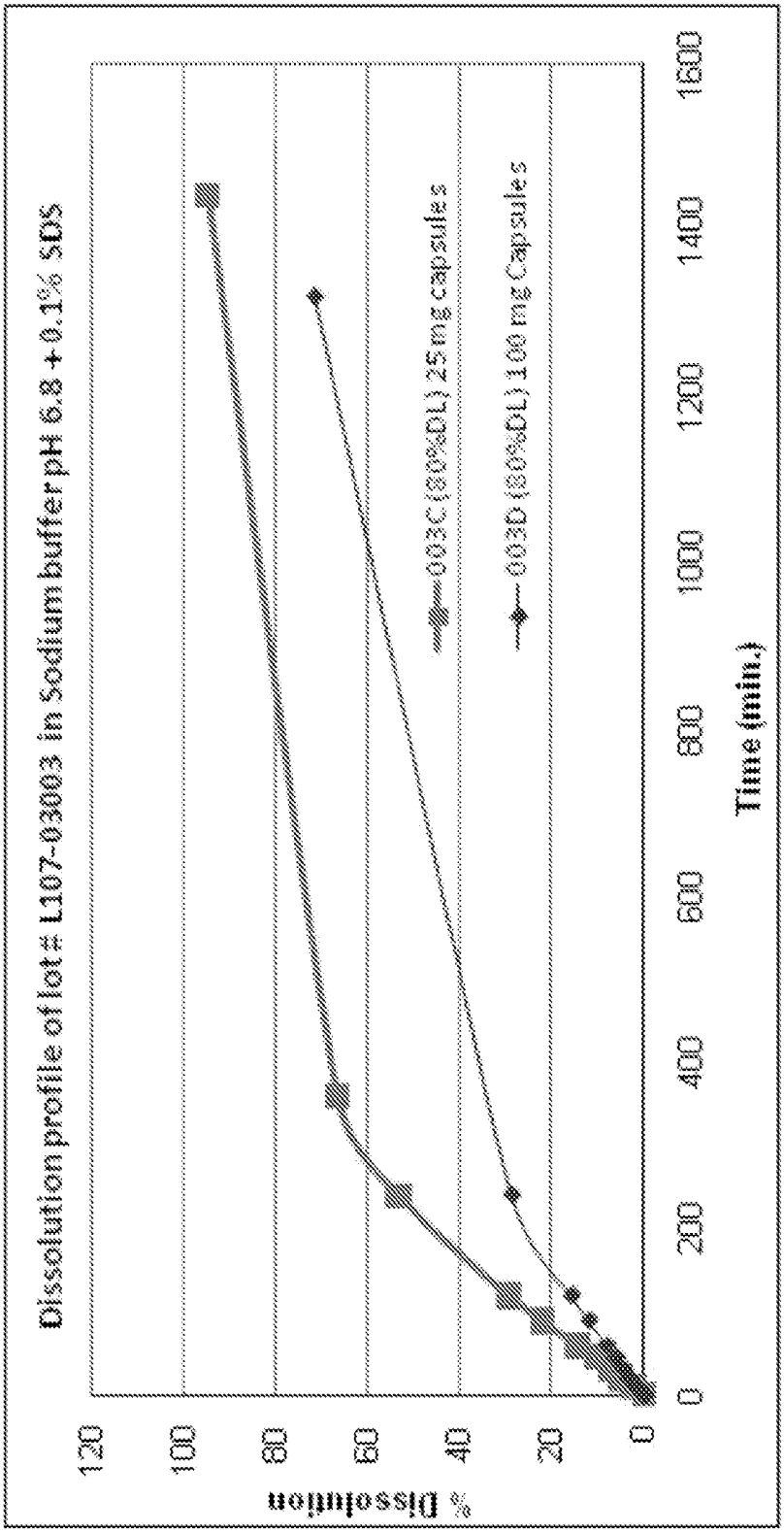

Dissolution profile of lot # L107-03003 in Sodium buffer pH 6.8 + 0.1% SDS
% Dissolution
120
100
80
60
40
20
0
0
200
400
600
800
1000
1200
1400
1600
Time (min.)
003C (80%DL) 25 mg capsules
003D (80%DL) 100 mg Capsules

Figure 10

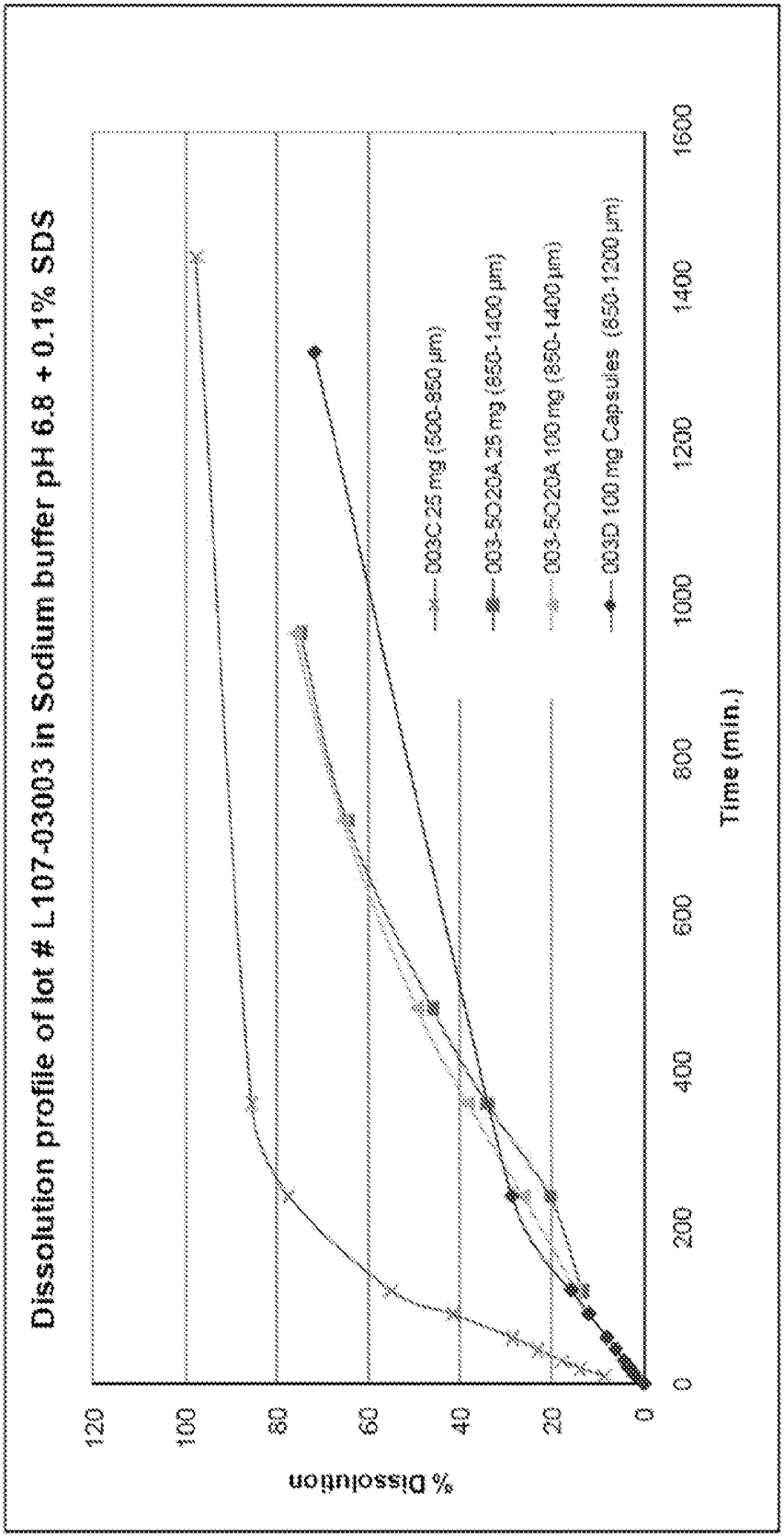

Dissolution profile of lot # L107-03003 in Sodium buffer pH 6.8 + 0.1% SDS
% Dissolution
120
100
80
60
40
20
0
0
200
400
600
800
1000
1200
1400
1600
Time (min.)
003C 25 mg (500-850 µm)
003-5O20A 25 mg (850-1400 µm)
003-5O20A 100 mg (850-1400 µm)
003D 100 mg Capsules (850-1200 µm)

Figure 11

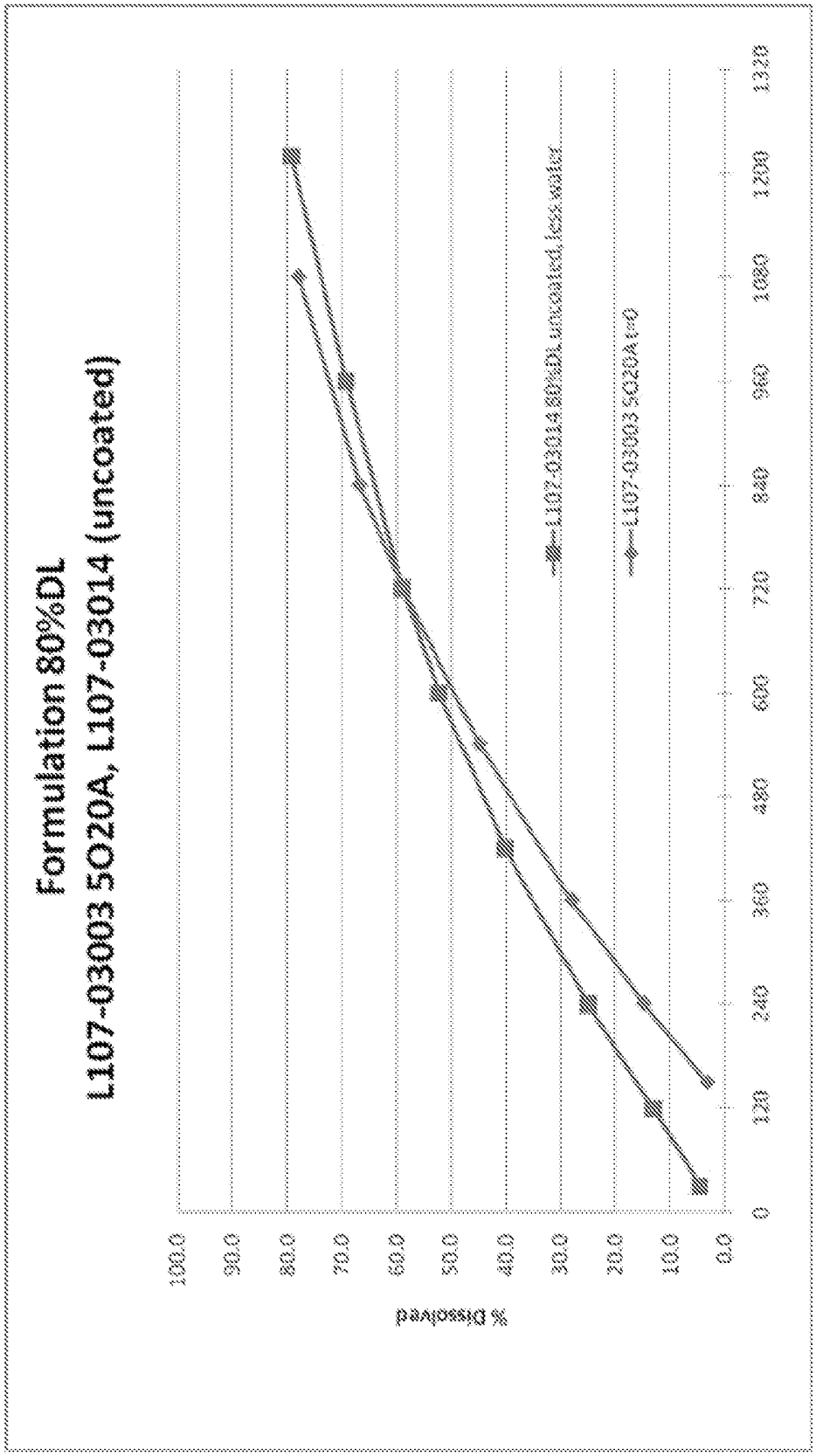

Formulation 80%DL
L107-03003 5O20A, L107-03014 (uncoated)
% Dissolved
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0
120
240
360
480
600
720
840
960
1080
1200
1320
L107-03014 80%DL uncoated, less water
L107-03003 5O20A t=0

Figure 12

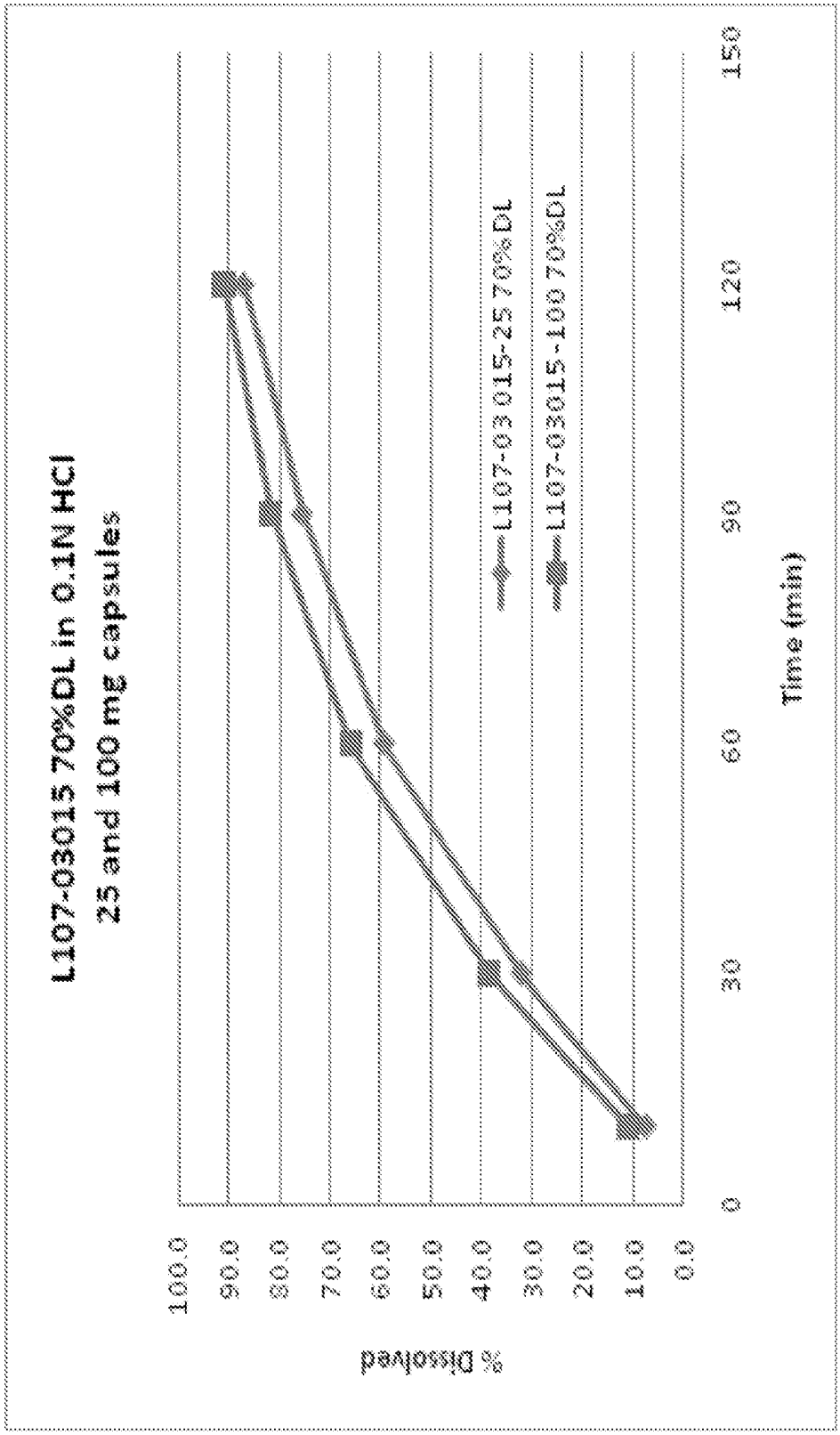

L107-03015 70%DL in 0.1N HCl
25 and 100 mg capsules
% Dissolved
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0
30
60
90
120
150
Time (min)
L107-03015-25 70%DL
L107-03015-100 70%DL

Figure 13

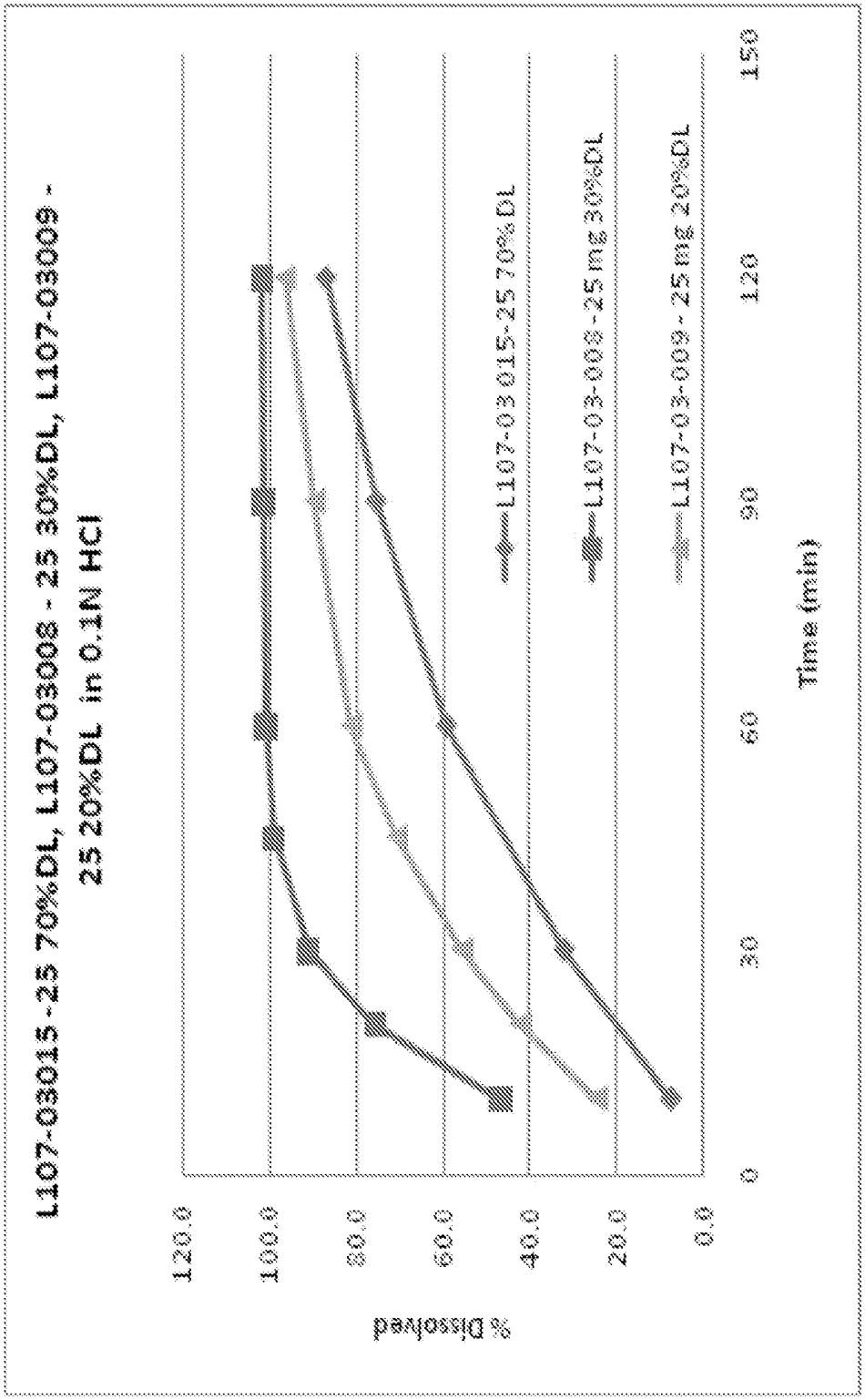

L107-03015 -25 70%DL, L107-03008 - 25 30%DL, L107-03009 - 25 20%DL in 0.1N HCl
% Dissolved
120.0
100.0
80.0
60.0
40.0
20.0
0.0
0
30
60
90
120
150
Time (min)
L107-03015-25 70%DL
L107-03-008 - 25 mg 30%DL
L107-03-009 - 25 mg 20%DL

Figure 14

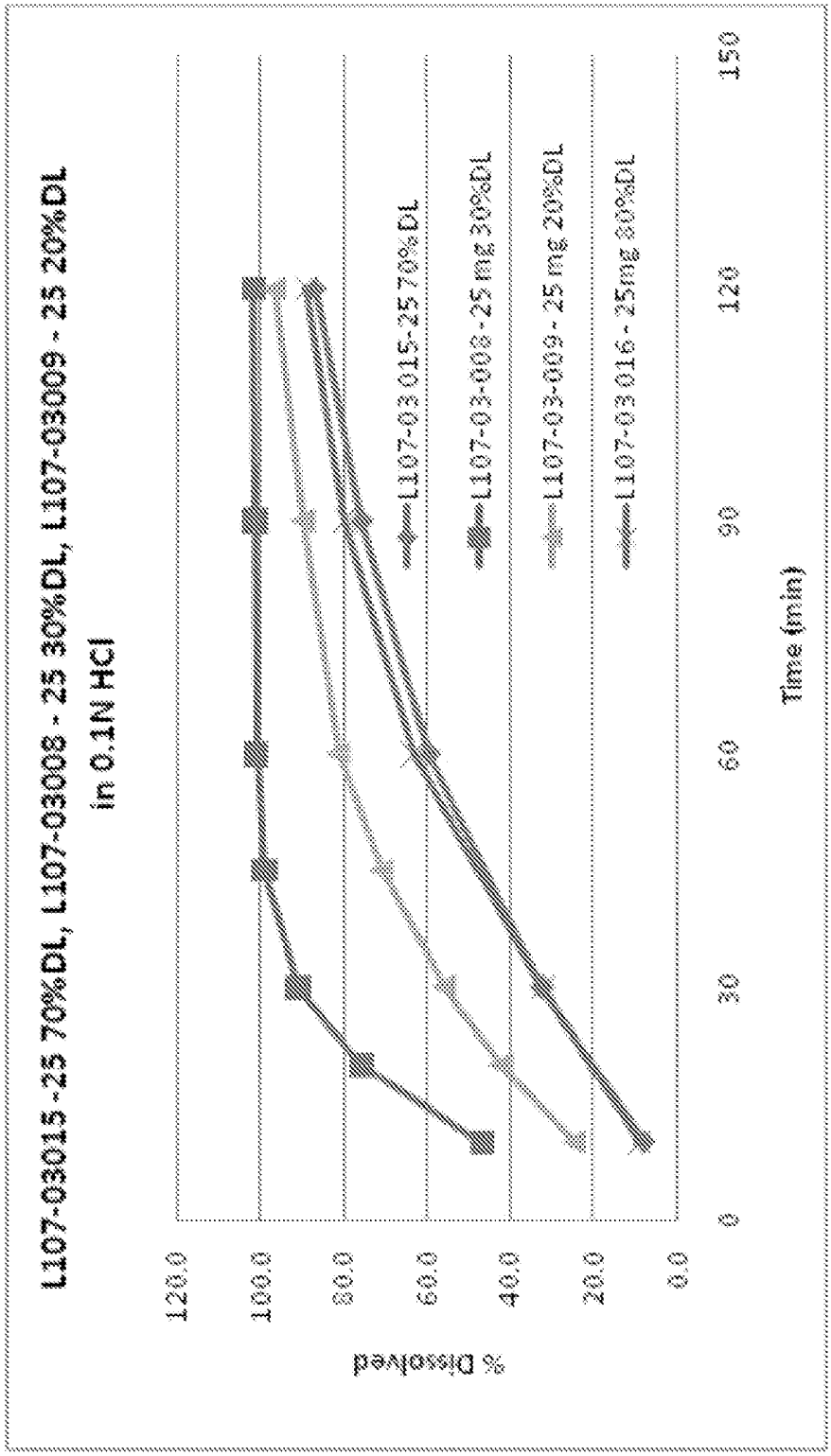

L107-03015 - 25 70%DL, L107-03008 - 25 30%DL, L107-03009 - 25 20%DL
in 0.1N HCl
% Dissolved
120.0
100.0
80.0
60.0
40.0
20.0
0.0
0
30
60
90
120
150
Time (min)
L107-03 015-25 70%DL
L107-03-008 - 25 mg 30%DL
L107-03-009 - 25 mg 20%DL
L107-03 016 - 25mg 80%DL

Figure 15

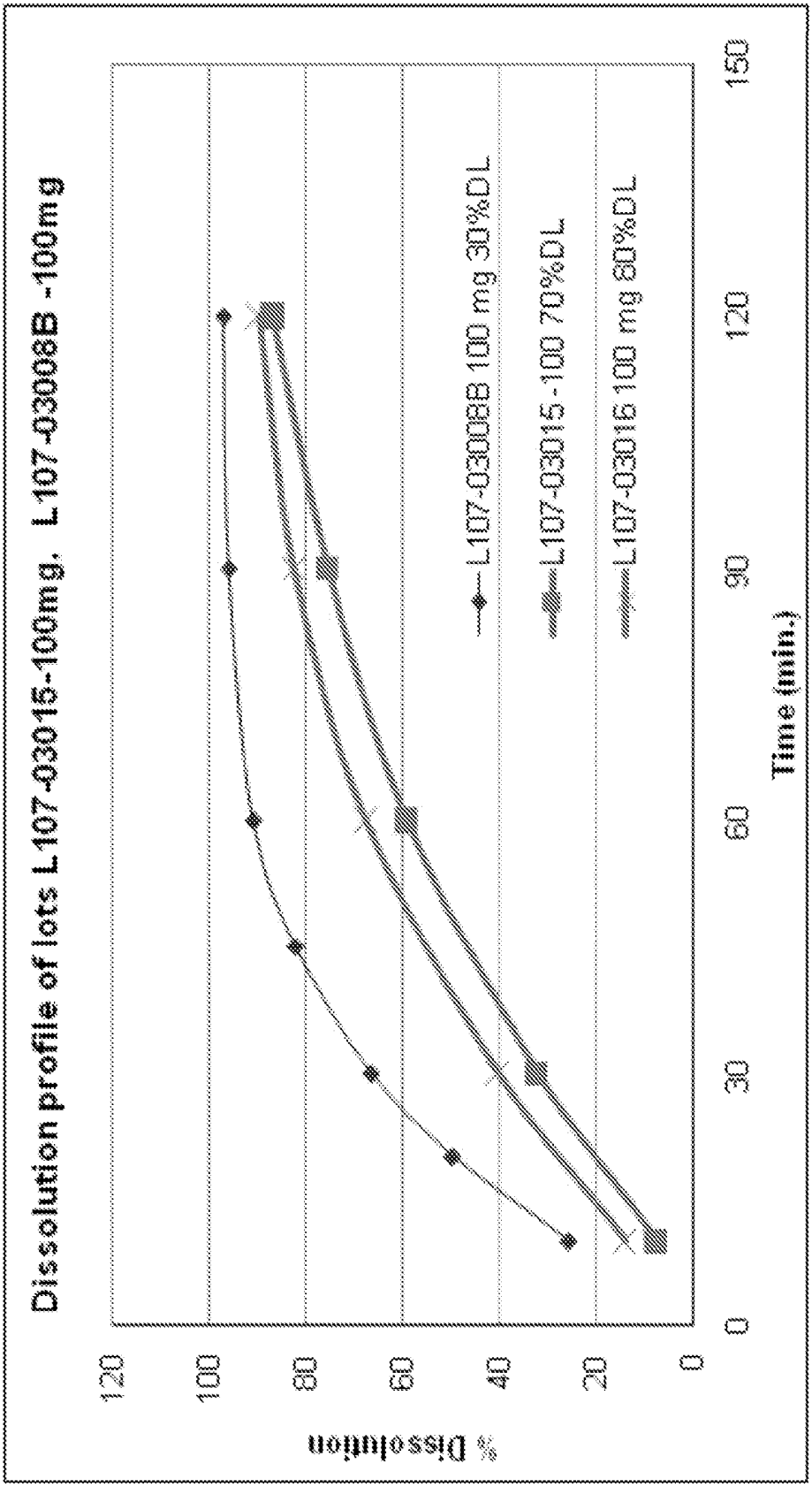

Dissolution profile of lots L107-03015-100mg, L107-03008B -100mg
% Dissolution
120
100
80
60
40
20
0
0
30
60
90
120
150
Time (min.)
L107-03008B 100 mg 30%DL
L107-03015-100 70%DL
L107-03016 100 mg 80%DL

Figure 16

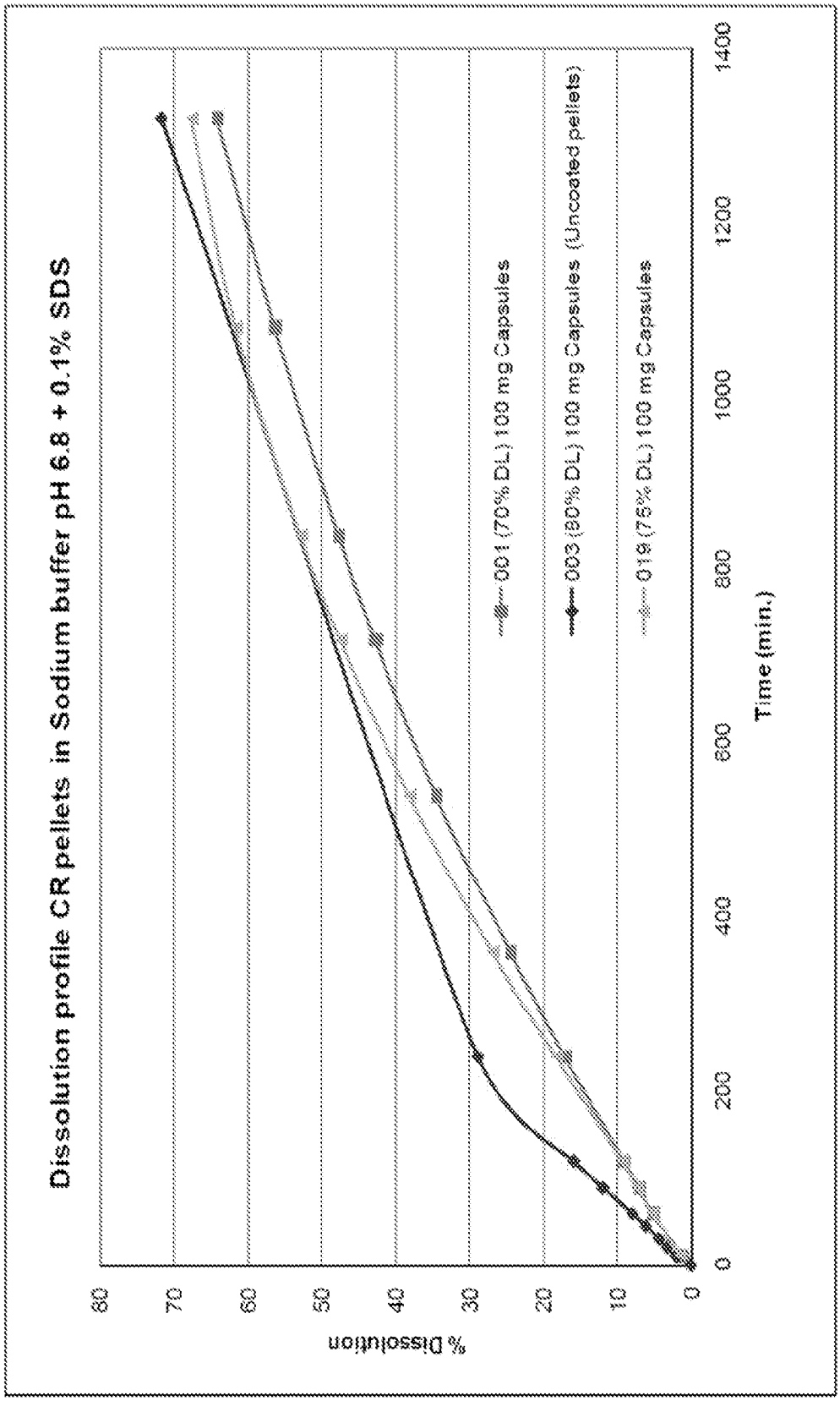

Dissolution profile CR pellets in Sodium buffer pH 6.8 + 0.1% SDS
% Dissolution
0
10
20
30
40
50
60
70
80
0
200
400
600
800
1000
1200
1400
Time (min.)
001 (70% DL) 100 mg Capsules
003 (80% DL) 100 mg Capsules (Uncoated pellets)
019 (75% DL) 100 mg Capsules

Figure 17

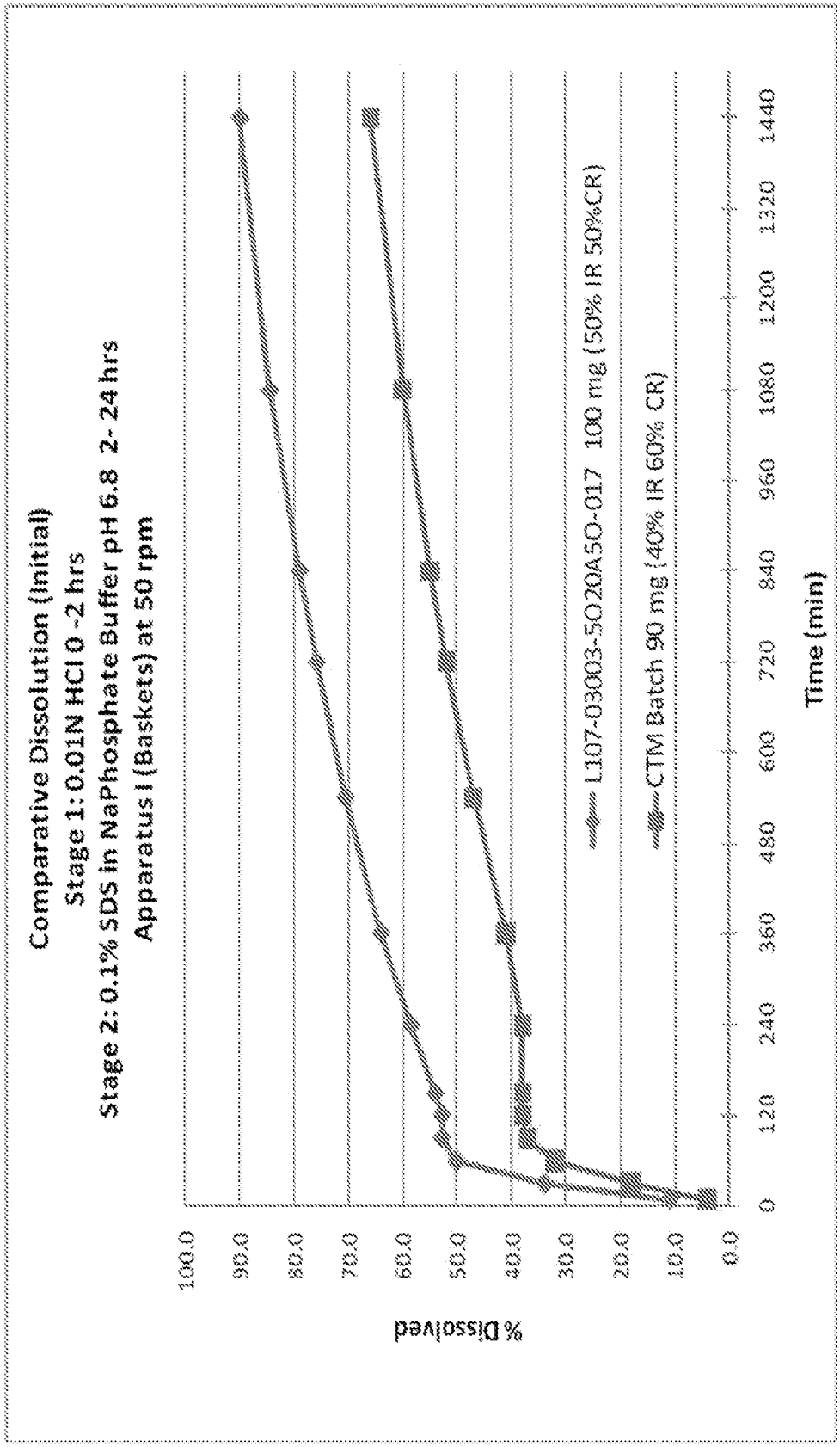

Comparative Dissolution (Initial)
Stage 1: 0.01N HCl 0 -2 hrs
Stage 2: 0.1% SDS in NaPhosphate Buffer pH 6.8 2- 24 hrs
Apparatus I (Baskets) at 50 rpm
% Dissolved
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
0
120
240
360
480
600
720
840
960
1080
1200
1320
1440
Time (min)
L107-03003-5O20A5O-017 100 mg (50% IR 50%CR)
CTM Batch 90 mg (40% IR 60% CR)

Figure 18

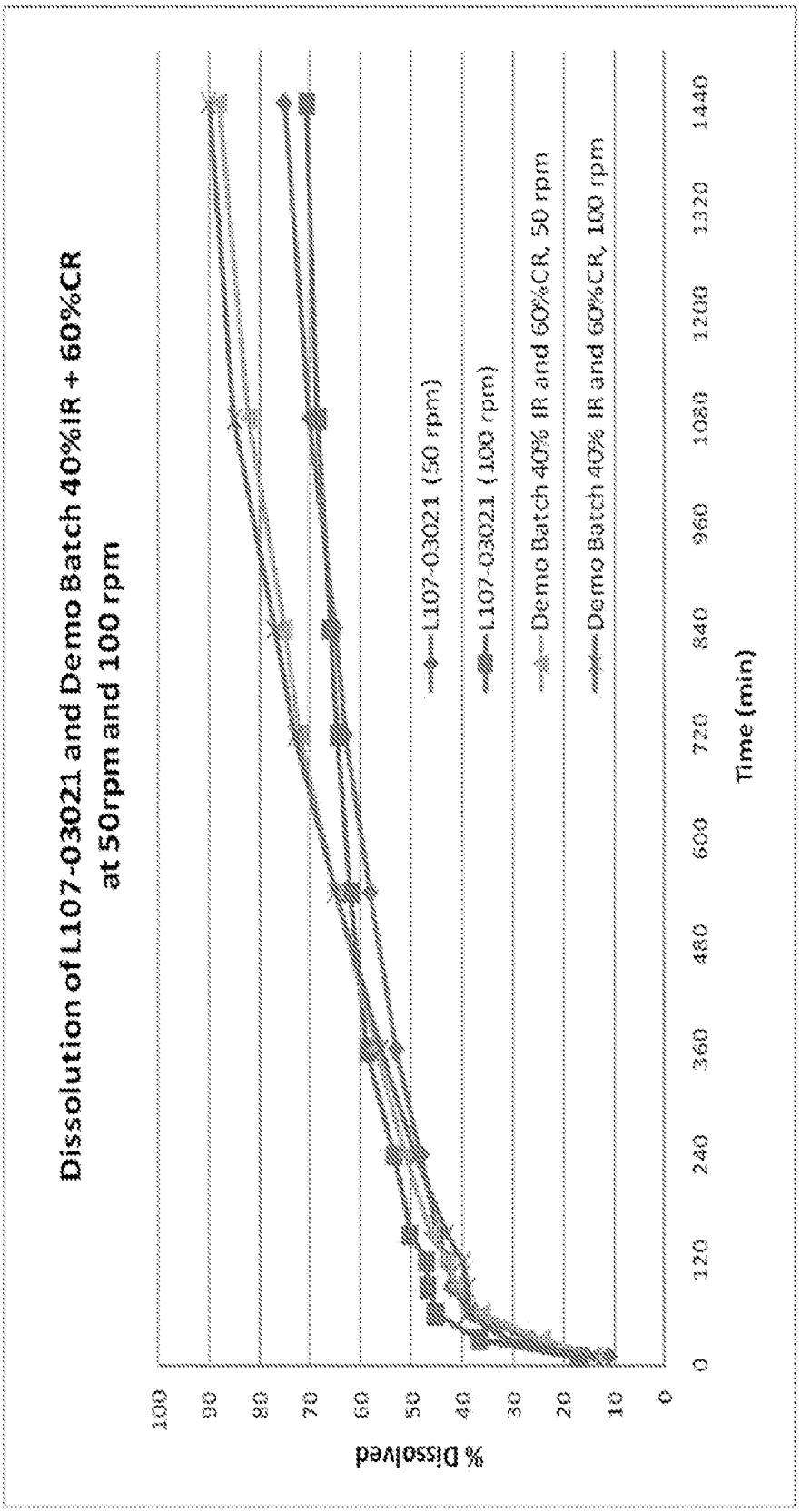

Dissolution of L107-03021 and Demo Batch 40%IR + 60%CR
at 50rpm and 100 rpm
% Dissolved
100
90
80
70
60
50
40
30
20
10
0
0
120
240
360
480
600
720
840
960
1080
1200
1320
1440
Time (min)
L107-03021 (50 rpm)
L107-03021 (100 rpm)
Demo Batch 40% IR and 60%CR, 50 rpm
Demo Batch 40% IR and 60%CR, 100 rpm

Figure 19

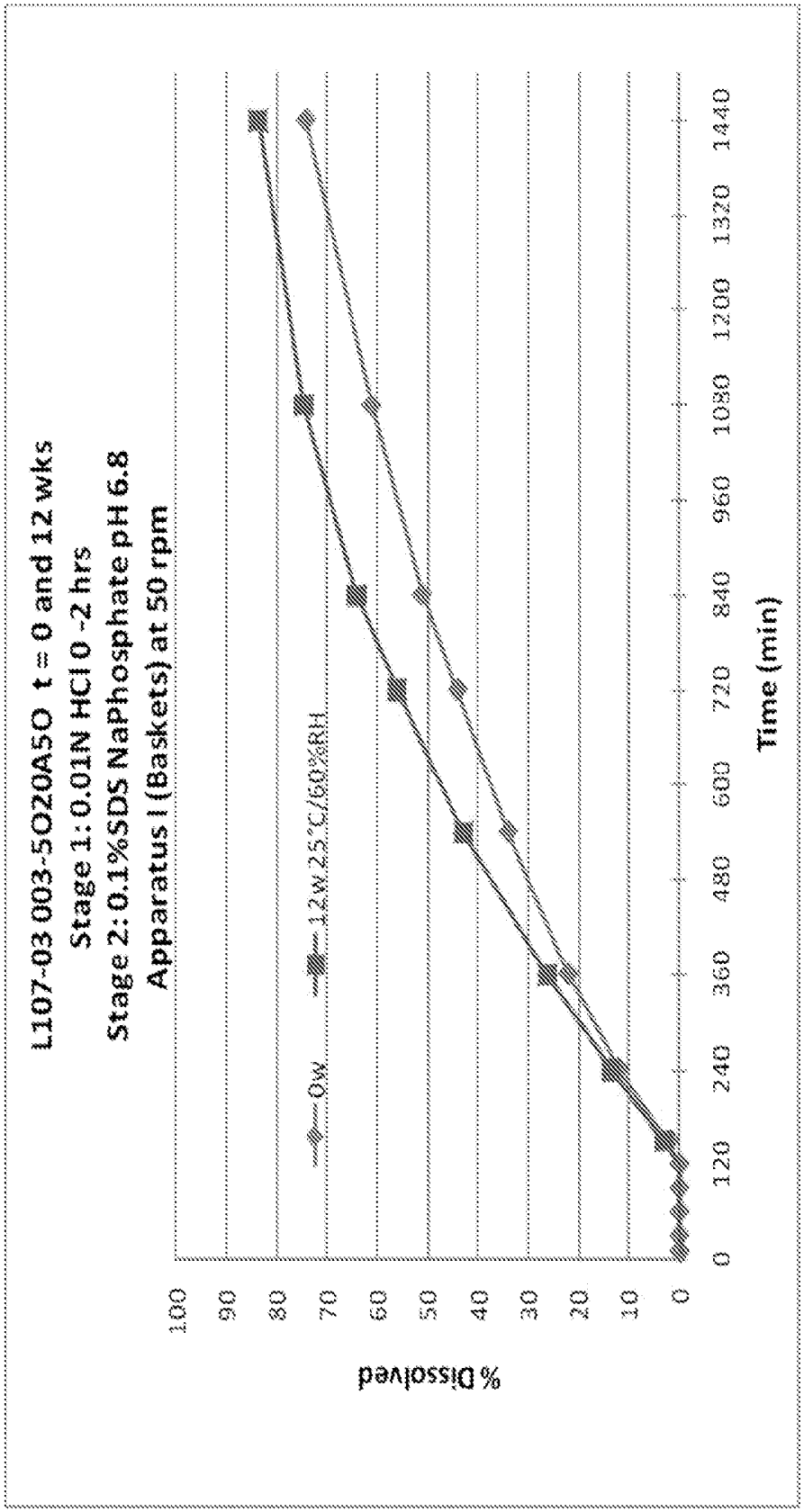

L107-03 003-5O20A5O t = 0 and 12 wks
Stage 1: 0.01N HCl 0 -2 hrs
Stage 2: 0.1%SDS NaPhosphate pH 6.8
Apparatus I (Baskets) at 50 rpm
0w
12w 25°C/60%RH
% Dissolved
100
90
80
70
60
50
40
30
20
10
0
0
120
240
360
480
600
720
840
960
1080
1200
1320
1440
Time (min)

Figure 20

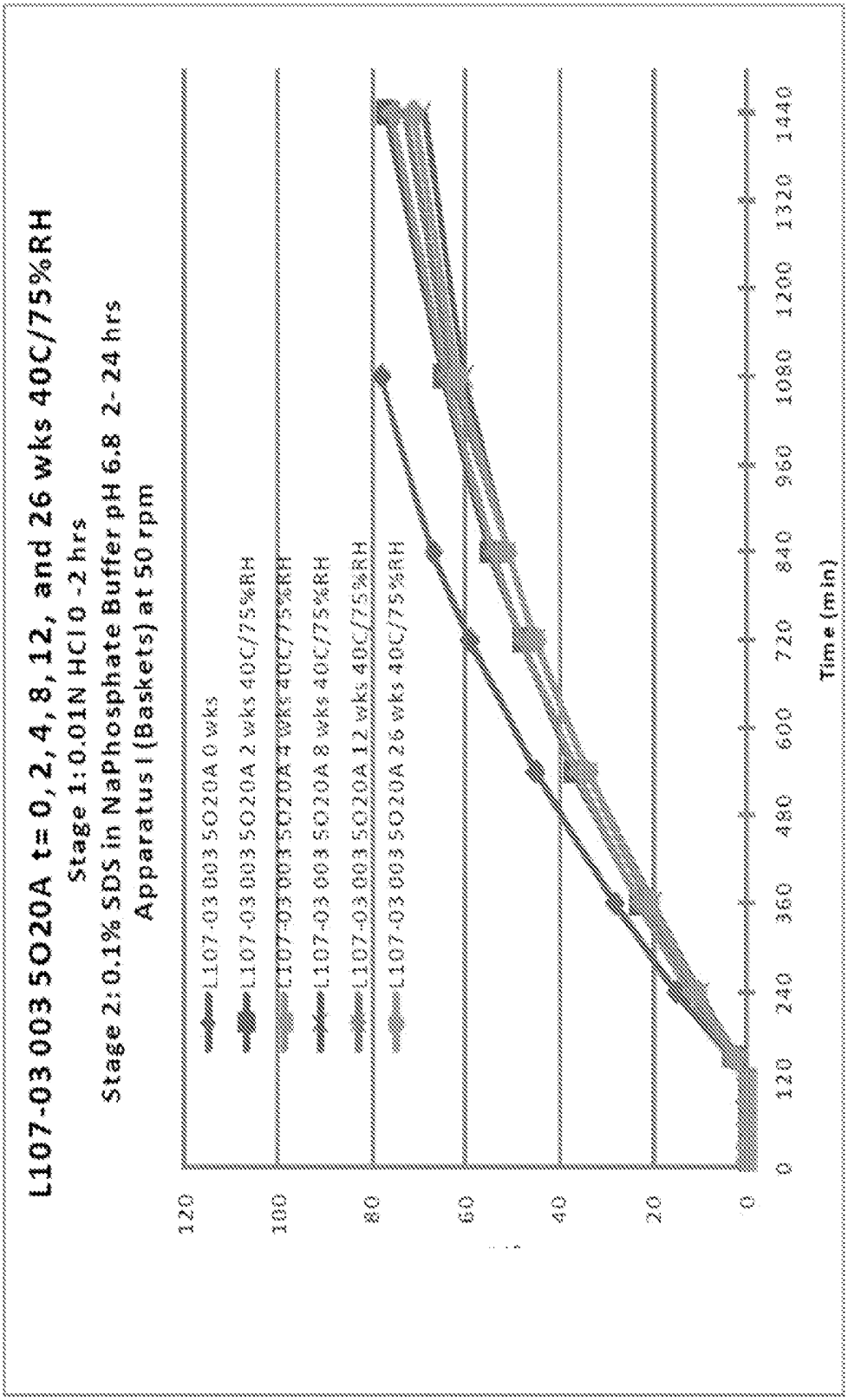

L107-03 003 5O20A t= 0, 2, 4, 8, 12, and 26 wks 40C/75%RH
Stage 1: 0.01N HCl 0 -2 hrs
Stage 2: 0.1% SDS in NaPhosphate Buffer pH 6.8 2- 24 hrs
Apparatus I (Baskets) at 50 rpm
L107-03 003 5O20A 0 wks
L107-03 003 5O20A 2 wks 40C/75%RH
L107-03 003 5O20A 4 wks 40C/75%RH
L107-03 003 5O20A 8 wks 40C/75%RH
L107-03 003 5O20A 12 wks 40C/75%RH
L107-03 003 5O20A 26 wks 40C/75%RH
120
100
80
60
40
20
0
0
120
240
360
480
600
720
840
960
1080
1200
1320
1440
Time (min)

Figure 21

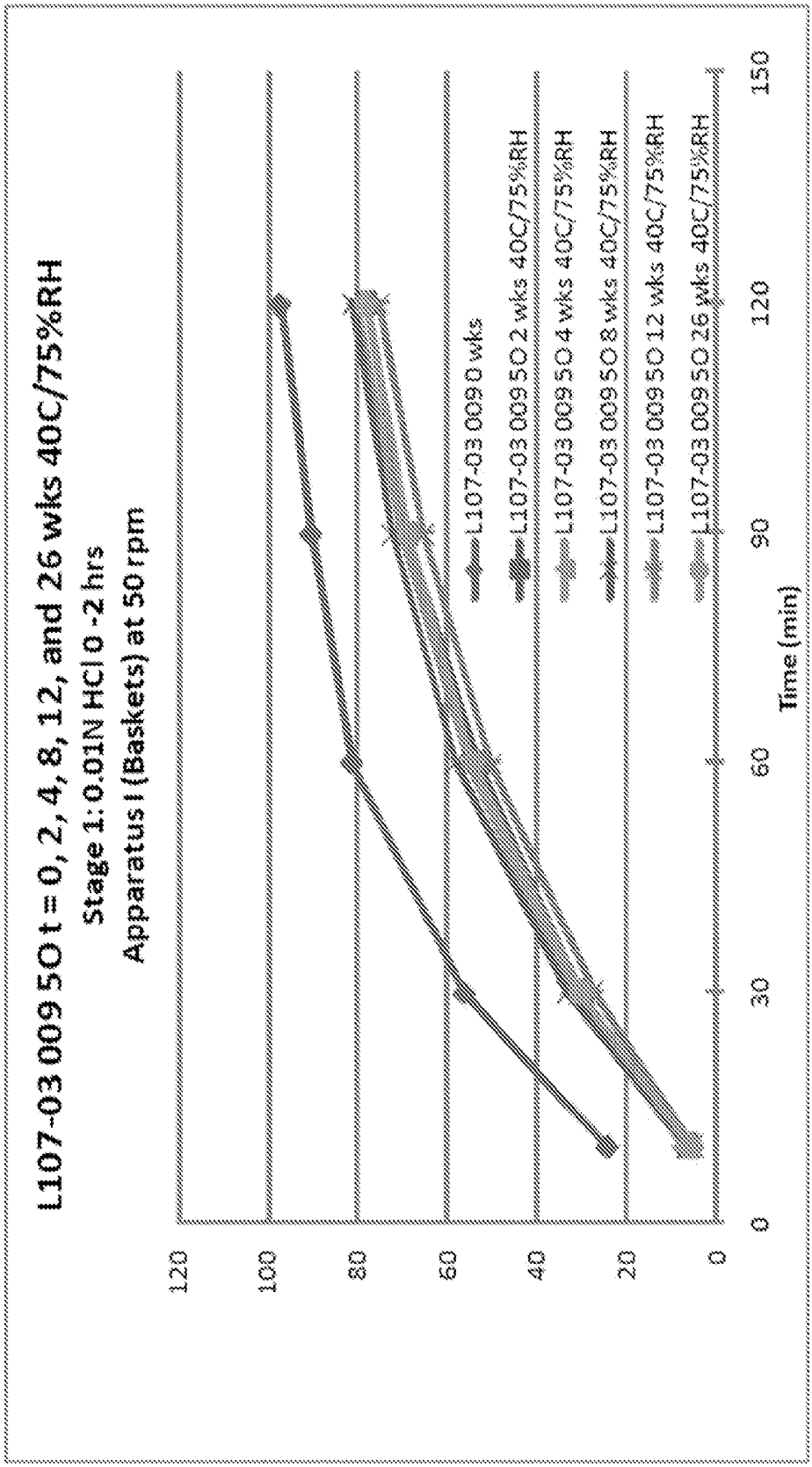

L107-03 009 5O t = 0, 2, 4, 8, 12, and 26 wks 40C/75%RH
Stage 1: 0.01N HCl 0 -2 hrs
Apparatus I (Baskets) at 50 rpm
120
100
80
60
40
20
0
0
30
60
90
120
150
Time (min)
L107-03 009 0 wks
L107-03 009 5O 2 wks 40C/75%RH
L107-03 009 5O 4 wks 40C/75%RH
L107-03 009 5O 8 wks 40C/75%RH
L107-03 009 5O 12 wks 40C/75%RH
L107-03 009 5O 26 wks 40C/75%RH

Figure 22

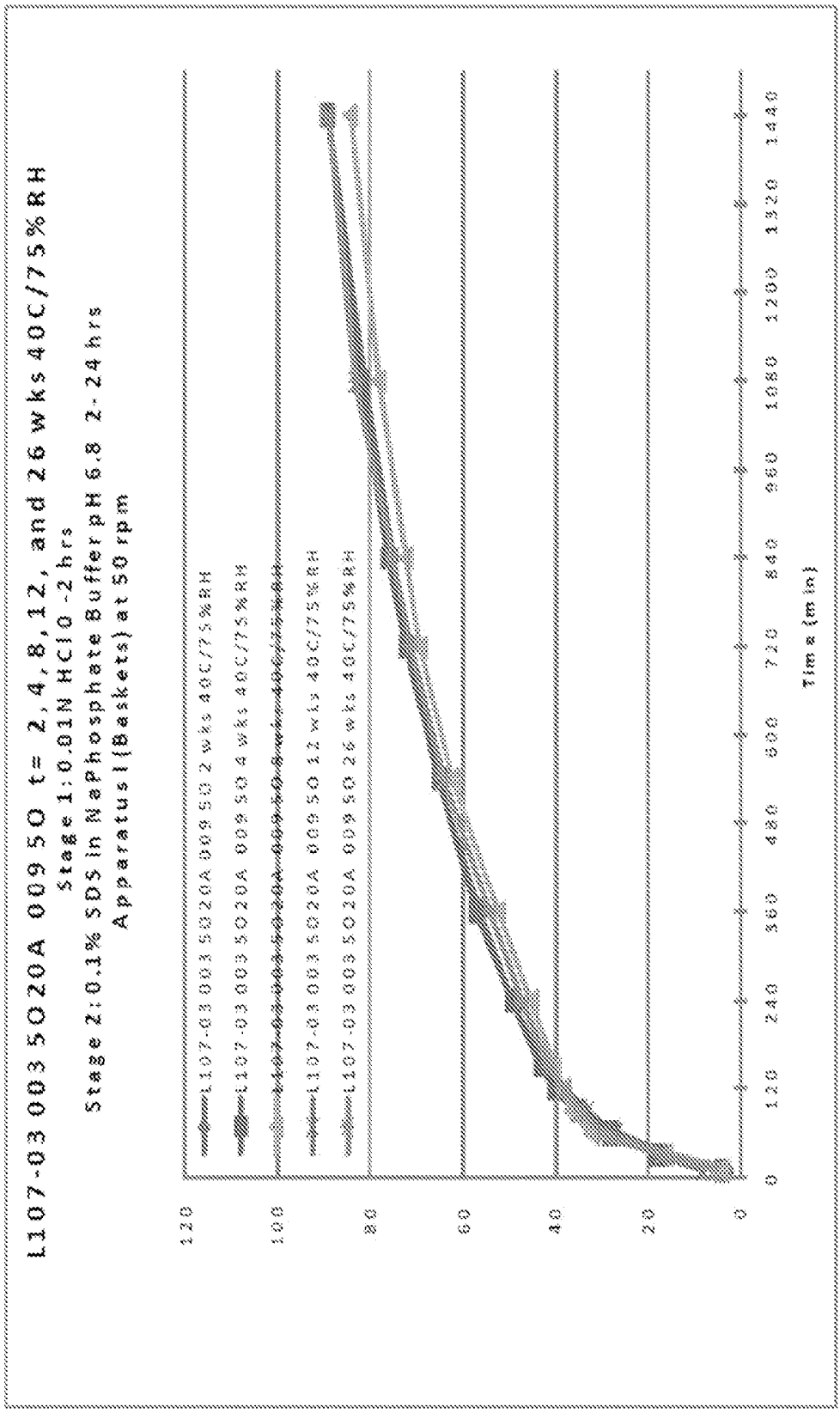

L107-03 003 5020A 009 5O t= 2,4,8,12, and 26 wks 40C/75%RH
Stage 1:0.01N HCl 0 -2 hrs
Stage 2:0.1% SDS in NaPhosphate Buffer pH 6.8 2-24 hrs
Apparatus I(Baskets) at 50 rpm
L107-03 003 5020A 009 5O 2 wks 40C/75%RH
L107-03 003 5020A 009 5O 4 wks 40C/75%RH
L107-03 003 5020A 009 5O 12 wks 40C/75%RH
L107-03 003 5020A 009 5O 26 wks 40C/75%RH
120
100
80
60
40
20
0
0
120
240
360
480
600
720
840
960
1080
1200
1320
1440
Time (min)

Figure 23

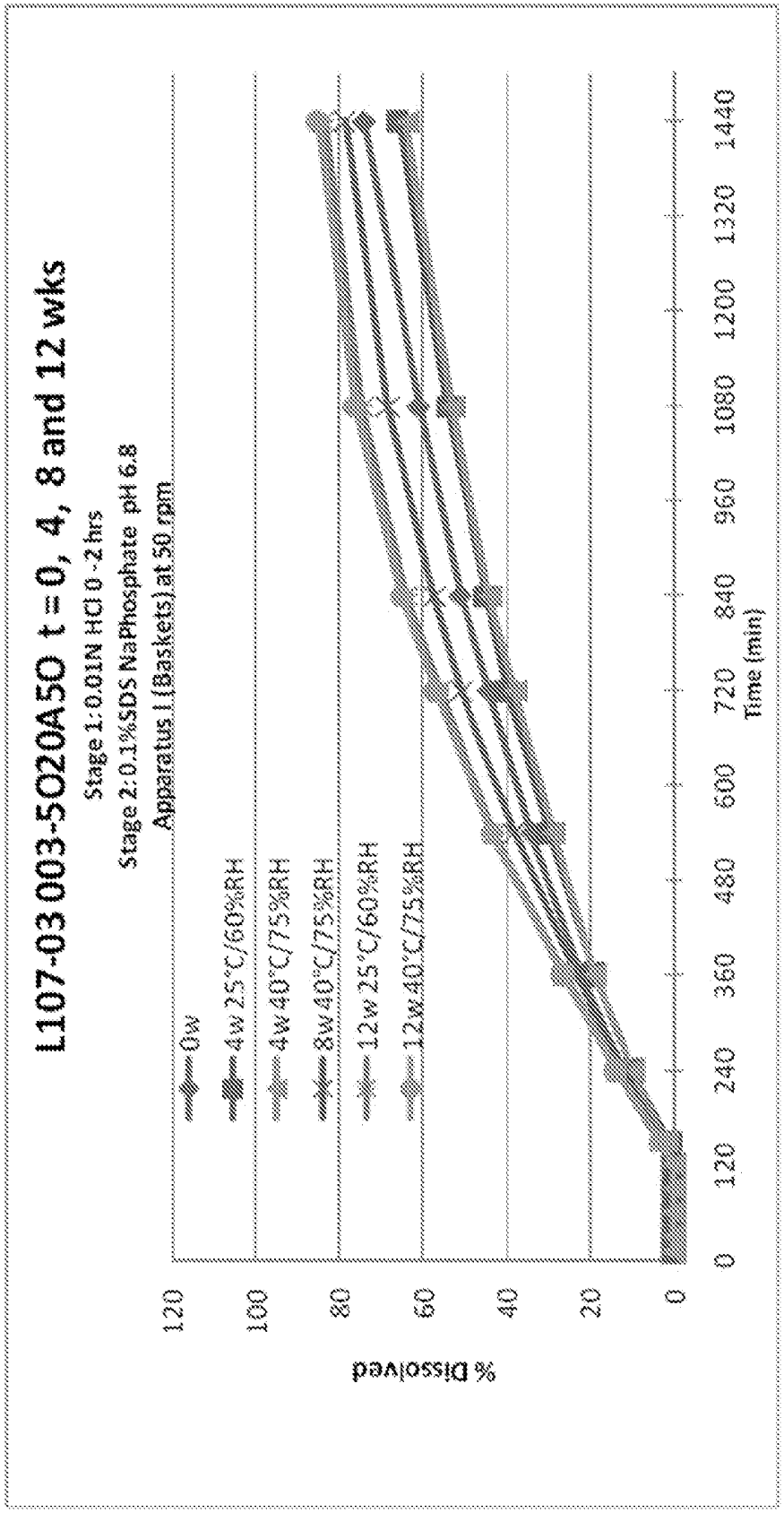

L107-03 003-5O20A5O t = 0, 4, 8 and 12 wks
Stage 1: 0.01N HCl 0 - 2 hrs
Stage 2: 0.1%SDS NaPhosphate pH 6.8
Apparatus I (Baskets) at 50 rpm
0w
4w 25°C/60%RH
4w 40°C/75%RH
8w 40°C/75%RH
12w 25°C/60%RH
12w 40°C/75%RH
% Dissolved
120
100
80
60
40
20
0
0
120
240
360
480
600
720
840
960
1080
1200
1320
1440
Time (min)

Figure 24

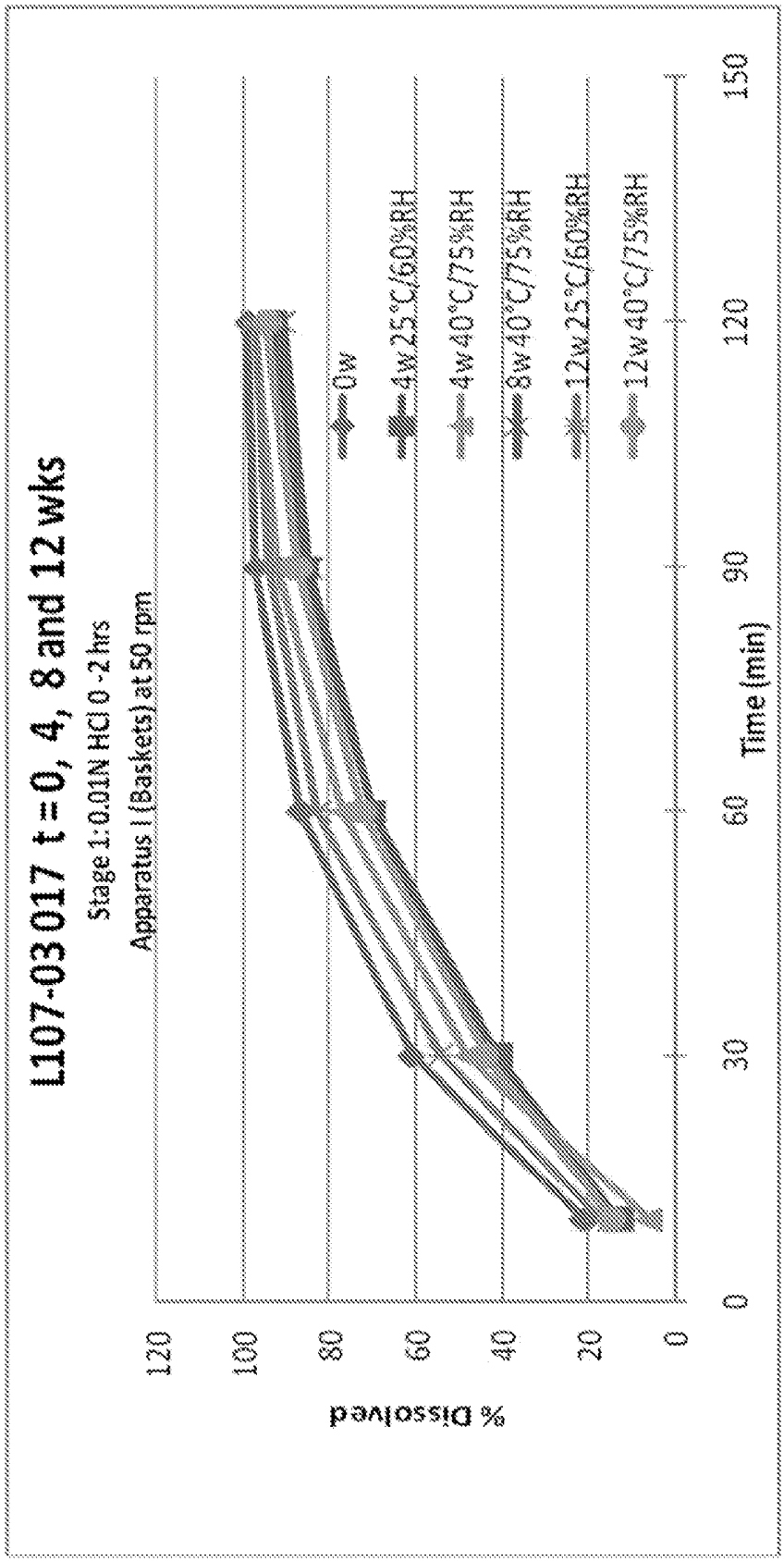

L107-03 017 t = 0, 4, 8 and 12 wks
Stage 1: 0.01N HCl 0 - 2 hrs
Apparatus I (Baskets) at 50 rpm
% Dissolved
120
100
80
60
40
20
0
0
30
60
90
120
150
Time (min)
0w
4w 25°C/60%RH
4w 40°C/75%RH
8w 40°C/75%RH
12w 25°C/60%RH
12w 40°C/75%RH

Figure 25

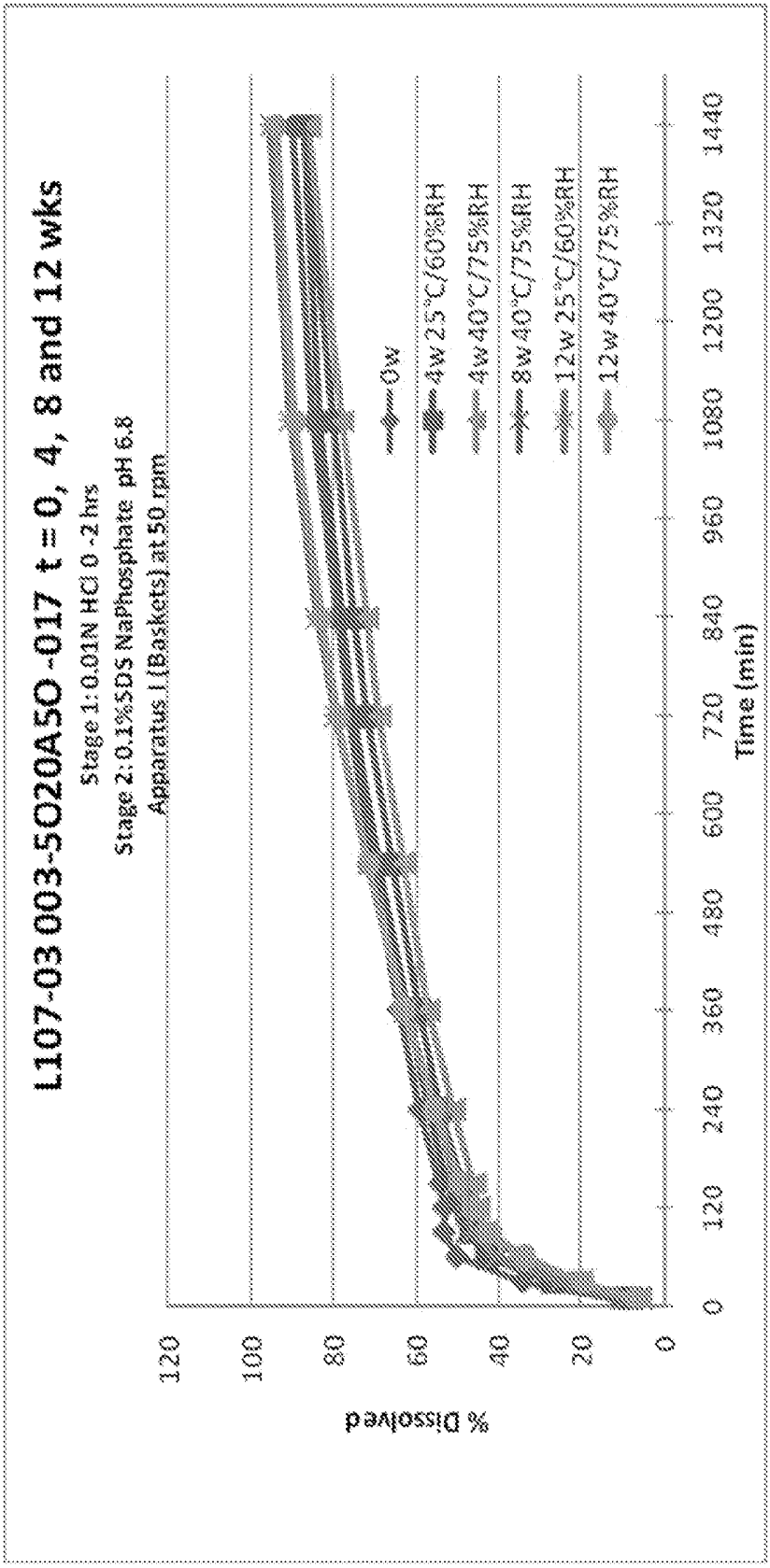

L107-03 003-5O20A5O -017 t = 0, 4, 8 and 12 wks
Stage 1: 0.01N HCl 0 -2 hrs
Stage 2: 0.1%SDS NaPhosphate pH 6.8
Apparatus I (Baskets) at 50 rpm
% Dissolved
120
100
80
60
40
20
0
0
120
240
360
480
600
720
840
960
1080
1200
1320
1440
Time (min)
0w
4w 25°C/60%RH
4w 40°C/75%RH
8w 40°C/75%RH
12w 25°C/60%RH
12w 40°C/75%RH

Figure 26

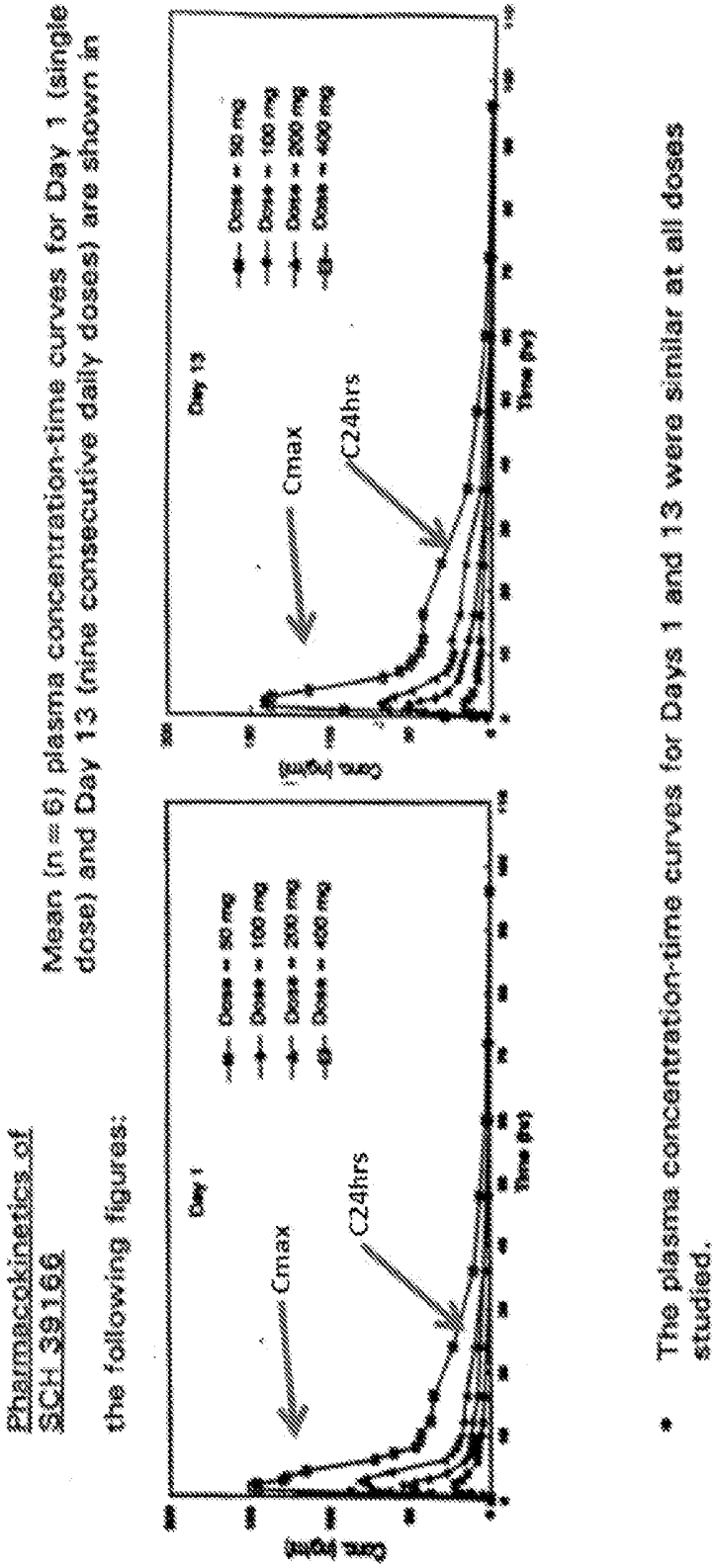
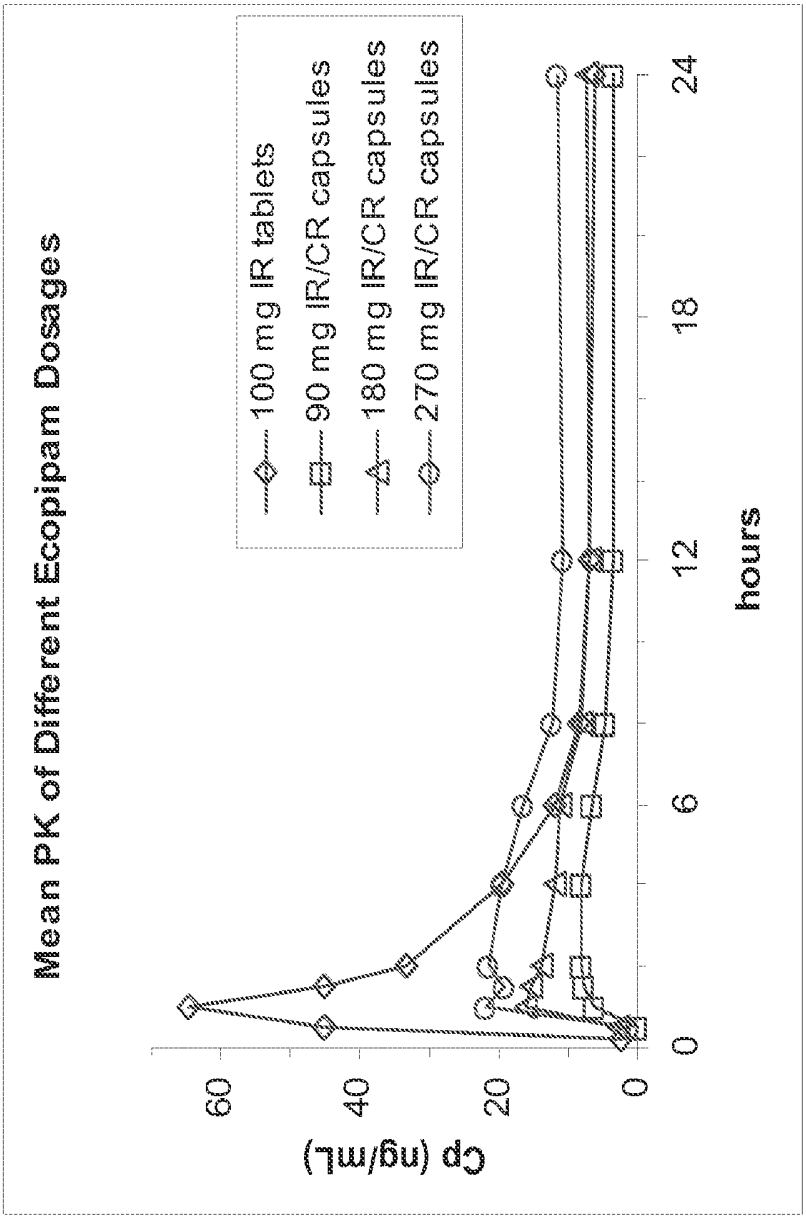

Pharmacokinetics of SCH 39166
the following figures:
Mean (n = 6) plasma concentration-time curves for Day 1 (single dose) and Day 13 (nine consecutive daily doses) are shown in
Day 1
Day 13
Cmax
C24hrs
Dose = 50 mg
Dose = 100 mg
Dose = 200 mg
Dose = 400 mg
Time (hr)
Conc (ng/ml)
* The plasma concentration-time curves for Days 1 and 13 were similar at all doses studied.

Figure 27


Mean PK of Different Ecopipam Dosages
100 mg IR tablets
90 mg IR/CR capsules
180 mg IR/CR capsules
270 mg IR/CR capsules
Cp (ng/mL)
60
40
20
0
0
6
12
18
24
hours

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 2013/050383

A. CLASSIFICATION OF SUBJECT MATTER

(see extra sheet)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K 9/16, 9/26, 9/52, 31/445, 31/55, 47/06 A61P 25/16

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PatSearch, Esp@cenet, Enterez PubMed, JOPAL, EAPO, DEPATISnet, USPTO, PAJ, RUPAT, ChemIDplus

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6410 527 B1 (SCHERING CORPORATION) 25.06.2002, col.1, lines 54-64, col.2, line 66-col. 3, line19, examples, claims	1-50
Y	US 6262049 B1 (SCHERING CORPORATION) 17.07.2001, abstract, col.2, line 66-col. 3, line 19, examples, claims	1-49
Y	«Promyshlennaya tekhologiya lekarctv», 2002, т.2, pp.353-356, 378-384, 408, drawing 16.8	1-50
Y	RU 2314798 C2 (BIODAR LTD) 20.01.2008, p.3, lines 29-54, p.4, lines 1-20, p.6, lines 20-37, claims	50

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

☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 September 2013 (23.09.2013)	31 October 2013 (31.10.2013)
Name and mailing address of the ISA/ FIPS Russia, 123995, Moscow, G-59, GSP-5, Berezhkovskaya nab., 30-1 Facsimile No. +7 (499) 243-33-37	Authorized officer E.Saibel Telephone No. 495 531 65 15

INTERNATIONAL SEARCH REPORT
Classification of subject matter

International application No.
PCT/US 2013/050383

A61K 9/16 (2006.01)
A61K 9/26 (2006.01)
A61K 9/52 (2006.01)
A61K 31/445 (2006.01)
A61K 31/55 (2006.01)
A61K 47/06 (2006.01)
A61P 25/16 (2006.01)