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DESCRIPTION

FIELD OF THE INVENTION

[0001] The present invention relates to compositions for the oral delivery of pharmacologically active agents, particularly for the delivery of a peptide active agent.

BACKGROUND

[0002] Oral delivery of active pharmaceutical ingredients is generally the delivery route of choice since it is convenient, relatively easy and generally painless, resulting in greater patient compliance relative to other modes of delivery. Solid dosage forms for oral delivery have been reported (Preformulation in Solid Dosage Form Development. 1st Edition CRC Press 2008), Ed: Adeyeye and Brittain; Pharmaceutical Dosage Forms: Tablets, Vol. 2: Rational Design and Formulation, 3rd Edition (CRC Press 2008), Ed: Augsberger and Hoag).

[0003] WO 02072075 e.g. reports bilayered tablets of peptides.

[0004] However, effective oral delivery of active pharmaceutical ingredients, such as peptides can be challenging because of the pre-systemic degradation of the API, poor permeability across the intestinal epithelium, low solubility, and varying pH in the gastrointestinal tract, thereby leading to low or erratic bioavailability. There is a need for oral formulations that are capable of providing suitable bioavailability of administered peptides and agents.

SUMMARY

[0005] Aspects of the invention provide modified release solid oral compositions as defined in the claims. Solid oral dosage forms are disclosed herein. Disclosed herein are solid oral dosage forms that include a therapeutically effective amount of an active pharmaceutical ingredient, such as a peptide or hormone. Such oral dosage forms are designed to be released in a suitable part of the GI tract to achieve maximal systemic bioavailability to treat or prevent a disease in a subject in need thereof.

[0006] Disclosed herein are modified release solid oral compositions. In some disclosures, the modified release solid dosage compositions comprise (a) a core comprising (i) an effective amount of active pharmaceutical ingredient, (ii) a pH lowering agent, (iii) an absorption enhancer, (iv) a filler comprising an hydrogel-forming polymer, and (v) less than 10% by weight of disintegrant; and (b) an enteric coating surrounding the core, the composition providing a pharmacokinetic profile for the active agent with a T_{lag} greater than 1.0 h and less than 16 h

post-administration and a $T_{\max}$ greater than (Tiag +0.5 h) and less than 20 h post-administration.

[0007] In some disclosures, the pharmacokinetic release profile targets release of the pharmaceutical active ingredient to the jejunum, the ileum or the jejunum and the ileum. In some disclosures, the composition is designed so that substantially no active pharmaceutical ingredient is released in the stomach, the duodenum or the stomach and duodenum post-administration.

[0008] In some disclosures, the composition further comprises a water soluble barrier beneath the enteric coating. In some disclosures, the water soluble barrier is in amount from about 6% to about 15% by weight. In some disclosures, the water-soluble barrier can be polyvinylpyrrolidone, hydroxymethylcellulose, hydroxypropylcellulose, methylcellulose or combinations thereof.

[0009] The absorption enhancer has a critical micelle concentration of from about 1.0 mM to about 40 mM or of from about 1.0 mM to about 15 mM.

[0010] The hydrogel-forming polymer has a viscosity of about 3,000 to about 120,000 cP at 20°C. The hydrogel-forming polymer comprises hydroxypropylcellulose, hydroxypropylmethylcellulose or a combination thereof. In some embodiments, the filler comprises, hydroxypropylcellulose, hydroxypropylmethylcellulose, or a combination thereof.

[0011] In some disclosures, the active pharmaceutical ingredient comprises a peptide. In some disclosures, the molecular weight of the peptide compound ranges from about 500 Daltons up to about 10,000 Daltons. In some disclosures, the peptide can be leuprolide, insulin, vasopressin, calcitonin, calcitonin gene-related peptide, parathyroid hormone, desmopressin, gonadotrophin releasing hormone (GnRH), luteinizing hormone-releasing factor, adrenocorticotropin, enkephalin, glucagon-like peptide-1, desmopressin, and 2,6-dimethyltyrosine-D-arginine-phenylalanine-lysine amide. or combinations thereof.

[0012] The absorption enhancer comprises a cationic surface active agent, an anionic surface active agent or a combination thereof. In some disclosures, the cationic surface active agent comprises an acylcamitine. In some disclosures, the anionic surface active agent comprises sodium dodecyl sulfate. In some disclosures, the absorption enhancer comprises sodium dodecyl sulfate.

[0013] The pH lowering agent comprises citric acid, tartaric acid or a combination thereof. In some disclosures, the pH lowering agent is in the form of coated acid particles. In some disclosures, the acid particles are coated with a water-soluble coating. In some disclosures, the pH lowering agent is in the form of coated citric acid particles. In some disclosures, the composition comprises from about 50 mg to about 500 mg of citric acid. In some disclosures, the composition comprises from about 250 mg to about 500 mg of citric acid. In some disclosures, the citric acid is in the form of coated citric acid.

[0014] The composition comprises from about 5 mg/cm² to about 25 mg/cm² of enteric coating.

[0015] In some disclosures, the modified release solid oral composition comprises (a) a core comprising (i) an effective amount of active pharmaceutical ingredient, (ii) a pH lowering agent, (iii) an absorption enhancer, (iv) a filler comprising an hydrogel-forming polymer, wherein the core is substantially free of disintegrant, and (b) an enteric coating surrounding the core, the composition providing a pharmacokinetic profile for the active agent with a T_{lag} greater than 1.0 h and less than 16 h post-administration and a T_{max} greater than ($T_{lag} + 0.5$ h) and less than 20 h post-administration.

[0016] In some disclosures, the pharmacokinetic release profile targets release of the pharmaceutical active ingredient to the jejunum, the ileum or the jejunum and the ileum. In some disclosures, the composition is designed so that substantially no active pharmaceutical ingredient is released in the stomach, the duodenum or the stomach and duodenum post-administration.

[0017] In some disclosures, the composition further comprises a water soluble barrier beneath the enteric coating. In some disclosures, the water soluble barrier is in amount from about 6% to about 15% by weight. In some disclosures, the water soluble barrier can be polyvinylpyrrolidone, hydroxymethylcellulose, hydroxypropylcellulose, methylcellulose and combinations thereof.

[0018] The absorption enhancer has a critical micelle concentration of from about 1.0 to about 40 mM or of from about 1.0 to about 15 mM.

[0019] The hydrogel-forming polymer has a viscosity of about 3,000 to about 120,000 cP at 20°C. In some disclosures, the hydrogel-forming polymer comprises hydroxypropylcellulose, hydroxypropylmethylcellulose or a combination thereof. In some disclosures, the filler comprises, hydroxypropylcellulose, hydroxypropylmethylcellulose, or a combination thereof.

[0020] The active pharmaceutical ingredient comprises a peptide of 500 Daltons up to 10,000 Daltons. In some disclosures, the peptide can be leuprolide, insulin, vasopressin, calcitonin, calcitonin gene-related peptide, parathyroid hormone, desmopressin, gonadotrophin releasing hormone (GnRH), luteinizing hormone-releasing factor, adrenocorticotropin, enkephalin, glucagon-like peptide-1, desmopressin, and 2,6-dimethyltyrosine-D-arginine-phenylalanine-lysine amide.

[0021] The absorption enhancer comprises a cationic surface active agent, an anionic surface active agent or a combination thereof. In some disclosures, the cationic surface active agent comprises an acylcamitine. In some disclosures, the anionic surface active agent comprises sodium dodecyl sulfate. In some disclosures, the absorption enhancer comprises sodium dodecyl sulfate.

[0022] The pH lowering agent comprises citric acid, tartaric acid or a combination thereof. In some disclosures, the pH lowering agent is in the form of coated acid particles. In some disclosures, the acid particles are coated with a water-soluble coating. In some disclosures, the pH lowering agent is in the form of coated citric acid particles. In some disclosures, the composition comprises from about 50 mg to about 500 mg of citric acid. In some disclosures, the composition comprises from about 250 mg to about 500 mg of citric acid. In some disclosures, the citric acid is in the form of coated citric acid.

[0023] The composition comprises from about 5 mg/cm² to about 25 mg/cm² of enteric coating.

[0024] There is disclosed a method of increasing plasma concentration of an active pharmaceutical ingredient, such as a peptide or hormone that includes orally administering to a subject in need thereof a pharmaceutical composition of the present disclosure.

[0025] Some disclosures relate to methods of treating a patient are disclosed. In some disclosures, the method of treating comprises (a) providing a solid oral dosage form comprising (i) a core comprising an effective amount of active pharmaceutical ingredient, a pH lowering agent, an absorption enhancer, a filler comprising an hydrogel-forming polymer, and less than 10% by weight of disintegrant; and (ii) an enteric coating surrounding the core; and (b) administering orally to a patient, the solid oral dosage form, wherein the solid oral dosage form provides a pharmacokinetic release profile for the active agent with a T_{lag} greater than 1.0 h and less than 16 h post-administration and a T_{max} greater than ($T_{lag}+0.5$ h) and less than 20 h post-administration.

[0026] In some disclosures, the pharmacokinetic release profile targets release of the pharmaceutical active ingredient to the jejunum, the ileum or the jejunum and the ileum.

[0027] In some disclosures, the solid oral dosage form is substantially free of disintegrant. In some disclosures, the solid oral dosage form further comprises a water soluble barrier beneath the enteric coating.

[0028] The absorption enhancer has a critical micelle concentration of from about 1.0 to about 40 mM. In some disclosures, the absorption enhancer has a critical micelle concentration of from about 1.0 to about 15 mM.

[0029] The hydrogel-forming polymer has a viscosity of about 3,000 to about 120,000 cP at 20°C. In some disclosures, the filler comprises microcrystalline cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, chitosan or a combination thereof. In some disclosures, the hydrogel-forming polymer comprises hydroxypropyl cellulose, hydroxypropyl methyl cellulose or a combination thereof.

[0030] The active pharmaceutical ingredient comprises a peptide of 500 Daltons up to about 10,000 Daltons. In some disclosures, the peptide is one of leuprolide, insulin, vasopressin, calcitonin, calcitonin gene-related peptide, parathyroid hormone, desmopressin, gonadotrophin releasing hormone (GnRH), luteinizing hormone-releasing factor, adrenocorticotropin, enkephalin, glucagon-like peptide-1, desmopressin, 2,6-dimethyltyrosine-D-arginine-phenylalanine-lysine amide and triptorelin.

[0031] The absorption enhancer comprises a cationic surface active agent, an anionic surface active agent or a combination thereof. In some disclosures, the cationic surface active agent comprises an acylcarnitine. In some disclosures, the anionic surface active agent comprises sodium dodecyl sulfate. In some disclosures, the absorption enhancer comprises sodium dodecyl sulfate.

[0032] The pH lowering agent comprises citric acid, tartaric acid or a combination thereof. In some disclosures, the pH lowering agent is in the form of coated acid particles. In some disclosures, the acid particles are coated with a water-soluble coating. In some disclosures, the pH lowering agent is in the form of coated citric acid particles. In some disclosures, the composition comprises from about 50 mg to about 500 mg of citric acid. In some disclosures, the composition comprises from about 250 mg to about 500 mg of citric acid. In some disclosures, the citric acid is in the form of coated citric acid.

[0033] The composition comprises from about 5 mg/cm² to about 25 mg/cm² of enteric coating.

[0034] These and other aspects of the present invention will become apparent upon reference to the following detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

[0035] The present invention will be further explained with reference to the attached drawings.

Figure 1 shows a linearity curve (RP-HPLC) for leuprolide.

Figure 2 shows RP-HPLC chromatograms of water, extracted placebo tablet, and leuprolide-spiked placebo extract.

Figure 3 shows RP-HPLC chromatograms of water, 0.9% sodium chloride solution (SC vehicle), and leuprolide-spiked SC vehicle.

Figure 4 shows average dissolution profiles of various leuprolide tablets of the present disclosure.

Figure 5 shows average dissolution profiles of various leuprolide tablets of the present disclosure.

Figure 6 shows stability of various leuprolide tablets of the present disclosure.

Figure 7 shows a linear time-concentration curve after subcutaneous administration to beagle dogs of 0.1 mg/kg of leuprolide.

Figure 8 shows a semi-log time-concentration curve after subcutaneous administration to beagle dogs of 0.1 mg/kg of leuprolide.

Figure 9 shows a linear time-concentration curve after oral administration to beagle dogs "Prototype A" tablets of the present disclosure containing 3.0 mg of leuprolide. The Prototype A tablets included 500 mg citric acid and 50 mg LLC, and were enteric coated.

Figure 10 shows a semi-log time-concentration curve after oral administration to beagle dogs "Prototype A" tablets of the present disclosure containing 3.0 mg of leuprolide. The Prototype A tablets included 500 mg citric acid and 50 mg LLC, and were enteric coated.

Figure 11 shows a linear time-concentration curve after oral administration to beagle dogs "Prototype B" tablets of the present disclosure containing 1.0 mg of leuprolide. The Prototype B tablets included 500 mg citric acid and 50 mg LLC, and were enteric coated.

Figure 12 shows a semi-log time-concentration curve after oral administration to beagle dogs "Prototype B" tablets of the present disclosure containing 1.0 mg of leuprolide. The Prototype B tablets included 500 mg citric acid and 50 mg LLC, and were enteric coated.

Figure 13 shows a linear time-concentration curve after oral administration to beagle dogs "Prototype C" tablets of the present disclosure containing 3.0 mg of leuprolide. The Prototype C tablets included 250 mg citric acid and 50 mg LLC, and were enteric coated.

Figure 14 shows a semi-log time-concentration curve after oral administration to beagle dogs "Prototype C" tablets of the present disclosure containing 3.0 mg of leuprolide. The Prototype C tablets included 250 mg citric acid and 50 mg LLC, and were enteric coated.

Figure 15 shows a linear time-concentration curve after oral administration to beagle dogs of unformulated containing 3.0 mg of leuprolide.

Figure 16 shows a semi-log time-concentration curve after oral administration to beagle dogs of unformulated containing 3.0 mg of leuprolide.

Figure 17 shows a linear time-concentration curve after oral administration to beagle dogs "Prototype E" tablets of the present disclosure containing 3.0 mg of leuprolide. The Prototype E tablets included 250 mg citric acid and 50 mg LLC, and were enteric coated.

Figure 18 shows a semi-log time-concentration curve after oral administration to beagle dogs "Prototype E" tablets of the present disclosure containing 3.0 mg of leuprolide. The Prototype E tablets included 250 mg citric acid and 50 mg LLC, and were enteric coated.

Figure 19 shows a linear time-concentration curve after oral administration to beagle dogs "Prototype G" tablets of the present disclosure containing 3.0 mg of leuprolide. The Prototype

G tablets included 250 mg citric acid and 50 mg LLC, and were enteric coated.

Figure 20 shows a semi-log time-concentration curve after oral administration to beagle dogs "Prototype G" tablets of the present disclosure containing 3.0 mg of leuprolide. The Prototype G tablets included 250 mg citric acid and 50 mg LLC, and were enteric coated.

Figure 21 shows a linear time-concentration curve after oral administration of various leuprolide tablets of the present disclosure to beagle dogs.

Figure 22 shows the values of C_{max} vs. T_{max} for the leuprolide tablet prototypes.

Figure 23 shows a bubble plot representation of the leuprolide data, showing T_{max} versus T_{lag} . The size of the bubble corresponds to the absolute bioavailability (also labeled on the data points).

Figure 24 shows the average PK curves for the intravenous (IV) and subcutaneous (SC) doses.

Figures 25A and 25B show the average curves for PO doses, corrected for T_{max} , for JSV-003-178: 250 CA/50 LLC/MR, 6% EC (pH 2.3), JSV-003-180: 250 CA/50 LLC, 10% EC (pH 2.3), JSV-003-182: 0 CA/0 LLC, 10% EC (pH 2.3), ULB-231-201: 250 CA/50 LLC/chitosan, 6% EC (pH 5.2), ULB-231-204: 250 CA/50 LLC/MR, 6% EC (pH 5.2), ULB-231-254: 250 CA/50 LLC/chitosan, 6% EC (pH 5.3), ULB-231-254: 250 CA/50 LLC/chitosan, 6% EC (pH 5.3), ULB-231-256: 250 CA/50 LLC/MR, 6% EC (pH 5.3) and ELB-020-014: 250 CA/50 SDS, 6% EC (pH 5.3).

Figure 26 shows the systemic bioavailability vs. T_{max} . "Conventional" denotes a core containing disintegrant, "MR" cores contain HPC or HPMC (no disintegrant), "chitosan" cores contain medium-weight chitosan (no disintegrant). Permeation enhancers were either LLC (lauroyl-L-carnitine) or SDS (sodium dodecyl sulfate).

Figure 27 is a bubble plot representation of the triptorelin data, showing T_{max} versus T_{lag} . The size of the bubble corresponds to the absolute bioavailability (also labeled on the data points).

DETAILED DESCRIPTION

[0036] It is to be understood that this invention is not limited to particular compositions, methods, and experimental conditions described, as such compositions, methods, and conditions may vary. It is also to be understood that the terminology used herein is for purposes of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only in the appended claims.

[0037] As used in this specification and the appended claims, the singular forms "a", "an", and

"the" include plural references unless the context clearly dictates otherwise. Thus, for example, references to "the method" includes one or more methods, and/or steps of the type described herein which will become apparent to those persons skilled in the art upon reading this disclosure and so forth.

[0038] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, the preferred methods and materials are now described.

Pharmaceutical compositions

[0039] As used herein, the terms "formulation" and "composition" are used interchangeably and refer to a mixture of two or more compounds, elements, or molecules. In some disclosures the terms "formulation" and "composition" may be used to refer to a mixture of one or more active agents with a pH lowering agent, an absorption enhancer or other excipients. All references to residence times in the gastrointestinal tract (GIT) assume a fasted state. All references to bioavailability (%F) denote absolute bioavailability (relative to intravenous injection), unless otherwise stated.

[0040] The terms "API", "active agent" and "drug" are used interchangeably herein to refer to a therapeutically, and/or prophylactically active compound that has physiologic, pharmaceutical, pharmacological, or therapeutic effect. The term is intended to include the API in any suitable form such as e.g. a pharmaceutically acceptable salt, complex, solvate or prodrug thereof or, if relevant, in any stereoisomer form including any enantiomeric or racemic form, or a combination of any of the above. Examples of API include, but are not limited to, a hormone, a peptide, or prodrug thereof.

[0041] As used herein, the terms "dosage form" and "pharmaceutical composition" are used interchangeably herein to refer to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of therapeutic agent calculated to produce the desired onset, tolerability, and therapeutic effects, in association with one or more suitable pharmaceutical excipients. Methods for preparing such dosage forms are known or will be apparent to those skilled in the art. The dosage forms of the present invention may take the form of tablets, pills, capsules, or the like. In some disclosures, the dosage form is a tablet. In other disclosures, the dosage form is a capsule.

[0042] As used herein, an "effective amount" or a "therapeutically effective amount" of an API refers to a non-toxic, but sufficient amount of the API, to achieve therapeutic results in treating a condition for which the API is known to be effective. It is understood that various biological factors may affect the ability of a substance to perform its intended task.

[0043] Numerous human hormones, neurotransmitters, and other important biological compounds have peptides as a substantial part of their molecular structures. Many diseases respond positively to raising the level of these peptide compounds in patients.

[0044] Therapeutically effective amounts of such biologically relevant therapeutically active agents may be administered to patients in a variety of ways, for example, by the oral route.

[0045] Delivering therapeutically active peptides by the oral route has been a challenge and a goal for many decades. Some of the challenges include, but are not limited to, digestive enzymes and strongly acidic environment of the stomach, intestinal digestive enzymes, components of pancreatic juices and secretions of the biliary system, and composition and thickness of outer and inner mucus layers of the intestine. Furthermore, the compositions and concentrations of intestinal components are not uniform, but vary within the segments of the intestine (duodenum, jejunum, ileum, colon). All of these factors, and more, are chemical and physical hurdles to the oral delivery of peptides and into systemic circulation. For examples, proteolytic enzymes of both the stomach and intestines may degrade peptides, rendering them inactive before they can be absorbed into the bloodstream. Any amount of peptide that survives proteolytic degradation by proteases of the stomach (typically having acidic pH optima) is later confronted with proteases of the small intestine and enzymes secreted by the pancreas (typically having neutral to basic pH optima).

[0046] The problem of the oral delivery of pharmaceutically active peptides and is further confounded by the fact that different peptides and may have different physical-chemical properties, such as: net charge, solubility, hydrophobicity, molecular weight, and for the peptides, protease sensitivity, and others. Thus, there is a need to control key aspects of the dosage form to enable oral delivery of active agents, with maximal bioavailability.

[0047] One skilled in the art will appreciate that, to increase efficiency and systemic bioavailability, the dosage form should deliver the active agent (e.g. peptide and any absorption-enhancing agents, to the part of the gastrointestinal tract best suited chemically and physically for absorption of that particular active agent.

[0048] Disclosed are pharmaceutical compositions (e.g. oral dosage forms) that enable the location and rate of release of the active agent and enhancing excipients from the pharmaceutical compositions in the gastrointestinal (GI) tract. In some disclosures, the dosage form comprises a core (comprising the API) and an enteric coat wherein the core, the coat or the core and the coat are designed to be released in a suitable part of the GI tract to achieve maximal systemic bioavailability to treat or prevent a disease in a subject in need thereof.

[0049] Disclosed is an oral delivery dosage form that can precisely target a therapeutically active agent beyond the duodenum without prematurely delivering drugs to the upper GI tract. The compositions according to the invention have delayed-release forms controlled by an enteric coating and, in some disclosures, the tablet core dissolution rate, and can reach beyond the distal part of the duodenum such as the jejunum and/or ileum and/or colon. Such

oral dosage forms can be advantageous in a number of ways. In some disclosures, such dosage forms can be used to minimize degradation and absorption through the upper GI tract and maximize the amount of therapeutically active agent delivered beyond the duodenum, for example, in the jejunum, ileum or colon. For peptide drugs, such oral dosage forms can be used to maximize overall systemic absorption of these active agents. As one skilled in the art will appreciate, by avoiding exposure of the protein or peptide active agents to the upper GI tract, intraluminal degradation and breakdown of the peptide active agents can be minimized to a large extent.

[0050] One of the conventional formulation principles was to make a tablet which dissolved as rapidly as possible after passage through the stomach. That principle was derived, in part, from the expectation that a very fast, concentrated release of the drug and enhancers as a concentrated bolus in the duodenum would result in the highest absorption and that variability would be reduced as a consequence of those higher overall bioavailabilities. The experimental data described herein, however, showed an unexpected and surprising trend in that the solid oral dosage form (e.g. tablet) which was slowest to open and dissolve showed the greatest active agent absorption with the most precise individual absorptions. While the rapidly dissolving formulation can have a highest individual absorption, the average and median %F values can be lower and less precise, when compared to the slow dissolution dosage form. Without being bound by the theory, the experimental data suggest that a longer lag time before dissolution, might moderate the extreme high and low absorption values commonly observed with conventional and more rapidly dissolving tablets.

[0051] In some disclosures, the acid-resistant coat thickness, the coat's buffer capacity, the composition of the core, or a combination thereof can be used to maximize the systemic bioavailability of the active agent by controlling key attributes of the dosage form, specifically:

1. 1. T_{lag} - the time delay between oral dose administration and the first measurable concentration of the active agent in systemic circulation
2. 2. T_{max} - the time at which the maximum concentration of API (C_{max}) is in systemic circulation
3. 3. The chemical nature of the permeation enhancer employed, specifically, the critical micelle concentration (CMC). The CMC is the concentration below which the surface tension of the aqueous phase remains linearly dependent of the concentration of surfactant, and at which the surfactant solution equilibrium favors surfactant monomers vs. micelles. Thus, free surfactant is available in solution to interact with the API and/or GIT.

[0052] In some disclosures, the dosage forms are designed to ensure that the active ingredients (e.g. API, absorption enhancer(s)) are released prior to entering the colon, based on the typical ranges of GIT transit times in humans. Absorption in the colon is very limited, the water content is low (which may retard dissolution of the tablet), and the dosage form may

become entrapped in fecal matter and so be physically unable to deliver the API and enhancers.

[0053] In some-disclosures, the T_{lag} is higher (e.g. at least about 0.5 h higher) than dosage forms having a conventional core and/or enteric coating. In some-disclosures, the T_{max} is greater than $(T_{lag}+0.5 \text{ h})$. In some disclosures, (a) the T_{lag} of the solid oral dosage form is about 1.0 h, or greater than about 1.0 h, and less than about 16 h post-administration; and (b) the T_{max} is greater than $T_{lag}+0.5 \text{ h}$ and less than 20 h post-administration. In some disclosures, the T_{lag} of the solid oral dosage greater than 1.5 h and less than about 16 h. In some disclosures, the T_{lag} of the solid oral dosage greater than 2.0 h and less than about 16 h. In some disclosures, the T_{max} is greater $T_{lag}+1.0 \text{ h}$ and less than 20 h post-administration. In some disclosures, the T_{max} is greater $T_{lag}+1.5 \text{ h}$ and less than 20 h post-administration. In some disclosures, the T_{max} is greater $T_{lag}+2.0 \text{ h}$ and less than 20 h post-administration. In some disclosures, (a) the T_{lag} of the solid oral dosage form is greater than about 1.0 h, and less than about 16 h post-administration; and (b) the T_{max} is greater 1.5 h and less than 20 h post-administration. In some disclosures, (a) the T_{lag} of the solid oral dosage form is greater than about 1.0 h, and less than about 16 h post-administration; and (b) the T_{max} is greater 2 h and less than 20 h post-administration. In some disclosures, (a) the T_{lag} of the solid oral dosage form is greater than about 1.0 h, and less than about 16 h post-administration; and (b) the T_{max} is greater 3 h and less than 20 h post-administration. In some disclosures, (a) the T_{lag} of the solid oral dosage form is greater than about 1.5 h, and less than about 16 h post-administration; and (b) the T_{max} is greater 2 h and less than 20 h post-administration. In some disclosures, (a) the T_{lag} of the solid oral dosage form is greater than about 1.5 h, and less than about 16 h post-administration; and (b) the T_{max} is greater 2.5 h and less than 20 h post-administration. In some disclosures, (a) the T_{lag} of the solid oral dosage form is greater than about 1.5 h, and less than about 16 h post-administration; and (b) the T_{max} is greater 3 h and less than 20 h post-administration. In some disclosures, (a) the T_{lag} of the solid oral dosage form is greater than about 2.0 h, and less than about 16 h post-administration; and (b) the T_{max} is greater 2.5 h and less than 20 h post-administration. In some disclosures, (a) the T_{lag} of the solid oral dosage form is greater than about 2.0 h, and less than about 16 h post-administration; and (b) the T_{max} is greater 3.0 h and less than 20 h post-administration. In some disclosures, (a) the T_{lag} of the solid oral dosage form is greater than about 2.0 h, and less than about 16 h post-administration; and (b) the T_{max} is greater 3.5 h and less than 20 h post-administration. In some disclosures, (a) the T_{lag} of the solid oral dosage form is greater than about 2.0 h, and less than about 16 h post-administration; and (b) the T_{max} is greater 4.0 h and less than 20 h post-administration.

[0054] Without being bound to the theory, the widths of these ranges can be necessary to allow for the release of the API and absorption enhancers in the appropriate segment of the intestine best suited to absorb a particular API (which can depend on the physical and

chemical nature of the API itself).

Enteric coat

[0055] In some disclosures, the solid dosage form can comprise an enteric coat surrounding the core of the dosage form. In some disclosures, the enteric coat can comprise polymers having pH- dependent release properties and lag time properties (delayed-release). In some disclosures, the dissolution profiles of the solid oral dosage form (e.g. tablets) can have a suitable enteric coat film layer thickness resulting in high average systemic bioavailability with improved precision. In some disclosures, the dosage form comprises from about 5 mg/cm² to 25 mg/cm² of an enteric coating. In some disclosures, the dosage form comprises from about 10 mg/cm² to 25 mg/cm² of an enteric coating. In some disclosures, the dosage form comprises from about 15 mg/ cm² to 25 mg/cm² of an enteric coating. In some disclosures, the dosage form comprises from about 20 mg/cm² to 25 mg/cm² of an enteric coating. In some disclosures, the dosage form comprises from about 5 mg/ cm² to 20 mg/cm² of an enteric coating. In some disclosures, the dosage form comprises from about 5 mg/cm² to about 15 mg/cm² of an enteric coating. In some disclosures, the dosage form comprises from about 5 mg/cm² to 10 mg/cm² of an enteric coating. In some disclosures, the solid oral dosage form can have about 15 mg/cm² enteric coat or an enteric coat corresponding to about 10% weight gain. In some disclosures, the dosage form comprises from about 10 mg/cm² to 15 mg/cm² of an enteric coating. In some disclosures, the dosage form comprises from about 10 mg/cm² to 20 mg/cm² of an enteric coating. In some disclosures, the dosage form comprises from about 15 mg/cm² to 20 mg/cm² of an enteric coating. In some disclosures, the dosage form comprises an enteric coating corresponding to about 7% weight gain. In some disclosures, the dosage form comprises an enteric coating corresponding to about 10% weight gain. In some disclosures, the dosage form comprises an enteric coating corresponding to about 15% weight gain. In some disclosures, the dosage form comprises an enteric coating corresponding to about 20% weight gain. In some disclosures, the dosage form comprises an enteric coating corresponding to about 5% weight gain. In some disclosures, the dosage form comprises from about 15 mg/ cm² enteric coat or an enteric coat corresponding to about 10% weight gain.

[0056] In some disclosures, bioavailabilities between about 1-20% with CVs in the about 50-60% can be achieved. In some disclosures, bioavailabilities between about 0.1-60% with CVs in the about 10-160% can be achieved. In some disclosures, bioavailabilities between 10-20% can be achieved. In some disclosures, bioavailabilities between 10-30% can be achieved. In some disclosures, bioavailabilities between 10-40% can be achieved. In some disclosures, bioavailabilities between 10-50% can be achieved. In some disclosures, bioavailabilities between 10-60% can be achieved. In some disclosures, bioavailabilities between 1-20% can be achieved. In some disclosures, bioavailabilities between 1-30% can be achieved. In some

disclosures, bioavailabilities between 1-40% can be achieved. In some disclosures, bioavailabilities between 1-50% can be achieved. In some disclosures, bioavailabilities between 1-60% can be achieved. In some disclosures, bioavailabilities between 20-30% can be achieved. In some disclosures, bioavailabilities between 20-40% can be achieved. In some disclosures, bioavailabilities between 20-50% can be achieved. In some disclosures, bioavailabilities between 20-60% can be achieved. In some disclosures, bioavailabilities between 30-40% can be achieved. In some disclosures, bioavailabilities between 30-50% can be achieved. In some disclosures, bioavailabilities between 30-60% can be achieved. In some disclosures, bioavailabilities between 40-50% can be achieved. In some disclosures, bioavailabilities between 40-60% can be achieved.

[0057] Without being bound by the theory, it is believed that the thickness of the coating material, and thus longer lag time before dissolution, can moderate the extreme high and low absorption values commonly observed with the more lightly coated and therefore more rapidly dissolving tablets.

[0058] In some disclosures, the dosage forms can be coated with an acid-resistant enteric coating, which differ in thickness and/or buffer capacity. As used herein, the term "buffer capacity" means the number of equivalents of base required to initiate dissolution of the enteric coat. The lower the pH of the enteric coating, the higher the buffer capacity is and vice-versa. Dosage forms with thick (e.g. about 7 to about 20% w/w) enteric coats and/or enhanced buffer capacity (e.g. pH of about 2.3 to about 4.7) are expected to open later in the gastrointestinal tract, and hence have a larger value of T_{lag} relative to tablets coated with thinner enteric coat and/or decreased buffer capacity (e.g. pH of about 4.8 to about 5.4). In some disclosures, dosage forms with about 10% w/w enteric coats and/or enhanced buffer capacity (e.g. about pH 2.3) are expected to open later in the gastrointestinal tract, and hence have a larger value of T_{lag} relative to tablets coated with thinner (e.g. about 6% w/w) enteric coat and/or decreased buffer capacity (about pH 5.2-5.3).

[0059] In some disclosures, the dosage form comprises a mixture of an enteric coat which dissolves at about pH 5.5 and above and of an enteric coat which dissolves at about pH 7.4 and above. In some disclosures, the enteric coat can comprise acrylate copolymers or mixtures thereof. In some disclosures, such mixtures can delay an onset of dissolution further down the small intestine. In some disclosures, the enteric coat can comprises a mixture of Eudragit® FS 30 D and Eudragit® L 30 D-55. EUDRAGIT® FS 30 D is a methyl acrylate, methyl methacrylate and methacrylic acid copolymer, which is soluble at pH above 7.0. Eudragit® L 30 D-55 is a poly(methacrylic acid-co-ethyl acrylate) copolymer which is soluble at pH above 5.5. For example, the enteric coat can comprise a mixture of Eudragit® FS 30 D: Eudragit® L 30 D-55 at a ratio of about 75:25 to 95:5. In some disclosures, the enteric coat can comprise a mixture of Eudragit® FS 30 D: Eudragit® L 30 D-55 at a ratio of about 75:25. In some disclosures, the enteric coat can comprise a mixture of Eudragit® FS 30 D: Eudragit® L 30 D-55 at a ratio of about 80:20. In some disclosures, the enteric coat can comprise a mixture of

Eudragit® FS 30 D: Eudragit® L 30 D-55 at a ratio of about 90:10.

Core

[0060] Disclosed is a dosage form that contains a core comprising an active pharmaceutical agent, at least one pH-lowering agent, at least one permeation enhancer, the core being enveloped by an acid-resistant protective coat and a water-soluble barrier layer. In some disclosures, the dosage form may comprise one or more of fillers, binders, glidants, lubricants, etc. suitable for manufacturing the final dosage form.

[0061] In some disclosures, the dosage form comprises an active agent, a pH-lowering agent, and an absorption enhancer. In some disclosures, the cores of the dosage form can include a filler/binder, and can include or be free a disintegrant, in order to vary the rate of release of the peptide and enhancing agents.

[0062] To achieve delayed dissolution and desired release profile, solid oral dosage form can include one or more of the following: (1) a core having a filler containing a hydrogel-forming polymer (e.g., HPC or HPMC), where a 2% solution of the polymer under standard conditions has a viscosity between 3,000 to 120,000 cP at 20°C; (2) a core substantially free of disintegrant; (3) an adequate enteric coat film thickness as described herein.

[0063] As used herein, the term "substantially" when used in a negative connotation refers to the complete or near complete lack of ingredient, structure characteristic, property, state, or result. For example, a composition that is "substantially free of" disintegrant would either completely lack disintegrant, or so nearly completely lack disintegrant that the effect would be the same as if it completely lacked disintegrant.

[0064] In some disclosures, the solid oral dosage form may include a reduced amount of disintegrant. In some disclosures, the solid oral dosage comprises less than 10% wt, less than 9% wt, less than 8% wt, less than 7% wt, less than 6% wt, less than 5% wt, less than 4% wt, less than 3.5% wt, less than 3% wt, less than 2.5% wt, less than 2% wt, less than 1.5% wt, less than 1% wt, less than 0.5% wt, less than 0.01% wt, less than 0.001%wt disintegrant. In some disclosures, the solid oral dosage does not include a tablet disintegrant.

[0065] In some disclosures, the solid oral dosage form may include a hydroxypropyl cellulose (HPC) filler, a hydroxypropyl methyl cellulose (HPMC) filler and/or other viscous additive, to slow the disintegration of the tablet core after the coating film layers dissolve.

[0066] In some disclosures, the solid oral dosage form may include one or more of the following (1) an enteric coat film layer thickness (about 15 mg/cm², or approximately 10% weight gain) and (2) a reduced amount of disintegrant or be substantially free of disintegrant, and (3) a viscous additive (e.g., but not limited to, a HPC or a HPMC filler).

[0067] In some disclosures, the solid oral dosage form may include (1) a mixture of Eudragit® L 30 D-55 and Eudragit® FS 30 D; (2) a reduced amount of tablet disintegrant or be substantially free of disintegrant, (3) and a viscous additive (e.g., but not limited to, a HPC or a HPMC filler).

[0068] In some disclosures, the filler/binder can include one or more of microcrystalline cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, and chitosan. As one of skilled in art would appreciate, chitosan is polymer with a mucoadhesive effect. In some disclosures, chitosan is present in up to about 10% by weight, up to about 15% by weight, up to about 20% by weight, up to about 25% by weight, up to about 30% by weight, up to about 35% by weight, up to about 40% by weight, so that the formulation becomes mucoadhesive. In some disclosures, the filler/binder can include a filler that do not modify viscosity, but modify the release of the API by other physical and/or chemical interactions (e.g. slow solubility). In some disclosures, the filler/binder can include a pharmaceutically acceptable wax (e.g., carnauba wax), gum (e.g., acacia, guar), alginic acid or salt thereof (e.g., sodium alginate), or hyaluronic acid. A slower release rate from the dosage form is expected to cause a delay in T_{max} .

[0069] In some disclosures, the filler/binder can include one or more of microcrystalline cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, chitosan, a pharmaceutically acceptable wax (e.g., carnauba wax), gum (e.g., acacia, guar), alginic acid or salt thereof (e.g., sodium alginate), and hyaluronic acid.

[0070] In some disclosures, the dosage forms can contain a permeation enhancer having a high critical micelle concentration (CMC) resulting in stronger surfactant properties. For example, the dosage forms can contain a permeation enhancer having a critical micelle concentration (CMC) of about 1.0 to about 40 mM. In some disclosures, the dosage forms contain a permeation enhancer having a critical micelle concentration (CMC) of about 1.0 to about 15 mM. In some disclosures, the permeation enhancer is sodium dodecyl sulphate SDS or a pharmaceutically acceptable surfactant having similar CMC.

[0071] In some disclosures, the dosage forms can be coated with an acid-resistant enteric coating, which different thickness and buffer capacity. Dosage forms with thick (e.g. about 10% w/w to about 20% w/w) enteric coats and/or enhanced buffer capacity (e.g. pH of about 2.3 to about 4.7) are expected to open later in the gastrointestinal tract, and hence have a larger value of T_{lag} relative to tablets coated with thinner (e.g. 6% w/w or lower) enteric coat and/or decreased buffer capacity (pH about 4.8-5.4).

[0072] In some disclosures, the systemic bioavailability of the active agent can be modulated by controlling the T_{lag} and T_{max} of the dosage form. In some disclosures, a longer T_{lag} can be achieved by increasing the thickness or buffer capacity of the enteric coat. In some disclosures, a longer T_{max} can be achieved by increasing the viscosity of the tablet core through the use of viscous fillers (HPC, HPMC, chitosan) in the absence of a disintegrant. In

some disclosures, a sufficient amount of active agent is included in the dosage form of the invention to achieve a therapeutically relevant level.

[0073] In some disclosures, the systemic bioavailability of the active agent can be increased by one or a combination of the following (1) increasing the T_{lag} (the time delay between oral dose administration and the first measurable concentration of the active agent in systemic circulation), (2) increasing T_{max} , and/or (3) increasing the surfactant strength of the permeation enhancer.

[0074] In some disclosures, T_{lag} can be increased by increasing the thickness and/or the buffer capacity of the enteric coat. In some disclosures, T_{max} can be increased by increasing the viscosity of the core of the dosage form. In some disclosures, the surfactant can comprise a surfactant having CMC of about 1.0 mM to about 40 mM.

Peptides

[0075] In some disclosures, the peptide compound is a compound that includes a plurality of amino acids and at least one peptide bond in its molecular structure. In some disclosures, the molecular weight of the peptide compound ranges from about 500 Daltons up to about 10,000 Daltons. In some disclosures, the peptide compound is a peptide hormone or analogue thereof. In some disclosures, the hormone or analogue thereof is selected from triptorelin, leuporelin and goserelin. In some embodiments, the hormone analogue is leuporelin.

[0076] Peptide compounds which may benefit from oral delivery in accordance with the present disclosure include any therapeutic agent that is physiologically active and has, as part of its molecular structure, a plurality of amino acids and at least one peptide bond. The terms "polypeptide," "peptide" and "protein" are used interchangeably herein to refer to a polymer of amino acid residues. The terms apply to naturally occurring amino acid polymers as well as amino acid polymers in which one or more amino acid residues are a non-natural amino acid. Additionally, such "polypeptides," "peptides" and "proteins" include amino acid chains of any length, including full length proteins, wherein the amino acid residues are linked by covalent peptide bonds. In some disclosures, the peptides can be cyclic peptides.

[0077] A "non-natural amino acid" refers to an amino acid that is not one of the 20 common amino acids, namely alanine, cysteine, aspartic acid, glutamic acid, phenylalanine, lysine, histidine, isoleucine, lysine, leucine, methionine, asparagine, proline, glutamine, arginine, serine, threonine, valine, tryptophan, and tyrosine, or pyrrolysine or selenocysteine. Other terms that may be used synonymously with the term "non-natural amino acid" is "non-naturally encoded amino acid," "unnatural amino acid," "non-naturally-occurring amino acid." The term "non-natural amino acid" includes, but is not limited to, amino acids which occur naturally by modification of a naturally encoded amino acid (including but not limited to, the 20 common amino acids or pyrrolysine and selenocysteine) but are not themselves incorporated into a

growing polypeptide chain by the translation complex. Examples of naturally-occurring amino acids that are not naturally-encoded include, but are not limited to, N-acetylglucosaminy-L-serine, N-acetylglucosaminy-L-threonine, and O-phosphotyrosine. Additionally, the term "non-natural amino acid" includes, but is not limited to, amino acids which do not occur naturally and may be obtained synthetically or may be obtained by modification of non-natural amino acids. Non-natural amino acids can include amino acids containing the D-isomer configuration since most proteins are comprised primarily or entirely of amino acids in the L-isomer configuration. Peptides containing non-natural amino acids, such as D-amino acids and those including substituted side chains can exhibit improved stability in the gastrointestinal tract as a result of reduced proteolysis.

[0078] In some disclosures, peptides can be distinguished from proteins on the basis of size, and as an arbitrary benchmark can be understood to contain approximately 90 or fewer amino acids. In some disclosures, a peptide of the present disclosure includes fewer than 10 amino acids, such as 9 amino acids. In some disclosures, a peptide of the present disclosure includes between about 10 amino acids and about 90 amino acids. In some disclosures, a peptide of the present disclosure includes between about 15 amino acids and about 85 amino acids. In some disclosures, a peptide of the present disclosure includes between about 20 amino acids and about 80 amino acids. In some disclosures, a peptide of the present disclosure includes between about 25 amino acids and about 75 amino acids. In some disclosures, a peptide of the present disclosure includes between about 30 amino acids and about 70 amino acids. In some disclosures, a peptide of the present disclosure includes between about 35 amino acids and about 65 amino acids. In some disclosures, a peptide of the present disclosure includes between about 40 amino acids and about 60 amino acids. In some disclosures, the molecular weight of the peptide compound ranges from about 1000 Daltons up to about 10,000 Daltons. In some disclosures of the present disclosure, degradation of the active ingredients by protease is suppressed by several mechanisms that would otherwise tend to cleave one or more of the peptide bonds of the active ingredient. In addition to natural amino acids, the amino acids may be D-amino acids or unnatural amino acids, some examples of which are discussed infra. The molecular structure may further include other substituents or modifications. For example, if the peptide active ingredient is salmon calcitonin, the salmon calcitonin may be amidated at its C-terminus. Some peptides may be amidated at locations that are not amidated in nature, or may be otherwise modified.

[0079] Peptide active ingredients of the present disclosure include, but are not limited to, leuprolide, insulin, vasopressin, calcitonin, calcitonin gene-related peptide, parathyroid hormone, desmopressin, gonadotrophin releasing hormone (GnRH) luteinizing hormone-releasing factor adrenocorticotropin enkephalin, glucagon-like peptide-1 (GLP-1), 2,6-dimethyltyrosine-D-arginine-phenylalanine-lysine amide (DMT-DALDA) and triptorelin.

[0080] In some disclosures, a solid oral dosage form of the present disclosure includes a peptide active ingredient selected from insulin and,

[0081] In some disclosures, the hormone or analogue thereof is selected from a triptorelin,

leuporelin and goserelin. As used herein, the term "leuprolide" refers to leuporelin or leuprolide acetate. Leuprolide acetate is a synthetic nonapeptide agonist analog of luteinizing hormone-releasing factor. When leuprolide is used, it preferably comprises from about 0.01% (w/w) to about 20.0% (w/w) by weight relative to the total weight of the overall solid oral dosage form (exclusive of any acid-resistant protective coating). In some embodiments, about 0.1% (w/w) to about 15.0% (w/w) of leuprolide is present in the solid oral dosage form (exclusive of any acid-resistant protective coating). In some embodiments, about 1.0% (w/w) to about 10.0% (w/w) of leuprolide is present in the solid oral dosage form (exclusive of any acid-resistant protective coating). Leuprolide acetate is commercially available (for example, from BACHEM, Torrance, Calif.).

The pH-Lowering Agent (Acid)

[0082] Proteolytic enzymes of both the stomach and intestines may degrade peptides, rendering them inactive before they can be absorbed into the bloodstream. Any amount of peptide that survives proteolytic degradation by proteases of the stomach (typically having acidic pH optima) is later confronted with proteases of the small intestine and enzymes secreted by the pancreas (typically having neutral to basic pH optima). Proteolytic degradation of peptides may contribute to limited systemic bioavailability of the peptide.

[0083] The acid is believed to lower the local intestinal pH (where the active agent has been released) to levels below the optimal range for many intestinal proteases. It is believed that this decrease in pH reduces the proteolytic activity of the intestinal proteases, thus affording protection to the peptide from potential degradation. The activity of these proteases is diminished by the temporarily acidic environment provided by the invention.

[0084] The total amount of the pH-lowering agent to be administered with each administration of peptide active ingredient should preferably be an amount which, when it is released into the intestine, is sufficient to lower the local intestinal pH substantially below the pH optima for proteases found there. The quantity required will necessarily vary with several factors including the type of pH-lowering agent used (discussed in section "pH-lowering agent") and the equivalents of protons provided by a given pH-lowering agent. In practice, the amount of pH-lowering agent expected to provide good bioavailability is an amount which, if the pharmaceutical composition of the invention were added to a solution of 10 milliliters of 0.1 M sodium bicarbonate, would lower the pH of that sodium bicarbonate solution to no higher than 5.5, and preferably no higher than 4.7, most preferably no higher than 3.5. The foregoing test for sufficient acidity is referenced elsewhere herein as "sodium bicarbonate test" and assumes sufficient passage of time for substantially complete dissolution of the pharmaceutical composition and intermixing thereof with the sodium bicarbonate solution.

[0085] In some disclosures, the amount of pH-lowering agent used in a solid oral dosage form of the present disclosure ranges from about 50 milligrams up to about 500 milligrams. In some disclosures, the amount of pH-lowering agent used in a solid oral dosage form of the present

[illegible]

[illegible]

some disclosures, the amount of pH-lowering agent used in a solid oral dosage form of the present disclosure is about 150 milligrams. In some disclosures, the amount of pH-lowering agent used in a solid oral dosage form of the present disclosure is about 175 milligrams. In some disclosures, the amount of pH-lowering agent used in a solid oral dosage form of the present disclosure is about 200 milligrams. In some disclosures, the amount of pH-lowering agent used in a solid oral dosage form of the present disclosure is about 225 milligrams. In some disclosures, the amount of pH-lowering agent used in a solid oral dosage form of the present disclosure is about 250 milligrams. In some disclosures, the amount of pH-lowering agent used in a solid oral dosage form of the present disclosure is about 300 milligrams. In some disclosures, the amount of pH-lowering agent used in a solid oral dosage form of the present disclosure is about 325 milligrams. In some disclosures, the amount of pH-lowering agent used in a solid oral dosage form of the present disclosure is about 350 milligrams. In some disclosures, the amount of pH-lowering agent used in a solid oral dosage form of the present disclosure is about 375 milligrams. In some disclosures, the amount of pH-lowering agent used in a solid oral dosage form of the present disclosure is about 400 milligrams. In some disclosures, the amount of pH-lowering agent used in a solid oral dosage form of the present disclosure is about 425 milligrams. In some disclosures, the amount of pH-lowering agent used in a solid oral dosage form of the present disclosure is about 450 milligrams. In some disclosures, the amount of pH-lowering agent used in a solid oral dosage form of the present disclosure is about 475 milligrams. In some disclosures, the amount of pH-lowering agent used in a solid oral dosage form of the present disclosure is about 500 milligrams or higher. The foregoing preferences relate to the total combined weight of all pH-lowering agents where two or more of such agents are used in combination.

[0086] The pH-lowering agent of the invention may be any pharmaceutically acceptable compound selected from citric acid, tartaric acid and a combination thereof that is not toxic in the gastrointestinal tract and is capable of either delivering hydrogen ions (a traditional acid) or of inducing higher hydrogen ion content from the local environment. It may also be any combination of such compounds. In some disclosures, the at least one pH-lowering agent has a pKa no higher than 4.2, or no higher than 3.0. In some disclosures, the pH lowering agent has a solubility in water of at least 30 grams per 100 milliliters of water at room temperature. In some disclosures, organic acids are used.

[0087] Any combination of pH lowering agents that achieves the required pH level of no higher than 5.5 in the sodium bicarbonate test discussed supra may be used. Some disclosures utilize, as at least one of the pH-lowering agents of the pharmaceutical composition, an acid selected from the group consisting of citric acid, tartaric acid and an acid salt of an amino acid.

[0088] In some disclosures, regardless of the acid chosen, the acid is in the form of acid particles coated with a protective coating discussed in a separate section, infra.

[0089] In some disclosures, the weight ratio of pH-lowering agent to the API can be from 0.1:1 to 10,000:1. In some disclosures, the weight ratio of pH-lowering agent to the API can exceed 20:1, 200:1, or 800:1 or 2000:1.

Water Soluble Barrier Layer

[0090] The water soluble barrier layer can be comprised of a compound that is water soluble in both acidic and basic environments. Examples of compounds useful for this purpose include but are not limited to hydroxypropylmethylcellulose, hydroxypropylcellulose, methylcellulose and polyvinylpyrrolidone. Preferably, water solubility is at least one gram, more preferably at least 11 grams, per 100 milliliters at room temperature. Polyvinylpyrrolidone is preferred in some disclosures. In some disclosures water solubility, at both pH 6.0 and pH 8.0, is in excess of 12 grams per 100 milliliters of water at room temperature. Good solubility in both acid and basic pH aids desirable quick dissolution in the intestinal region where pH is generally basic, but where the pharmaceutical composition's release of significant quantities of acid might at least temporarily impede dissolution of a material that was not also readily soluble in an aqueous acid environment. In some disclosures, the water-soluble barrier layer is present at a weight which is from about 7.0% to about 12.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the water-soluble barrier layer is present at a weight of about 7.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the water-soluble barrier layer is present at a weight of about 12.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the water-soluble barrier layer is present at a weight of from about 6.0% to about 15.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the water-soluble barrier layer is present at a weight of about 13.0% to about 15.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the water-soluble barrier layer is present at a weight of from about 12 to about 19 mg/cm².

Coated Acid Particles

[0091] In some disclosures, the acid is provided, at least in part, by acid particles coated with a protective coating to reduce undesirable acid interaction with other components of the formulation, such as the peptide active agent and the outer enteric coating. In some disclosures, the coating is an hydrophilic coating. In some disclosures, the coating is water soluble coating.

[0092] When coated acid particles are used, the particles are coated with a pharmaceutically acceptable protective coating that is non-acidic and preferably has a solubility in water of at least one gram, and preferably at least 10 grams, per 100 milliliters of water at room temperature. As the coating is for the purpose of reducing acid interaction with other components of the pharmaceutical composition, it is important that the coating not itself be acidic such that its own acidity could undesirably cause some of the acid interactions that it is the coating's purpose to prevent.

[0093] Appropriate coating materials include but are not limited to monosaccharides (e.g. glucose and fructose), polysaccharides (e.g. maltodextrin), and acid salts (e.g. sodium citrate). When acid salts are used, it is preferred, but not required, that they be salts of the acid being coated (e.g., sodium citrate-coated citric acid particles). In some disclosures, coated citric acid particles used in a solid dosage form of the present disclosure are Citro DC available from Jungbunzlauer. Citro DC is a direct compressible type of citric acid coated with a thin layer of maltodextrin. In some disclosures, coated citric acid particles used in a solid dosage form of the present disclosure are CITROCOAT® N available from Jungbunzlauer. When used as the acid, citric acid or other organic acids can be coated by spraying a coating solution which contains, for example, glucose or sodium citrate onto granules of an organic acid in a fluid-bed dryer. Coatings discussed herein may be used on particles of other acids discussed herein.

[0094] Preferred average size of the acid-coated particles is from 30 mesh to 140 mesh.

Absorption/permeation Enhancer

[0095] An absorption enhancer (also referred herein as permeation enhancer) is included in the solid oral dosage form. The absorption enhancers can be present in a quantity that constitutes from 0.1 to 20.0 percent by weight, relative to the overall weight of the solid oral dosage form (exclusive of any enteric coating). In some disclosures, absorption enhancers can be surface active agents which act both as solubility enhancers and uptake enhancers. Generically speaking, "solubility enhancers" improve the ability of the components of the disclosure to be solubilized in either the aqueous environment into which they are originally released or into the lipophilic environment of the mucous layer lining the intestinal walls, or both. "Transport (uptake) enhancers" (which are frequently the same surface active agents used as solubility enhancers) are those which facilitate the ease by which API cross the intestinal wall.

[0096] One or more absorption enhancers may perform one function only (e.g., solubility), or one or more absorption enhancers may perform the other function only (e.g., uptake), within the scope of the disclosure. It is also possible to have a mixture of several compounds some of which provide improved solubility, some of which provide improved uptake and/or some of which perform both functions. Without intending to be bound by theory, it is believed that uptake enhancers may act by (1) increasing disorder of the hydrophobic region of the membrane exterior of intestinal cells, allowing for increased transcellular transport; or (2) leaching membrane proteins resulting in increased transcellular transport; or (3) widening the pore radius between cells for increased paracellular transport.

[0097] Surface active agents are believed to be useful both as solubility enhancers and as uptake enhancers. For example, detergents are useful in (1) solubilizing all of the active components quickly into the aqueous environment where they are originally released, (2) enhancing lipophilicity of the components of the disclosure, especially the API, aiding its

passage into and through the intestinal mucus, (3) enhancing the ability of the normally polar API to cross the epithelial barrier of the brush border membrane; and (4) increasing transcellular and/or paracellular transport as described above.

[0098] Surface active agents used as the absorption enhancers can be free flowing powders for facilitating the mixing and loading of during the manufacturing process. Because of inherent characteristics of some peptide active ingredients (e.g., their isoelectric point, molecular weight, amino acid composition, etc.) certain surface active agents interact best with certain peptides. The surface active agent used as an absorption enhancer may be selected from the group consisting of (i) anionic surface active agents, (ii) cationic surface agents, (iii) mixtures of anionic surface active agents (especially those having linear hydrocarbon regions) together with negative charge neutralizers. Negative charge neutralizers include but are not limited to acyl carnitines, cetyl pyridinium chloride, and the like. In some disclosures, the anionic surface active agent is one of a cholesterol derivative (e.g., bile acids), sodium lauryl sulfate (SLS, also known as Sodium dodecyl sulfate (SDS)) or a combination thereof. In some disclosures, the cationic surface agent is an acylcamitine or the like.

[0099] In some disclosures, the absorption enhancer is soluble at acid pH, particularly in the 3.0 to 5.0 range.

[0100] In some disclosures, a mixture of cationic surface active agents and anionic surface active agents that are cholesterol derivatives, both of which are soluble at acid pH, are used.

[0101] In some disclosures, an acid soluble bile acid is used together with a cationic surface active agent. In some disclosures, an acyl carnitine and a sucrose ester is used. In some disclosures, when a particular absorption enhancer is used alone, it is a cationic surface active agent. Acyl carnitines (e.g., lauroyl carnitine), phospholipids and bile acids are particularly good absorption enhancers, especially acyl carnitine. Anionic surfactants such as cholesterol derivatives or SLS are also used in some disclosures, Sodium lauryl sulfate is an hydrophobic surfactant. In some disclosures, the permeation enhancer is sodium dodecyl sulphate (SDS) or a pharmaceutically acceptable surfactant having suitable CMC.

[0102] It is the intent of these preferences to avoid interactions with the API that interfere with absorption of active ingredient into the blood. For example, the API may become entrapped in micelles of the surfactant, and thus physically unavailable for permeation across the intestinal epithelium.

[0103] To reduce the likelihood of side effects, preferred detergents, when used as the absorption enhancers of the disclosure, are either biodegradable or reabsorbable (e.g. biologically recyclable compounds such as bile acids, phospholipids, and/or acyl carnitines), preferably biodegradable. Acyl carnitines are believed particularly useful in enhancing paracellular transport. When a bile acid (or another anionic detergent lacking linear hydrocarbons) is used in combination with a cationic detergent, some peptides, such as salmon calcitonin, can be better transported both to and through the intestinal wall. In some

disclosures, and without intending to be bound by theory, cationic ion exchange agents (e.g. detergents) are included to provide solubility enhancement by another possible mechanism. In particular, they may prevent the binding of the peptide active ingredient to mucus. Preferred cationic ion exchange agents include protamine chloride or any other polycation.

[0104] Preferred absorption enhancers include one or more of: (a) salicylates such as sodium salicylate, 3-methoxysalicylate, 5-methoxysalicylate and homovanilate; (b) bile acids such as taurocholic, tauorodeoxycholic, deoxycholic, cholic, glycholic, lithocholate, chenodeoxycholic, ursodeoxycholic, ursocholic, dehydrocholic, fusidic, etc.; (c) non-ionic surfactants such as polyoxyethylene ethers (e.g. Brij 36T, Brij 52, Brij 56, Brij 76, Brij 96, Texaphor A6, Texaphor A14, Texaphor A60 etc.), p-t-octyl phenol polyoxyethylenes (Triton X-45, Triton X-100, Triton X-114, Triton X-305 etc.) nonylphenoxypolyoxyethylenes (e.g. Igepal CO series), polyoxyethylene sorbitan esters (e.g. Tween-20, Tween-80 etc.); (d) anionic surfactants such as dioctyl sodium sulfosuccinate; (e) lyso-phospholipids such as lysolecithin and lysophosphatidylethanolamine; (f) acylcarnitines, acylcholines and acyl amino acids such as lauroyl-L-carnitine, myristoylcarnitine, palmitoylcarnitine, lauroylcholine, myristoylcholine, palmitoylcholine, hexadecyllysine, N-acylphenylalanine, N-acylglycine etc.; (g) water soluble phospholipids such as diheptanoylphosphatidylcholine, dioctylphosphatidylcholine etc.; (h) medium-chain glycerides which are mixtures of mono-, di- and triglycerides containing medium-chain-length fatty acids (caprylic, capric and lauric acids); (i) ethylene-diaminetetraacetic acid; (j) cationic surfactants such as cetylpyridinium chloride; (k) fatty acid derivatives of polyethylene glycol such as Labrasol, Labrafac, etc.; (l) alkylsaccharides such as lauryl maltoside, lauroyl sucrose, myristoyl sucrose, palmitoyl sucrose, etc..., (m) sodium lauryl sulfate (SLS), or a pharmaceutically acceptable surfactant having similar CMC or any combinations of the foregoing.

Acid-Resistant Protective Vehicle

[0105] An acid-resistant protective vehicle can be utilized to separate the peptide compound from stomach proteases. Any carrier or vehicle that protects the peptide from stomach proteases and then dissolves so that the other ingredients of the invention may be released in the intestine is suitable. Examples include cellulose acetate phthalate, hydroxypropyl methylethylcellulose succinate, hydroxypropyl methylcellulose phthalate, carboxyl methylethylcellulose and methacrylic acid-methyl methacrylate copolymer. In some disclosures, the peptide, absorption enhancers such as solubility and/or uptake enhancer(s) (when included), chymotrypsin inhibitor, and pH-lowering agent(s), are included in a sufficiently viscous protective syrup to permit protected passage of the components of the invention through the stomach.

[0106] Suitable enteric coatings for protecting the peptide from stomach proteases may be applied, for example, to capsules after the remaining components of the invention have been loaded within the capsule. In other disclosures, enteric coating is coated on the outside of a tablet or coated on the outer surface of particles of active components which are then pressed

into tablet form, or loaded into a capsule, which is itself preferably coated with an enteric coating.

[0107] It is desirable that all components of the disclosure be released from the carrier or vehicle, and solubilized in the intestinal environment as simultaneously as possible. In some disclosures, the vehicle or carrier can release the active components in the small intestine where uptake enhancers that increase transcellular or paracellular transport are less likely to cause undesirable side effects than if the same uptake enhancers were later released in the colon. It is emphasized, however, that the present disclosure is believed effective in the colon as well as in the small intestine. In some disclosures, the acid resistant protective vehicle is present at a weight which is from about 3.0% to about 10.0% of the weight of the remainder of the solid oral dosage form (the "remainder" being the solid oral dosage form exclusive of enteric coating itself). In some disclosures, the acid resistant protective vehicle is present at a weight of about 3.6% of the weight of the remainder of the solid oral dosage form. In some disclosures, the acid resistant protective vehicle is present at a weight of about 7.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the acid resistant protective vehicle is present at a weight of about 10.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, a composition of the present disclosure is an enteric coated capsule that is sufficient to prevent breakdown of the solid oral dosage form of the disclosure in 0.1N HCl for at least two hours, then capable of permitting complete release of all contents of the solid oral dosage form within thirty minutes after pH is increased to 6.8 or pH 6.8 to 7.5 in a dissolution bath in which said composition is rotating at greater than 100 revolutions per minute hours. In disclosures in which the water-soluble barrier layer of the disclosure is used, less enteric coating may be required, sometimes less than the amount of water-soluble barrier layer.

[0108] In some disclosures, a composition of the present disclosure is an enteric coated tablet that is sufficient to prevent breakdown of the solid oral dosage form of the disclosure in 0.1N HCl for at least two hours, then capable of permitting complete release of all contents of the solid oral dosage form within thirty-sixty minutes after pH is increased to 6.8 (e.g. pH 6.8-7.5) in an apparatus 2 (paddle) in which said composition is rotating at greater than 100 revolutions per minute.

Filler

[0109] The filler is a hydroxypropylcellulose, or hydroxypropylmethylcellulose. To achieve the desired release profile, a high molecular weight (high viscosity) hydroxypropylcellulose (HPC) can be used. High molecular weight (high viscosity) hydroxypropylcellulose is known to effectively sustain the release of drugs. In some embodiments, the filler has a viscosity of about 3,000 to 120,000 cP at 20°C.

Optional Pharmaceutical Binder

[0110] In some disclosures, the solid oral dosage form is in tablet form and a pharmaceutical binder can be included in the solid oral dosage form. Preferred binders include but are not limited to KOLLIDON VA64, KOLLIDON VA64 fine, KOLLIDON 30, AVICEL PH-101, HPC, PHARMACOAT 606, and MALDEX.

Optional Pharmaceutical Disintegrant

[0111] In some disclosures, a pharmaceutical tablet is used as a preferred single oral dosage form. In some disclosures, a pharmaceutically acceptable disintegrant is included. Any disintegrant that performs the function of enhancing dissolution speed may be used. In some disclosures, the disintegrants include but are not limited to KOLLIDON CL, POLYPLASDONE, EXPLOTAB, and AC-DI-SOL, available from International Specialty Products, JRS Pharma and FMC Biopolymer, respectively. In some disclosures, the disintegrant is present in an amount between 1 and 15 percent by weight relative to the total tablet weight (%wt, when tablets are used), exclusive of any water-soluble barrier layer and any acid-resistant protective vehicle. In some disclosures, the solid oral dosage form may include a reduced amount of disintegrant. In some disclosures, the solid oral dosage comprises less than 4% wt, less than 3.5% wt, less than 3% wt, less than 2.5% wt, less than 2% wt, less than 1.5% wt, less than 1% wt, less than 0.5% wt, less than 0.01% wt, less than 0.001% wt disintegrant. In some disclosures, the solid oral dosage does not include a tablet disintegrant.

Optional Pharmaceutical Glidant

[0112] In some disclosures, a pharmaceutically acceptable glidant is included. Any glidant that performs the function of enhancing powder flow may be used. Preferred glidants include but are not limited to talc, calcium silicate, magnesium silicate, silicon dioxide. Preferably, the glidant is present in an amount between 0.1 and 2.0 percent by weight relative to the weight of the pharmaceutical composition, exclusive of any water-soluble barrier layer and any acid-resistant protective vehicle.

Optional Pharmaceutical Lubricant

[0113] In some disclosures, a pharmaceutically acceptable lubricant is included. Any lubricant that performs the function of preventing powder from sticking to the tooling may be used. Preferred lubricants include but are not limited to stearic acid, magnesium stearate, and hydrogenated vegetable oil type 1. In some disclosures, the lubricant is present in an amount between 0.2 and 5.0 percent by weight relative to the weight of the solid oral dosage form, exclusive of any water-soluble barrier layer and any acid-resistant protective vehicle.

Optional Antioxidant

[0114] In some disclosures, a pharmaceutically acceptable antioxidant is included. Any antioxidant that performs the function of preventing the oxidation of labile amino acids in peptides, such as methionine or tryptophan may be used. Preferred antioxidants include but are not limited to sodium pyruvate, derivatives of sodium pyruvate, ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, sodium bisulfite, and sodium metabisulfite. In some disclosures, the antioxidant is present in an amount between 0.5 and 5 mg per tablet.

Miscellaneous Other Optional Ingredients

[0115] In some disclosures, another peptide (such as albumin, casein, soy protein, other animal or vegetable proteins and the like) can be included to reduce nonspecific adsorption (e.g., binding of peptide to the intestinal mucus barrier) thereby lowering the necessary concentration of the expensive peptide active ingredient. When added, the peptide is in some disclosures, from 1.0 to 10.0 percent by weight relative to the weight of the overall solid oral dosage form (excluding any water-soluble barrier layer and any acid-resistant protective vehicle). Preferably, this additional peptide is not physiologically active and is most preferably a food peptide such as soybean peptide or the like. Without intending to be bound by theory, this additional non-physiologically active peptide, may also increase bioavailability by acting as a protease scavenger that desirably competes with the peptide active ingredient for protease interaction. The second peptide may also aid the active compound's passage through the liver.

[0116] All solid oral dosage forms of the present disclosure may optionally also include common pharmaceutical carriers, diluents or fillers. The solid oral dosage forms may include gelatin capsules, preservatives, colorants and the like in their usual known sizes and amounts.

[0117] The optional ingredients discussed herein are not exclusive. Other pharmaceutically acceptable agents may also be included. All optional components may be combined in any combination. Because most preferences stated herein provide benefits by different mechanisms, such combinations should be beneficial.

Inhibitor of Proteolytic Degradation of the Active Agent

[0118] When the active agent is a protein or a peptide, a protease inhibitor may be added that prevents or reduces of the proteolytic degradation of the active agent, which may occur under in the environmental conditions of the gastrointestinal tract. Preferably, the protease inhibitor that prevents or reduces the proteolytic degradation of the active agent should be pharmaceutically acceptable in relation to the certain application in animals or in humans. In

some disclosures, inhibitors of trypsin or chymotrypsin can be added.

Other Optional Preferences

[0119] When prepared in tablet form, it is preferred that the maximum weight loss during friability testing be no greater than 1%. As used herein, friability testing refers to the technique described in "Tablet Friability", Chapter 1216, USP 28 page 2745.

[0120] When absorption enhancers are used, it is preferred that the weight ratio of pH-lowering agent(s) (exclusive of coating on any coated acid particles being used) to absorption enhancer(s) be between 5:2 and 20:1, 4:1-12:1, or between 5:1-10:1. The total weight of all pH-lowering agents and the total weight of all absorption enhancers in a given solid oral dosage forms is included in the foregoing preferred ratios. For example, if a solid oral dosage forms includes two pH-lowering agents and three absorption enhancers, the foregoing ratios will be computed on the total combined weight of both pH-lowering agents and the total combined weight of all three absorption enhancers.

[0121] In some disclosures, the pH-lowering agent, the API, the absorption enhancer, when used, (whether single compounds or a plurality of compounds in each category) are uniformly dispersed in the solid oral dosage forms. In some disclosures, the solid oral dosage forms comprise granules that include a pharmaceutical binder having the API, the pH-lowering agent and the absorption enhancer uniformly dispersed within said binder. In some disclosures, granules may consist of an acid core, surrounded by a uniform layer of organic acid, a layer of enhancer and a layer of the API that is surrounded by an outer layer of organic acid. Granules may be prepared from an aqueous mixture consisting of pharmaceutical binders such as polyvinyl pyrrolidone or hydroxypropyl methylcellulose, together with the pH-lowering agents, optional absorption enhancers, and API of the disclosure.

[0122] In some disclosures, API, acid (preferably coated acid), absorption enhancer, a pharmaceutical binder (when necessary), a disintegrant (when used), a glidant, a stabilizer (when necessary) and a lubricant are thoroughly intermixed, compressed into tablet form, coated with a water-soluble barrier layer (preferably adding at least about 3% to the weight of the tablet (e.g. about 3-6%), which is in turn coated with an enteric coating that adds another about 4-15% to the weight of the tablet (e.g. 4-7%). In some disclosures, the water soluble layer adds more than the enteric coating (e.g. 6% and 4%, respectively).

[0123] In some disclosures, a single tablet is used at each administration because a single tablet best provides simultaneous release of the API, pH-lowering agent and absorption enhancers. This is desirable because the acid is best able to reduce undesirable proteolytic attack on the peptide when released in close time proximity to release of the peptide. Near simultaneous release is best achieved by administering all components of the invention as a single tablet. However, the invention also includes, for example, dividing the required amount of acid, and enhancers among two or more tablets which may be administered together such

that they together provide the necessary amount of all ingredients. "Pharmaceutical composition" and "solid oral dosage form" as used herein include a complete dosage appropriate to a particular administration to a human patient regardless of how it is subdivided so long as it is for substantially simultaneous administration.

[0124] In some disclosures, the single dosage form for oral delivery of an API comprises from about 250 mg to about 500 mg of citric acid; from about 11 mg/cm² to about 19 mg/cm² of a water-soluble undercoat; and from about 5 mg/cm² to about 15 mg/cm² of an enteric coating; wherein the API and the citric acid are in the same layer of the dosage form.

[0125] In some disclosures, the solid oral dosage form comprises an API intermixed with coated acid particles, the coated acid particles comprising an acid that is coated with a pharmaceutically acceptable protective coating to separate the acid from the API in the solid oral dosage form; an acid resistant protective vehicle; and a water-soluble barrier layer that separates the pH-lowering agent from the acid resistant protective vehicle, wherein the acid resistant protective vehicle is present at a weight from about 7% to about 10%, and wherein the water-soluble barrier layer is present at a weight from about 3.0% to about 12.0%.

[0126] In some disclosures, the coated acid particles can be present at a range from about 250 mg to about 500 mg. In some disclosures, the acid include carboxylic acids such as acetylsalicylic, acetic, ascorbic, citric, fumaric, glucuronic, glutaric, glyceric, glycolic, glyoxylic, isocitric, isovaleric, lactic, maleic, oxaloacetic, oxalosuccinic, propionic, pyruvic, succinic, tartaric, valeric, and the like. In some disclosures, the acid is selected from citric acid, tartaric acid and an acid salt of an amino acid.

[0127] In some disclosures, the absorption enhancer comprises an acyl carnitine, or SDS.

[0128] In some disclosures, a solid oral dosage form of the present disclosure includes an acid protective vehicle such as an outer layer of enteric coating. Such vehicles are desirable for enhancing bioavailability, but can slow uptake of the API into the bloodstream. In some disclosures, uniform dissolution of the acid protective vehicle in the intestines may be facilitated by keeping the acid of the solid oral dosage form away from the vehicle during its dissolution. This may be accomplished in accordance with the invention in one of or more of the following ways. First, the use of a protective water soluble barrier layer between the acid protective vehicle and the acid (pH-lowering agent) of the solid oral dosage form can enhance the more uniform release of all solid oral dosage form in the intestines by permitting most of the acid protective vehicle to dissolve in the intestines before the acid (pH-lowering agent) of the solid oral dosage form is released or otherwise comes in contact with the acid protective vehicle. Otherwise the acid (pH-lowering agent) could adversely affect the dissolution of the acid protective vehicle (which is insoluble in acid environment). This water soluble barrier layer is expected to provide this benefit regardless of the form in which the acid (pH-lowering agent) is supplied, and even when coated acid particles (used in other disclosures of the invention) are not present. In some disclosures, the water-soluble barrier layer adds at least 3% to the weight

of the solid oral dosage form, exclusive of any acid-protective vehicle. In some disclosures, the water-soluble barrier layer adds from about 3% to about 12% to the weight of the solid oral dosage form, exclusive of any acid-protective vehicle.

[0129] Second, the acid (pH-lowering agent) of the composition may be provided in the form of coated acid particles. The coating on these particles is a pharmaceutically acceptable protective coating that is non-acidic and has a solubility in water of at least one gram per 100 milliliters of water at room temperature. In addition to desirably separating the pharmaceutical acid (pH-lowering agent) from the peptide compound, this coating on the acid particles may help protect the solid oral dosage form's acid resistant protective vehicle from the undesirable effects acid can have on quick uniform dissolution of the outer coating in the intestines. This is true even in disclosures of the present disclosure that do not include the protective water soluble barrier layer. In some, but not all, disclosures of the present disclosure, both (1) the protective water soluble barrier layer is present, and (2) the acid (pH-lowering agent) is supplied, at least in part, in the form of coated acid particles.

[0130] Likewise, providing acid (pH-lowering agent) to the solid oral dosage form in the form of the foregoing coated acid particles provides numerous advantages that are independent of any effect on enteric coating, and independent of whether or not a protective water soluble barrier layer is used. Such coated acid particles may therefore be used advantageously even in disclosures of the present disclosure that include neither outer coating of acid protective vehicle, nor protective barrier layer. In particular, acid (pH-lowering agent) in the form of coated particles may desirably be thoroughly intermixed with the peptide compound, while undesirable acid-peptide interaction is minimized. Without intending to be bound by theory, this thorough intermixing is believed to facilitate uniform release of each component together so that acid (pH-lowering agent) may better protect the peptide compound, in the intestinal environment, by reducing peptide degradation from the activity of local proteases having neutral or basic pH optima.

[0131] In some but not all disclosures, an absorption enhancer is included in a solid oral dosage form to further enhance bioavailability. In some disclosures, coated acid particles, API, absorption enhancer, acid protective vehicle and protective water soluble barrier layer are all present. The use of coated acid particles, in addition to reducing undesirable acid interactions with other components discussed herein, desirably reduces acid interaction with absorption enhancer (when used) or with surfactant (when used).

[0132] In some disclosures, coated acid, API, and, optionally, one or more of any optional components discussed herein, e.g. an absorption enhancer, are thoroughly intermixed. The mixture is then coated with both a protective water soluble barrier layer and an outer acid-protective vehicle. In some disclosures, the water soluble barrier layer lies just inside of an acid protective vehicle layer, and separates the vehicle layer from the intermixed remaining contents. In some disclosures, the acid resistant protective vehicle is present at a weight which is from about 3.0% to about 10.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the acid resistant protective vehicle is present at a weight of about

3.6% of the weight of the remainder of the solid oral dosage form. In some disclosures, the acid resistant protective vehicle is present at a weight of about 7.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the acid resistant protective vehicle is present at a weight of about 10.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the water-soluble barrier layer is present at a weight which is from about 6.0% to about 15.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the water-soluble barrier layer is present at a weight which is from about 7.0% to about 12.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the water-soluble barrier layer is present at a weight of about 7.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the water-soluble barrier layer is present at a weight of about 12.0% of the weight of the remainder of the solid oral dosage form.

[0133] The acid protective vehicle preferably constitutes an outermost protective layer surrounding the remainder of the solid oral dosage form. The vehicle does not dissolve in the acidic stomach environment, thus protecting the peptide compound from stomach proteases. Without intending to be bound by theory, it is believed that, later, in the basic pH environment of the intestines, the vehicle dissolves quickly without interference from the pharmaceutical acid from which the vehicle is separated by either the barrier layer, or the coating on the acid particles, or both. It is believed that, once the protective vehicle dissolves, the water-soluble barrier layer and the coating surrounding the acid particles release the remaining components of the composition.

[0134] The acid (also referred herein as pH lowering agent) is believed to lower the local intestinal pH (where the active agent has been released) to levels below the optimal range for many intestinal proteases. It is believed that this decrease in pH reduces the proteolytic activity of the intestinal proteases, thus affording protection to the peptide compound from potential degradation. The activity of these proteases is diminished by the temporarily acidic environment provided by a solid oral dosage form of the present disclosure. In some disclosures, sufficient acid is provided so that local intestinal pH is lowered temporarily to 5.5 or below. In some disclosures, sufficient acid is provided so that local intestinal pH is lowered temporarily to 4.7 or below. In some disclosures, sufficient acid is provided so that local intestinal pH is lowered temporarily to 3.5 or below. The sodium bicarbonate test, described in the section captioned "the pH-Lowering Agent", is indicative of the required acid amount. Preferably, conditions of reduced intestinal pH persist for a time period sufficient to protect the API (e.g. peptide, hormone or analogue thereof) from proteolytic degradation until at least some of the peptide compound has had an opportunity to cross the intestinal wall into the bloodstream. Optionally, absorption enhancers, when used, may synergistically promote peptide absorption into the blood while conditions of reduced proteolytic activity prevail. Preferred absorption enhancers and their use are discussed in more detail in a separate section.

[0135] Acid and API (i.e.. peptide compound) and, the absorption enhancer, should be released together to the extent possible. The acid is then better able to protect, for example,

the peptide compound by reducing degradation of the peptide compound by action of neutral or basic-acting proteases until the peptide compound crosses the intestinal wall into the bloodstream. A concomitant release of absorption enhancer (when used) can further enhance that crossing of the intestinal wall. In a tablet of the present disclosure, additional optional materials, discussed in separate sections herein, aid in forming tablets of appropriate hardness that resist breaking prior to administration, and undergo consistent and complete dissolution at the appropriate time after administration.

[0136] The API comprises a peptide compound.

[0137] The API is a peptide compound that includes a plurality of amino acids and at least one peptide bond in its molecular structure. The molecular weight of the peptide compound ranges from 500 Daltons up to 10,000 Daltons. In some disclosures, the peptide compound is a peptide hormone or analogue thereof. In some disclosures, the hormone or analogue thereof is a gonadotrophin releasing hormone (GnRH) analogue including, but not limited to, triptorelin, leuporelin and goserelin. In some disclosures, the hormone analogue is leuporelin. In some disclosures, the single oral dosage form is a single tablet or capsule. In some disclosures, an average particle size of the coated acid particles is between 30 mesh and 140 mesh.

[0138] A single dosage form for oral delivery of a peptide compound includes from about 1 mg to about 3 mg of a gonadotrophin releasing hormone (GnRH) analogue; from about 250 mg to about 500 mg of citric acid; from about 11 mg/cm² to about 19 mg/cm² of a water-soluble undercoat; and from about 5 mg/cm² to about 15 mg/cm² of an enteric coating; wherein the gonadotrophin releasing hormone (GnRH) analogue and the citric acid are in the same layer of the dosage form. In some disclosures, the absorption enhancer is an acyl carnitine. In some disclosures, the absorption enhancer is lauroyl-L-carnitine. In some disclosures, the gonadotrophin releasing hormone (GnRH) analogue is selected from the group consisting of triptorelin, leuporelin and goserelin. In some disclosures, the gonadotrophin releasing hormone analogue is leuporelin.

[0139] In some disclosures, the solid oral dosage form comprises a peptide compound intermixed with coated acid particles, the coated acid particles comprising citric acid that is coated with a pharmaceutically acceptable protective coating to separate the acid from the peptide compound in the solid oral dosage form, the coated acid particles present at a range from about 250 mg to about 500 mg; an acid resistant protective vehicle; and a water-soluble barrier layer that separates the pH-lowering agent from the acid resistant protective vehicle, wherein the acid resistant protective vehicle is present at a weight from about 7% to about 10%, and wherein the water-soluble barrier layer is present at a weight from about 3.0% to about 12.0%. In some disclosures, the solid oral dosage form further comprises a cellulose filler. In some disclosures, the cellulose filler is a high viscosity cellulose filler. In some disclosures, the solid oral dosage form further comprises an absorption enhancer. In some disclosures, the solid oral dosage form further comprises a pharmaceutical binder. In some disclosures, when the solid oral dosage form is ingested, the acid-resistant protective vehicle is breached in the intestine in the distal part of the duodenum, the jejunum, the ileum, or the

colon, the citric acid is released from the coated acid particles. In some disclosures, the citric acid can reduce the activity of intestinal proteases.

[0140] One of the mechanisms by which the present disclosure is believed to accomplish the goal of enhanced bioavailability is aided by having an enteric coating having a suitable thickness, and active components of the pharmaceutical composition released together as uniformly as possible. The acid-resistant protective vehicle should normally add less than about 30% to the weight of the remainder of solid oral dosage form (i.e., the other components of the composition excluding the acid-resistant protective vehicle). When a water-soluble barrier layer is used in addition to the acid-resistant protective vehicle, less acid-resistant protective vehicle may be required. In some disclosures, the acid resistant protective vehicle is present at a weight which is from about 3.0% to about 10.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the acid resistant protective vehicle is present at a weight of about 3.6% of the weight of the remainder of the solid oral dosage form. In some disclosures, the acid resistant protective vehicle is present at a weight of about 7.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the acid resistant protective vehicle is present at a weight of about 10.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the water-soluble barrier layer is present at a weight which is from about 7.0% to about 12.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the water-soluble barrier layer is present at a weight of about 7.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the water-soluble barrier layer is present at a weight of about 12.0% of the weight of the remainder of the solid oral dosage form.

[0141] According to disclosures illustrated herein, there is disclosed a solid oral dosage form that includes a therapeutically effective amount of at least one hormone or analogue thereof; at least one pharmaceutically acceptable pH-lowering agent; an acid resistant protective vehicle; and a water-soluble barrier layer that separates the pH-lowering agent from the acid resistant protective vehicle. In some disclosures, the pH-lowering agent is present in the solid oral dosage form in a quantity which, if the solid oral dosage form were added to ten milliliters of 0.1M aqueous sodium bicarbonate solution, would be sufficient to lower the pH of said solution to no higher than 5.5. In some disclosures, the acid resistant protective vehicle is present at a weight which is from about 3.0% to about 10.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the acid resistant protective vehicle is present at a weight of about 3.6% of the weight of the remainder of the solid oral dosage form. In some disclosures, the acid resistant protective vehicle is present at a weight of about 7.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the acid resistant protective vehicle is present at a weight of about 10.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the water-soluble barrier layer is present at a weight which is from about 7.0% to about 12.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the water-soluble barrier layer is present at a weight of about 7.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the water-soluble barrier layer is present at a weight of about 12.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the solid oral dosage form further includes an

absorption enhancer. In some disclosures, the absorption enhancer is a surface active agent. In some disclosures, the surface active agent is absorbable or biodegradable. In some disclosures, the surface active agent is selected from the group consisting of acylcarnitines, phospholipids and bile acids. In some disclosures, the surface active agent is an acyl carnitine. In some disclosures, the solid oral dosage form further comprises a pharmaceutical binder. In some disclosures, the hormone, or analogue thereof, is selected from a gonadotrophin releasing hormone (GnRH) analogue including, but not limited to, triptorelin, leuprorelin and goserelin. In some embodiments, the hormone analogue is leuprorelin. The acid is selected from citric acid and tartaric acid. In some disclosures, the single oral dosage form is a single tablet or capsule. In some disclosures, an average particle size of the coated acid particles is between 30 mesh and 140 mesh.

[0142] Disclosed herein is a solid oral dosage form of leuprolide that results in about 5% to about 10% absolute oral bioavailability. In some disclosures, a sufficient amount of active agent is included in the dosage form of the invention to achieve a serum level (C_{max}) of the active agent of from about 45,000 to about 131,000 (pg/mL) (mg/kg).

[0143] In some disclosures, a solid oral dosage form comprising about 500 mg of citric acid and 50 mg of LLC is linear with respect to dose in the range of 1 mg to 3 mg of leuprolide.

[0144] Disclosed herein is a solid oral dosage form for oral delivery of a peptide active ingredient that includes a therapeutically effective amount of at least one peptide active ingredient; at least one pharmaceutically acceptable pH-lowering agent; an acid resistant protective vehicle; and a water-soluble barrier layer that separates the pH-lowering agent from the acid resistant protective vehicle. In some disclosures, the pH-lowering agent is present in the solid oral dosage form in a quantity which, if the solid oral dosage form were added to ten milliliters of 0.1M aqueous sodium bicarbonate solution, would be sufficient to lower the pH of said solution to no higher than 5.5. In some disclosures, the acid resistant protective vehicle is present at a weight which is from about 3.0% to about 10.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the acid resistant protective vehicle is present at a weight of about 3.6% of the weight of the remainder of the solid oral dosage form. In some disclosures, the acid resistant protective vehicle is present at a weight of about 7.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the acid resistant protective vehicle is present at a weight of about 10.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the water-soluble barrier layer is present at a weight which is from about 7.0% to about 12.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the water-soluble barrier layer is present at a weight of about 7.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the water-soluble barrier layer is present at a weight of about 12.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the solid oral dosage form further includes an absorption enhancer. In some disclosures, the absorption enhancer is a surface active agent. In some disclosures, the surface active agent is absorbable or biodegradable. In some disclosures, the surface active agent is selected from the group consisting of acylcarnitines, phospholipids and bile acids. In some disclosures, the surface

active agent is an acyl carnitine. In some disclosures, the solid oral dosage form further comprises a pharmaceutical binder. In some disclosures, the peptide active ingredient is human calcitonin. In some disclosures, the peptide active ingredient is salmon calcitonin. In some disclosures, the peptide active ingredient is eel calcitonin. The pH-lowering agent is selected from citric acid and tartaric acid. In some disclosures, the single oral dosage form is a single tablet or capsule.

[0145] Disclosed herein is a solid oral dosage form that includes a therapeutically effective amount of at least one hormone or analogue thereof intermixed with coated acid particles, the coated acid particles comprising at least one pharmaceutically acceptable acid that is coated with a pharmaceutically acceptable protective coating to separate the acid from the hormone or analogue thereof in the solid oral dosage form; an acid resistant protective vehicle; and a water-soluble barrier layer that separates the pH-lowering agent from the acid resistant protective vehicle, wherein the hormone or analogue thereof and the coated acid particles are in the same layer of the solid oral dosage form, wherein total acid in the solid oral dosage form is in a quantity which, if added to ten milliliters of 0.1 M aqueous sodium bicarbonate solution, would be sufficient to lower the pH of the solution to no higher than 5.5. In some disclosures, the acid resistant protective vehicle is present at a weight which is from about 3.0% to about 10.0% of the weight of the remainder of the solid oral dosage form. In some disclosures the acid resistant protective vehicle is present at a weight of about 3.6% of the weight of the remainder of the solid oral dosage form. In some disclosures, the acid resistant protective vehicle is present at a weight of about 7.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the acid resistant protective vehicle is present at a weight of about 10.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the water-soluble barrier layer is present at a weight which is from about 7.0% to about 12.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the water-soluble barrier layer is present at a weight of about 7.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the water-soluble barrier layer is present at a weight of about 12.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the solid oral dosage form further comprises a cellulose filler. In some disclosures, the solid oral dosage form further comprises an absorption enhancer. In some disclosures, the absorption enhancer is an acyl carnitine. In some disclosures, the absorption enhancer is lauroyl-L-carnitine. In some disclosures, the solid oral dosage form further comprises a pharmaceutical binder. In some disclosures, when the solid oral dosage form is ingested, the acid-resistant protective vehicle is breached in the intestine, the acid is released from the coated acid particles, and the acid reduces the activity of intestinal proteases. In some disclosures, the hormone or analogue thereof is selected from a gonadotrophin releasing hormone (GnRH) analogue including, but not limited to, triptorelin, leuprorelin and goserelin. In some embodiments, the hormone analogue is leuprorelin. In some disclosures, the acid is selected from citric acid, tartaric acid and an acid salt of an amino acid. In some disclosures, the single oral dosage form is a single tablet or capsule. In some disclosures, an average particle size of the coated acid particles is between 30 mesh and 140 mesh.

[0146] Disclosed herein is a solid oral dosage form that includes a therapeutically effective

amount of at least one peptide active ingredient intermixed with coated acid particles, the coated acid particles comprising at least one pharmaceutically acceptable acid that is coated with a pharmaceutically acceptable protective coating to separate the acid from the peptide active ingredient in the solid oral dosage form; an acid resistant protective vehicle; and a water-soluble barrier layer that separates the pH-lowering agent from the acid resistant protective vehicle, wherein the peptide active ingredient and the coated acid particles are in the same layer of the solid oral dosage form, wherein total acid in the solid oral dosage form is in a quantity which, if added to ten milliliters of 0.1 M aqueous sodium bicarbonate solution, would be sufficient to lower the pH of the solution to no higher than 5.5. In some disclosures, the protective coating of the coated acid particles comprises maltodextrin. In some disclosures, the acid resistant protective vehicle is present at a weight which is from about 3.0% to about 10.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the acid resistant protective vehicle is present at a weight of about 3.6% of the weight of the remainder of the solid oral dosage form. In some disclosures, the acid resistant protective vehicle is present at a weight of about 7.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the acid resistant protective vehicle is present at a weight of about 10.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the water-soluble barrier layer is present at a weight which is from about 7.0% to about 12.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the water-soluble barrier layer is present at a weight of about 7.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the water-soluble barrier layer is present at a weight of about 12.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the solid oral dosage form further comprises a cellulose filler. In some disclosures, the solid oral dosage form further comprises an absorption enhancer. In some disclosures, the absorption enhancer is an acyl carnitine. In some disclosures, the absorption enhancer is lauroyl-L-carnitine. In some disclosures, the solid oral dosage form further comprises a pharmaceutical binder. In some disclosures, when the solid oral dosage form is ingested, the acid-resistant protective vehicle is breached in the intestine, the acid is released from the coated acid particles, and the acid reduces the activity of intestinal proteases. In some disclosures, the peptide active ingredient is human calcitonin. In some disclosures, the peptide active ingredient is salmon calcitonin. In some disclosures, the peptide active ingredient is eel calcitonin. In some disclosures, the acid is selected from citric acid, tartaric acid and an acid salt of an amino acid. In some disclosures, the single oral dosage form is a single tablet or capsule. In some disclosures, an average particle size of the coated acid particles is between 30 mesh and 140 mesh.

[0147] Disclosed herein is a single dosage form for oral delivery of a hormone or analogue thereof comprising: (A) said hormone or analogue thereof; (B) at least one pharmaceutically acceptable acid wherein acid is present in said dosage form in a quantity which, if added to 10 milliliters of 0.1M aqueous sodium bicarbonate solution, would be sufficient to lower the pH of said solution to no higher than 5.5; (C) an acid resistant protective vehicle effective to transport said dosage form through the stomach of a patient while preventing contact between said hormone or analogue thereof and stomach proteases; and (D) a water soluble barrier layer that separates said acid from said protective vehicle; wherein said hormone or analogue

thereof and said acid are in the same layer of said dosage form. In some disclosures, the total acid in the solid oral dosage form is in a quantity which, if added to ten milliliters of 0.1 M aqueous sodium bicarbonate solution, would be sufficient to lower the pH of the solution to no higher than 5.5. In some disclosures, the acid resistant protective vehicle is present at a weight which is from about 3.0% to about 10.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the acid resistant protective vehicle is present at a weight of about 3.6% of the weight of the remainder of the solid oral dosage form. In some disclosures, the acid resistant protective vehicle is present at a weight of about 7.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the acid resistant protective vehicle is present at a weight of about 10.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the water-soluble barrier layer is present at a weight which is from about 7.0% to about 12.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the water-soluble barrier layer is present at a weight of about 7.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the water-soluble barrier layer is present at a weight of about 12.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the solid oral dosage form further comprises a cellulose filler. In some disclosures, the solid oral dosage form further comprises an absorption enhancer. In some disclosures, the absorption enhancer is an acyl carnitine. In some disclosures, the absorption enhancer is lauroyl-L-carnitine. In some disclosures, the solid oral dosage form further comprises a pharmaceutical binder. In some disclosures, when the solid oral dosage form is ingested, the acid-resistant protective vehicle is breached in the intestine, the acid is released from the coated acid particles, and the acid reduces the activity of intestinal proteases. In some disclosures, the hormone or analogue thereof is selected from a gonadotrophin releasing hormone (GnRH) analogue including, but not limited to, triptorelin, leuporelin and goserelin. In some disclosures, the hormone analogue is leuporelin

[0148] Disclosed herein is a single dosage form for oral delivery of a peptide active ingredient comprising: (A) said peptide active ingredient; (B) at least one pharmaceutically acceptable acid wherein acid is present in said dosage form in a quantity which, if added to 10 milliliters of 0.1M aqueous sodium bicarbonate solution, would be sufficient to lower the pH of said solution to no higher than 5.5; (C) an acid resistant protective vehicle effective to transport said dosage form through the stomach of a patient while preventing contact between said peptide active ingredient and stomach proteases; and (D) a water soluble barrier layer that separates said acid from said protective vehicle; wherein said peptide active ingredient and said acid are in the same layer of said dosage form. In some disclosures, the total acid in the solid oral dosage form is in a quantity which, if added to ten milliliters of 0.1 M aqueous sodium bicarbonate solution, would be sufficient to lower the pH of the solution to no higher than 5.5. In some disclosures, the acid resistant protective vehicle is present at a weight which is from about 3.0% to about 10.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the acid resistant protective vehicle is present at a weight of about 3.6% of the weight of the remainder of the solid oral dosage form. In some disclosures, the acid resistant protective vehicle is present at a weight of about 7.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the acid resistant protective vehicle is present at a weight of about 10.0% of the weight of the remainder of the solid oral dosage form. In some

disclosures, the water-soluble barrier layer is present at a weight which is from about 7.0% to about 12.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the water-soluble barrier layer is present at a weight of about 7.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the water-soluble barrier layer is present at a weight of about 12.0% of the weight of the remainder of the solid oral dosage form. In some disclosures, the amount of water-soluble barrier layer exceeds the amount of acid-protective vehicle.

[0149] In some disclosures, the solid oral dosage form further comprises a cellulose filler. In some disclosures, the solid oral dosage form further comprises an absorption enhancer. In some disclosures, the absorption enhancer is an acyl carnitine. In some disclosures, the absorption enhancer is lauroyl-L-carnitine. In some disclosures, the solid oral dosage form further comprises a pharmaceutical binder. In some disclosures, when the solid oral dosage form is ingested, the acid-resistant protective vehicle is breached in the intestine, the acid is released from the coated acid particles, and the acid reduces the activity of intestinal proteases. In some disclosures, the peptide active ingredient is human calcitonin. In some disclosures, the peptide active ingredient is salmon calcitonin. In some disclosures, the peptide active ingredient is eel calcitonin. In some disclosures, the acid is selected from citric acid, tartaric acid and an acid salt of an amino acid. In some disclosures, the single oral dosage form is a single tablet or capsule. In some disclosures, an average particle size of the coated acid particles is between 30 mesh and 140 mesh.

[0150] Disclosed herein is a pharmaceutical tablet for oral delivery of a physiologically active peptide agent comprising: (A) the active peptide agent; (B) L-lauroyl carnitine; (C) coated citric acid particles intermixed with the active peptide agent, wherein the coating separates the citric acid from the active peptide agent in the composition, wherein total citric acid, exclusive of coating, exceeds 100 milligrams per tablet; (D) at least one chymotrypsin inhibitor; (E) a cellulose filler; (F) a pharmaceutical binder; (G) an outer layer of an acid-resistant enteric coating effective to transport the pharmaceutical tablet through the stomach of a patient while preventing contact between the active peptide agent and stomach proteases; and (H) a water soluble barrier layer beneath the outer layer of enteric coating that separates the enteric coating from the coated acid, the barrier layer comprising a compound selected from hydroxypropylmethylcellulose, hydroxypropylcellulose, methylcellulose and polyvinylpyrrolidone, and being present in an amount higher than three percent by weight relative to the total weight of the pharmaceutical, exclusive of the outer layer and the barrier layer, wherein the tablet has been compressed into tablet form such that the maximum weight loss during friability testing is no greater than 1%, and wherein the tablet reduces the activity of neutral to basic-acting proteases upon dissolution in the small intestine by reducing intestinal pH.

[0151] Disclosed herein is a pharmaceutical tablet for oral delivery of a hormone or analogue thereof comprising: (A) the hormone or analogue thereof; (B) L-lauroyl carnitine; (C) coated citric acid particles intermixed with the hormone or analogue thereof, wherein the coating separates the citric acid from the hormone or analogue thereof in the tablet, wherein total citric

acid, exclusive of coating, exceeds 100 milligrams per tablet; (D) a cellulose filler; (E) a pharmaceutical binder; (F) an outer layer of an acid-resistant enteric coating effective to transport the pharmaceutical tablet through the stomach of a patient while preventing contact between the hormone or analogue thereof and stomach proteases; and (G) a water soluble barrier layer beneath the outer layer of enteric coating that separates the enteric coating from the coated acid, the barrier layer comprising a compound selected from hydroxypropylmethylcellulose, hydroxypropylcellulose, methylcellulose and polyvinylpyrrolidone, and being present in an amount higher than three percent by weight relative to the total weight of the pharmaceutical tablet, exclusive of the outer layer and the barrier layer, wherein the tablet has been compressed into tablet form such that the maximum weight loss during friability testing is no greater than 1%, and wherein the tablet reduces the activity of neutral to basic-acting proteases upon dissolution in the small intestine by reducing intestinal pH.

[0152] Disclosed herein is a pharmaceutical tablet for oral delivery of a peptide active ingredient comprising: (A) the peptide active ingredient; (B) L-lauroyl carnitine; (C) coated citric acid particles intermixed with the peptide active ingredient, wherein the coating separates the citric acid from the peptide active ingredient in the tablet, wherein total citric acid, exclusive of coating, exceeds 100 milligrams per tablet; (D) a cellulose filler; (E) a pharmaceutical binder; (F) an outer layer of an acid-resistant enteric coating effective to transport the pharmaceutical tablet through the stomach of a patient while preventing contact between the peptide active ingredient and stomach proteases; and (G) a water soluble barrier layer beneath the outer layer of enteric coating that separates the enteric coating from the coated acid, the barrier layer comprising a compound selected from hydroxypropylmethylcellulose, hydroxypropylcellulose, methylcellulose and polyvinylpyrrolidone, and being present in an amount higher than three percent by weight relative to the total weight of the pharmaceutical tablet, exclusive of the outer layer and the barrier layer, wherein the tablet has been compressed into tablet form such that the maximum weight loss during friability testing is no greater than 1%, and wherein the tablet reduces the activity of neutral to basic-acting proteases upon dissolution in the small intestine by reducing intestinal pH.

[0153] Disclosed herein is a method of treating prostate cancer that includes orally administering to a subject in need thereof, for a suitable period of time, a pharmaceutical tablet that includes (A) a gonadotrophin releasing hormone (GnRH) analogue; (B) an absorption enhancer; (C) coated acid particles intermixed with the GnRH analogue, wherein the coating separates the citric acid from the GnRH analogue in the tablet; (D) an outer layer of an acid-resistant enteric coating effective to transport the pharmaceutical tablet through the stomach of a patient while preventing contact between triptorelin and stomach proteases; and (E) a water soluble barrier layer beneath the outer layer of enteric coating that separates the enteric coating from the coated acid particles.

[0154] Disclosed herein is a method of treating endometriosis that includes orally administering to a subject in need thereof, for a suitable period of time, a pharmaceutical tablet that includes (A) a gonadotrophin releasing hormone (GnRH) analogue; (B) an absorption enhancer; (C)

coated acid particles intermixed with the GnRH analogue, wherein the coating separates the citric acid from the GnRH analogue in the tablet; (D) an outer layer of an acid-resistant enteric coating effective to transport the pharmaceutical tablet through the stomach of a patient while preventing contact between the GnRH analogue and stomach proteases; and (E) a water soluble barrier layer beneath the outer layer of enteric coating that separates the enteric coating from the coated acid particles.

[0155] Disclosed herein is a method of treating uterine fibroids that includes orally administering to a subject in need thereof, for a suitable period of time, a pharmaceutical tablet that includes (A) a gonadotrophin releasing hormone (GnRH) analogue; (B) an absorption enhancer; (C) coated acid particles intermixed with the GnRH analogue, wherein the coating separates the citric acid from the GnRH analogue in the tablet; (D) an outer layer of an acid-resistant enteric coating effective to transport the pharmaceutical tablet through the stomach of a patient while preventing contact between the GnRH analogue and stomach proteases; and (E) a water soluble barrier layer beneath the outer layer of enteric coating that separates the enteric coating from the coated acid particles.

[0156] Disclosed herein is a method of treating breast cancer that includes orally administering to a subject in need thereof, for a suitable period of time, a pharmaceutical tablet that includes (A) a gonadotrophin releasing hormone (GnRH) analogue; (B) an absorption enhancer; (C) coated acid particles intermixed with the GnRH analogue, wherein the coating separates the citric acid from the GnRH analogue in the tablet; (D) an outer layer of an acid-resistant enteric coating effective to transport the pharmaceutical tablet through the stomach of a patient while preventing contact between the GnRH analogue and stomach proteases; and (E) a water soluble barrier layer beneath the outer layer of enteric coating that separates the enteric coating from the coated acid particles.

[0157] Disclosed herein is a method of treating precocious puberty that includes orally administering to a subject in need thereof, for a suitable period of time, a pharmaceutical tablet that includes (A) a gonadotrophin releasing hormone (GnRH) analogue; (B) an absorption enhancer; (C) coated acid particles intermixed with the GnRH analogue, wherein the coating separates the citric acid from the GnRH analogue in the tablet; (D) an outer layer of an acid-resistant enteric coating effective to transport the pharmaceutical tablet through the stomach of a patient while preventing contact between the GnRH analogue and stomach proteases; and (E) a water soluble barrier layer beneath the outer layer of enteric coating that separates the enteric coating from the coated acid particles.

[0158] Disclosed herein are modified release solid oral compositions. In some disclosures, the modified release solid dosage composition comprise (a) a core comprising: (i) an effective amount of active pharmaceutical ingredient, (ii) a pH lowering agent, (iii) an absorption enhancer, (iv) a filler comprising an hydrogel-forming polymer, and (v) less than 10% by weight of disintegrant; and (b) an enteric coating surrounding the core, the composition providing a pharmacokinetic profile for the active agent with a T_{lag} greater than 1.0 h and less than 16 h post-administration and a T_{max} greater than ($T_{lag} + 0.5$ h) and less than 20 h post-

administration.

[0159] In some disclosures, the pharmacokinetic release profile targets release of the pharmaceutical active ingredient to the jejunum, the ileum or the jejunum and the ileum. In some disclosures, the composition is designed so that substantially no active pharmaceutical ingredient is released in the stomach, the duodenum or the stomach and duodenum post-administration.

[0160] In some disclosures, the composition further comprises a water soluble barrier beneath the enteric coating. In some disclosures, the water soluble barrier is in amount from about 6% to about 15% by weight. In some disclosures, the water soluble barrier is one of polyvinylpyrrolidone, hydroxymethylcellulose, hydroxypropylcellulose, methylcellulose and combinations thereof.

[0161] The absorption enhancer has a critical micelle concentration of 1.0 mM to 40 mM. In some disclosure, the absorption enhancer has a critical micelle concentration of about 1.0 mM to about 15 mM.

[0162] The hydrogel-forming polymer has a viscosity of 3,000 to 120,000 cP at 20°C. In some disclosures, the filler comprises microcrystalline cellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, chitosan or a combination thereof. In some disclosures, the hydrogel-forming polymer comprises hydroxypropylcellulose, hydroxypropylmethylcellulose or a combination thereof.

[0163] The active pharmaceutical ingredient comprises a peptide of 500 Daltons up to 10,000 Daltons. In some disclosures, the peptide is one of leuprolide, insulin, vasopressin, calcitonin, calcitonin gene-related peptide, parathyroid hormone, desmopressin, gonadotrophin releasing hormone (GnRH), luteinizing hormone-releasing factor, adrenocorticotropin, enkephalin, glucagon-like peptide-1, desmopressin 2,6-dimethyltyrosine-D-arginine-phenylalanine-lysine amide and triptorelin.

[0164] The absorption enhancer comprises a cationic surface active agent, an anionic surface active agent or a combination thereof. In some disclosures, the cationic surface active agent comprises an acylcarnitine. In some disclosures, the anionic surface active agent comprises sodium dodecyl sulfate. In some disclosures, the absorption enhancer comprises sodium dodecyl sulfate.

[0165] The pH lowering agent comprises citric acid, tartaric acid or a combination thereof. In some disclosures, the pH lowering agent is in the form of coated acid particles. In some disclosures, the acid particles are coated with a water-soluble coating. In some disclosures, the pH lowering agent is in the form of coated citric acid particles. In some disclosures, the composition comprises from about 50 mg to about 500 mg of citric acid. In some disclosures, the composition comprises from about 250 mg to about 500 mg of citric acid. In some disclosures, the citric acid is in the form of coated citric acid.

[0166] In some disclosures, the composition comprises from about 5 mg/cm² to about 25 mg/cm² of enteric coating.

[0167] In some disclosures, the modified release solid oral composition comprises (a) a core comprising: (i) an effective amount of active pharmaceutical ingredient, (ii) a pH lowering agent, (iii) an absorption enhancer, (iv) a filler comprising an hydrogel-forming polymer, wherein the core is substantially free of disintegrant; and (b) an enteric coating surrounding the core, wherein the composition provides a pharmacokinetic profile for the active agent with a T_{lag} greater than 1.0 h and less than 16 h post-administration and a T_{max} greater than (T_{lag} +0.5 h) and less than 20 h post-administration.

[0168] In some disclosures, the pharmacokinetic release profile targets release of the pharmaceutical active ingredient to the jejunum, the ileum or the jejunum and the ileum. In some disclosures, the composition is designed so that substantially no active pharmaceutical ingredient is released in the stomach, the duodenum or the stomach and duodenum post-administration.

[0169] In some disclosures, the composition further comprises a water soluble barrier beneath the enteric coating. In some disclosures, the water soluble barrier is in amount from about 6% to about 15% by weight. In some disclosures, the water soluble barrier is one of polyvinylpyrrolidone, hydroxymethylcellulose, hydroxypropylcellulose, methylcellulose and combinations thereof.

[0170] The absorption enhancer has a critical micelle concentration of from about 1.0 to about 40 mM or of from about 1.0 to about 15 mM.

[0171] The hydrogel-forming polymer has a viscosity of about 3,000 to about 120,000 cP at 20°C. In some disclosures, the filler comprises, hydroxypropylcellulose, hydroxypropylmethylcellulose, or a combination thereof. In some disclosures, the hydrogel-forming polymer comprises hydroxypropylcellulose, hydroxypropylmethylcellulose or a combination thereof.

[0172] The active pharmaceutical ingredient comprises a peptide of 500 Daltons up to 10,000 Daltons. In some disclosures, the peptide is one of leuprolide, insulin, vasopressin, calcitonin, calcitonin gene-related peptide, parathyroid hormone, desmopressin, gonadotrophin releasing hormone (GnRH), luteinizing hormone-releasing factor, adrenocorticotropin, enkephalin, glucagon-like peptide-1, desmopressin, 2,6-dimethyltyrosine-D-arginine-phenylalanine-lysine amide and triptorelin.

[0173] The absorption enhancer comprises a cationic surface active agent, an anionic surface active agent or a combination thereof. In some disclosures, the cationic surface active agent comprises an acylcarnitine. In some disclosures, the anionic surface active agent comprises sodium dodecyl sulfate. In some disclosures, the absorption enhancer comprises sodium

dodecyl sulfate.

[0174] The pH lowering agent comprises citric acid, tartaric acid or a combination thereof. In some disclosures, the pH lowering agent is in the form of coated acid particles. In some disclosures, the acid particles are coated with a water-soluble coating. In some disclosures, the pH lowering agent is in the form of coated citric acid particles. In some disclosures, the composition comprises from about 50 mg to about 500 mg of citric acid. In some disclosures, the composition comprises from about 250 mg to about 500 mg of citric acid. In some disclosures, the citric acid is in the form of coated citric acid.

[0175] In some disclosures, the composition comprises from about 5 mg/cm² to about 25 mg/cm² of enteric coating.

Methods of treatment

[0176] Methods of treating a patient are disclosed. In some disclosures, the method of treating comprises (a) providing a solid oral dosage form comprising (i) a core comprising an effective amount of active pharmaceutical ingredient, a pH lowering agent, an absorption enhancer, a filler comprising an hydrogel-forming polymer, and less than 10% by weight of disintegrant; and (ii) an enteric coating surrounding the core; and (b) administering orally to a patient, the solid oral dosage form, wherein the solid oral dosage form provides a pharmacokinetic release profile for the active agent with a T_{lag} greater than 1.0 h and less than 16 h post-administration and a T_{max} greater than ($T_{lag}+0.5$ h) and less than 20 h post-administration.

[0177] In some disclosures, the pharmacokinetic release profile targets release of the pharmaceutical active ingredient to the jejunum, the ileum or the jejunum and the ileum.

[0178] In some disclosures, the solid oral dosage form is substantially free of disintegrant. In some disclosures, the solid oral dosage form further comprises a water soluble barrier beneath the enteric coating.

[0179] In some disclosures, the absorption enhancer has a critical micelle concentration of about 1.0 to about 40 mM. In some disclosures, the absorption enhancer has a critical micelle concentration of about 1.0 to about 15 mM.

[0180] The hydrogel-forming polymer has a viscosity of about 3,000 to about 120,000 cP at 20°C. In some disclosures, the filler comprises hydroxypropyl cellulose, hydroxypropyl methyl cellulose, or a combination thereof. In some disclosures, the hydrogel-forming polymer comprises hydroxypropyl cellulose, hydroxypropyl methyl cellulose or a combination thereof.

[0181] The active pharmaceutical ingredient comprises a peptide of 500 Daltons up to 10,000 Daltons. In some disclosures, the peptide is one of leuprolide, insulin, vasopressin, calcitonin,

calcitonin gene-related peptide, parathyroid hormone, desmopressin, gonadotrophin releasing hormone (GnRH), luteinizing hormone-releasing factor, adrenocorticotropin, enkephalin, glucagon-like peptide-1, desmopressin, 2,6-dimethyltyrosine-D-arginine-phenylalanine-lysine amide and triptorelin.

[0182] The absorption enhancer comprises a cationic surface active agent, an anionic surface active agent or a combination thereof. In some disclosures, the cationic surface active agent comprises an acylcarnitine. In some disclosures, the anionic surface active agent comprises sodium dodecyl sulfate. In some disclosures, the absorption enhancer comprises sodium dodecyl sulfate.

[0183] The pH lowering agent comprises citric acid, tartaric acid or a combination thereof. In some disclosures, the pH lowering agent is in the form of coated acid particles. In some disclosures, the acid particles are coated with a water-soluble coating. In some disclosures, the pH lowering agent is in the form of coated citric acid particles. In some disclosures, the composition comprises from about 50 mg to about 500 mg of citric acid. In some disclosures, the composition comprises from about 250 mg to about 500 mg of citric acid. In some disclosures, the citric acid is in the form of coated citric acid.

[0184] In some disclosures, the composition comprises from about 5 mg/cm² to about 25 mg/cm² of enteric coating.

[0185] The compositions of the invention may be administered orally in an effective amount within the dosage ranges described herein in a regimen of single or multiple (twice, etc.) daily or single or multiple weekly doses. In some disclosures, the compositions of the invention may be administered orally in an effective amount for a suitable period of time to treat a disease in a subject in need thereof. As used herein, the term "a suitable period of time" refers to the period of time starting when a subject begins treatment for a condition using a method of the present disclosure, throughout the treatment, and up until when the subject stops treatment due to either a reduction in symptoms associated with the condition or due to a laboratory diagnosis indicating that the condition is under control. In an disclosure, a suitable period of time is one (1) week. In some disclosures, a suitable period of time is between one (1) week and two (2) weeks. In some disclosures, a suitable period of time is two (2) weeks. In some disclosures, a suitable period of time is between two (2) weeks and three (3) weeks. In some disclosures, a suitable period of time is three (3) weeks. In an disclosure, a suitable period of time is between three (3) weeks and four (4) weeks. In a disclosure, a suitable period of time is four (4) weeks. In some disclosures, a suitable period of time is between four (4) weeks and five (5) weeks. In some disclosures, a suitable period of time is five (5) weeks. In some disclosures, a suitable period of time is between five (5) weeks and six (6) weeks. In some disclosures, a suitable period of time is six (6) weeks. In some disclosures, a suitable period of time is between six (6) weeks and seven (7) weeks. In some disclosures, a suitable period of time is seven (7) weeks. In some disclosures, a suitable period of time is between seven (7) weeks and eight (8) weeks. In some disclosures, a suitable period of time is eight (8) weeks. In some disclosures, a suitable period of time is between one (1) month and eight (8) months. In

some disclosures, a suitable period of time is between two (2) months and six (6) months. In some disclosures, a suitable period of time is between three (3) months and five (5) months.

[0186] According to aspects of the invention, the compositions of the present invention provide the predictable delivery of an active agent with surprisingly low inter-subject variability in terms of maximum plasma concentration ($C_{\max}$) and the time to reach the maximum plasma concentration ($T_{\max}$). In some disclosures, the delivery of the therapeutic agent optimizes absorption beyond the duodenum.

[0187] In some disclosures, the solid oral dosage form in accordance with the present disclosure may be used to treat patients who suffer from disease states including, but not limited to, bacterial or viral infectious diseases, metabolic disorders, cardiovascular, neurological, endocrine, pulmonary, or oncological diseases.

[0188] In some disclosures, a solid oral dosage form of a gonadotrophin releasing hormone (GnRH) analogue in accordance with the present disclosure may be used to treat patients who suffer from hormone-responsive cancers. The present disclosure may be used, for example, to treat prostate cancer or breast cancer. In a specific disclosure of the present disclosure, a solid oral dosage form of a GnRH analogue in accordance with the present disclosure may be used to treat patients who suffer from estrogen-dependent conditions. The present disclosure may be used, for example, to treat endometriosis or uterine fibroids, to treat precocious puberty, and to control ovarian stimulation in In Vitro Fertilization.

[0189] According to disclosures illustrated herein, a patient having prostate cancer can be treated with a solid oral dosage form of the present disclosure. In an disclosure, such treatment includes orally administering the patient, for a suitable period of time, a pharmaceutical tablet that includes (A) a gonadotrophin releasing hormone (GnRH) analogue; (B) an absorption enhancer; (C) coated acid particles intermixed with the GnRH analogue, wherein the coating separates the citric acid from the GnRH analogue in the tablet; (D) an outer layer of an acid-resistant enteric coating effective to transport the pharmaceutical tablet through the stomach of a patient while preventing contact between the GnRH analogue and stomach proteases; and (E) a water soluble barrier layer beneath the outer layer of enteric coating that separates the enteric coating from the coated acid particles. In exemplary disclosures, amounts of leuprolide that may be administered to a patient being treated for prostate cancer can measure between 1-20 mg per day, once or twice daily, for 4, 12, 16 or 24 weeks and continued as necessary.

[0190] According to disclosures illustrated herein, a patient having endometriosis can be treated with a solid oral dosage form of the present disclosure. In an disclosure, such treatment includes orally administering the patient, for a suitable period of time, a pharmaceutical tablet that includes (A) a gonadotrophin releasing hormone (GnRH) analogue; (B) an absorption enhancer; (C) coated acid particles intermixed with the GnRH analogue, wherein the coating separates the citric acid from the GnRH analogue in the tablet; (D) an outer layer of an acid-resistant enteric coating effective to transport the pharmaceutical tablet

through the stomach of a patient while preventing contact between the GnRH analogue and stomach proteases; and (E) a water soluble barrier layer beneath the outer layer of enteric coating that separates the enteric coating from the coated acid particles. In exemplary disclosures, amounts of leuprolide that may be administered to a patient being treated for endometriosis can measure between 0.5-20 mg per day, once or twice daily, for up to 6 months.

[0191] According to disclosures illustrated herein, a patient having uterine fibroids can be treated with a solid oral dosage form of the present disclosure. In an disclosure, such treatment includes orally administering the patient, for a suitable period of time, a pharmaceutical tablet that includes (A) a gonadotrophin releasing hormone (GnRH) analogue; (B) an absorption enhancer; (C) coated acid particles intermixed with the GnRH analogue, wherein the coating separates the citric acid from the GnRH analogue in the tablet; (D) an outer layer of an acid-resistant enteric coating effective to transport the pharmaceutical tablet through the stomach of a patient while preventing contact between the GnRH analogue and stomach proteases; and (E) a water soluble barrier layer beneath the outer layer of enteric coating that separates the enteric coating from the coated acid particles. In exemplary disclosures, amounts of leuprolide that may be administered to a patient being treated for uterine fibroids can measure between 0.5-20 mg per day, once or twice daily, for up to 3 months.

[0192] According to disclosures illustrated herein, a patient having breast cancer can be treated with a solid oral dosage form of the present disclosure. In an disclosure, such treatment includes orally administering the patient, for a suitable period of time, a pharmaceutical tablet that includes (A) a gonadotrophin releasing hormone (GnRH) analogue; (B) an absorption enhancer; (C) coated acid particles intermixed with the GnRH analogue, wherein the coating separates the citric acid from the GnRH analogue in the tablet; (D) an outer layer of an acid-resistant enteric coating effective to transport the pharmaceutical tablet through the stomach of a patient while preventing contact between the GnRH analogue and stomach proteases; and (E) a water soluble barrier layer beneath the outer layer of enteric coating that separates the enteric coating from the coated acid particles. In exemplary disclosures, amounts of leuprolide that may be administered to a patient being treated for breast cancer can measure between 0.5-20 mg per day, once or twice daily, for up to 24 months.

[0193] According to disclosures illustrated herein, a patient having precocious puberty can be treated with a solid oral dosage form of the present disclosure. In an disclosure, such treatment includes orally administering the patient, for a suitable period of time, a pharmaceutical tablet that includes (A) a gonadotrophin releasing hormone (GnRH) analogue; (B) an absorption enhancer; (C) coated acid particles intermixed with the GnRH analogue, wherein the coating separates the citric acid from the GnRH analogue in the tablet; (D) an outer layer of an acid-resistant enteric coating effective to transport the pharmaceutical tablet through the stomach of a patient while preventing contact between the GnRH analogue and stomach proteases; and (E) a water soluble barrier layer beneath the outer layer of enteric

coating that separates the enteric coating from the coated acid particles. In exemplary disclosures, amounts of leuprolide that may be administered to a patient being treated for precocious puberty can measure between 1-40 mg per day, once or twice daily. Treatment should be continued until the appropriate age of the onset of puberty, at the discretion of the physician.

Methods of Manufacturing

[0194] Any suitable methods can be used to mix the formulation comprising the API. In some disclosures, the solid dosage form is a tablet or the like. In some disclosures, the core of the solid dosage form can be manufactured with varying amounts of the active agent, active excipients (pH lowering agent, permeation enhancer), binder/filler, and with or without disintegrant. In some disclosures, the core can be seal coated with an immediate release water-soluble film barrier layer and then enteric coated.

[0195] In some disclosures, the API and active excipients were dry-blended with inert excipients (binder, filler, optionally disintegrant), lubricant was optimally added and then directly compressed into tablet cores or the like using a hand press.

[0196] In some disclosures, the solid dosage forms are tablets and the tablets can be tested for in-process tests (weight, hardness, friability, disintegration time), then coated with immediate-release coating followed by enteric coating.

[0197] The invention is further illustrated by the following non-limiting examples.

EXAMPLES

Reference Example 1: Enteric Coat Film Layer Thickness

[0198] Tablets were manufactured with varying amounts of the functional excipient citric acid, with and without lauroyl-L-carnitine (LLC). A non-enhanced tablet, Prototype D, was manufactured with no functional excipients. The cores were seal coated with an immediate release water-soluble film barrier layer and then enteric coated. Briefly, the drug substance and active excipients were dry-blended with inert excipients (binder, filler, disintegrant), lubricant was added (magnesium stearate) and then directly compressed into tablet cores using a hand press.

[0199] Prototype E was formulated to dissolve slowly upon transition to the neutral medium, but otherwise similar to Prototype C. Prototype G was formulated to dissolve rapidly upon transition to the neutral medium, but otherwise similar to Prototype C. The results of Prototype

C served as the center-point.

[0200] **Table 1** shows the tablet formulations active excipient contents. The coating quantities are described in terms of weight/surface area, primarily for scaling and comparison to different sized tablets, and also in terms of overall weight gain, which is calculated based on the targeted weight/surface area value on a per-batch basis.

Table 1. Tablet Formulations Active Excipient Contents

Item	Prototype Tablet A	Prototype Tablet B	Prototype Tablet C	Prototype Tablet D	Prototype Tablet E (SLOW)	Prototype Tablet G (FAST)
Leuprolide	3 mg	1 mg	3 mg	3 mg	3 mg	3 mg
Citric Acid	500 mg	500 mg	250 mg	None	250 mg	250 mg
Lauroyl-L-Carnitine	50 mg	50 mg	50 mg	None	50 mg	50 mg
Immediate Release Coat	19 mg/cm ² (10% weight gain)	19 mg/cm ² (10% weight gain)	19 mg/cm ² (12% weight gain)	19 mg/cm ² (12% weight gain)	19 mg/cm ² (12% weight gain)	11 mg/cm ² (7% weight gain)
Enteric Coat	10 mg/cm ² (6% weight gain)	10 mg/cm ² (6% weight gain)	10 mg/cm ² (7% weight gain)	10 mg/cm ² (7% weight gain)	15 mg/cm ² (10% weight gain)	5 mg/cm ² (3.6% weight gain)

Tableting In-Process Controls

[0201] In-process characterizations during tableting operations were performed according the following USP compendial tests:

- USP <1216> *Tablet Friability* (Distek model DF3 Automated Friabilator)
- USP <1217> *Tablet Breaking Force* (Pharmatron model 6D or MT50 Tablet Testers)
- USP<701> *Disintegration*, method described for uncoated tablets (Distek 3100 series bathless disintegration system)

Assay of Tablets and SC Solution by RP-HPLC

[0202] The method involves a gradient elution of leuprolide using a C18 column and Water/MeCN/IPA/TFA buffer system with detection at 220 nm, see **Table 2**.

[0203] *Diluent*: 3.33 mg/mL lauroyl-L-carnitine in water.

3 mg Tablet Standard: Dilute reference standard (1.0 mg/mL) to 0.2 mg/mL with *Diluent*.

1 mg Tablet Standard: Dilute reference standard (1.0 mg/mL) to 0.067 mg/mL with *Diluent*.

[0204] *Tablet Extraction*: An individual tablet was added to a tared vial and weighed. For tablets containing LLC in the formulation, the tablet was crushed in the same vial and 15 mL of water was added. For the unformulated tablets (without LLC), *Diluent* was used in place of water. The mixtures were placed on a stir plate and mixed for 30 minutes. Approximately 2 mL of the mixture was transferred to a polypropylene microtube and clarified by centrifugation.

[0205] *Tablet Assay Calculation*: The assay of each test article was measured relative to the responses in the working standards. Tablet soluble matter and extract solution density were considered in the calculations.

[0206] *SC Solution Standard*: Reference standard (1.0 mg/mL) was diluted 1:10 using a solution of 0.9% sodium chloride.

[0207] *SC Test Article*: Inject neat.

Table 2. HPLC Method

Stationary Phase	Proto 200 C18 5µm, 100 x 2.1 mm (Higgins Analytical PN RS-10210D185)	
Mobile Phase A	5% acetonitrile, 0.1% trifluoroacetic acid	
Mobile Phase B	70% acetonitrile, 20% 2-propanol, 0.07% trifluoroacetic acid	
Column Temperature	50°C	
Flow Rate	1.2 mL/minute	
Run Time	6 minutes	
Detection	220 nm	
Injection Volume	7 µL for 3 mg tablet assay,	
	20 µL for 1 mg tablet assay, and	
	15 µL for SC solution assay	
Time Program	Time	% Mobile Phase B
	0.0	20%
	3.5	30%
	3.6	100%
	5.0	100%
	5.1	20%

Stationary Phase	Proto 200 C18 5µm, 100 x 2.1 mm (Higgins Analytical PN RS-10210D185)	
	6.0	20%

[0208] A rapid RP-HPLC method for leuprolide assay was developed utilizing an aqueous/acetonitrile/2-propanol/TFA solvent system and a C18 stationary phase. The method demonstrated linearity across a wide range of column loads indicating suitability for the analysis of test articles at various concentrations (see **FIG. 1**) The same method was used for determining assay of the SC solution and tablet assay and content uniformity with only minor modifications to injection volumes and standard preparations. For reference, the column loads for SC and Tablet test articles ranged from 1.33 to 1.5 µg. Representative chromatograms are provided in **FIG. 2** and **FIG. 3**. Overlaid with blank injections, the figures demonstrate that leuprolide is fully resolved from any potentially interfering peaks in the tablet and vehicle matrices. Leuprolide elutes at about 2.2 minutes

Dissolution Method

[0209] The dissolution procedure was performed according to USP chapter <711>, Apparatus 2 (paddles) for Delayed Release Dosage Forms. The acid stage was conducted in 300 mL of 0.1 N hydrochloric acid with a 50 rpm paddle speed for 120 minutes. The buffer stage was performed using 500 mL of 50 mM phosphate, pH 6.8, with a paddle speed of 50 rpm for 60 minutes (plus an infinity time point). Samples were taken at the end of the acid stage and after 10, 20, 30, 45 and 60 minutes in the buffer stage and after the infinity time point. Samples were assayed according to a rapid RP-HPLC method described above with modifications to the standard preparations and injection volumes to accommodate the more dilute solutions.

[0210] The subcutaneous (SC) comparator was formulated to a final concentration of 0.1 mg/mL in an isotonic sodium chloride solution. Briefly, leuprolide acetate was dissolved in 0.9% sodium chloride to a concentration of 0.1 mg/mL, and stored refrigerated. The comparator was shipped to the animal test site on ice and sterile filtered immediately prior to dosing of the dogs. The formulation was tested during the week before dosing and again upon return of the remaining solution. A summary of the analytical test results is presented in **Table 3**.

Table 3. Subcutaneous (SC) Formulation and Dose

Formulation	Assay Date	Concentration (mg/mL)
0.1 mg/mL Leuprolide in 0.9% Sodium Chloride	before dosing	0.1010
	after dosing	0.1006

[0211] The tablets were characterized by in-process and final product tests as follows:

In process tests: friability, breaking force, disintegration time

[0212] Final product tests: content uniformity, assay (calculated from CU), dissolution.

[0213] The stability of the prototypes was confirmed after dosing (testing for assay only). The concentration of a SQ solution was verified before and after administration.

[0214] A small quantity of tablets from Prototype A (3 mg strength, 500 mg citric acid and 50 mg LLC) were packaged in HDPE bottles with desiccant and tested placed in a brief stability study (6 months, 5°C and 25°C, assay and degradation, only).

[0215] The tablets were analyzed for assay, content uniformity and dissolution (acid stage and buffer stage). The assay and content uniformity results are summarized in **Table 4A** and **4B**, and indicate good overall recovery and excellent content uniformity.

Table 4A. Assay and Content Uniformity of tablets in Prototypes A-D

Unit No.	Prototype A		Prototype B		Prototype C		Prototype D	
	mg/unit	%LC (3mg)	mg/unit	%LC (1mg)	mg/unit	%LC (3mg)	mg/unit	%LC (3mg)
1	2.91	97.1%	0.98	98.4%	2.70	89.9%	2.93	97.7%
2	2.88	95.9%	0.97	96.5%	2.52	84.1%	2.63	87.7%
3	2.85	95.0%	0.94	93.9%	2.77	92.2%	2.83	94.3%
4	2.88	95.9%	0.96	95.6%	2.76	91.9%	2.87	95.6%
5	2.90	96.8%	0.99	99.2%	2.80	93.5%	2.84	94.8%
6	2.87	95.7%	0.91	91.3%	2.78	92.8%	2.90	96.6%
7	2.90	96.8%	0.99	98.6%	2.87	95.6%	2.92	97.3%
8	2.85	95.0%	0.98	98.3%	2.52	83.9%	2.90	96.6%
9	2.88	95.9%	0.95	95.1%	2.70	89.9%	2.86	95.3%
10	2.91	97.1%	0.97	97.5%	2.53	84.5%	2.81	93.7%
Average	2.88	96.1%	0.96	96.4%	2.69	89.8%	2.85	95.0%
SD	0.02	0.8%	0.03	2.5%	0.13	4.2%	0.09	2.9%

[0216] The assay and content uniformity results for the coated prototype E tablets are summarized in **Table 4B**, and indicate good overall recovery and excellent content uniformity. Because prototype G was made from the same tablet cores as prototype E, the assay and uniformity was assigned to both batches.

Table 4B. Assay and Content Uniformity of Tablet in Prototypes E/G

Sample	mg/Tablet	%LC
Leuprolide Prototype E - CU1	2.77	92.3%
Leuprolide Prototype E - CU2	2.76	92.0%
Leuprolide Prototype E - CU3	2.91	96.9%
Leuprolide Prototype E - CU4	2.75	91.5%
Leuprolide Prototype E - CU5	2.73	90.9%
Leuprolide Prototype E - CU6	2.69	89.5%
Leuprolide Prototype E - CU7	2.80	93.4%

Sample	mg/Tablet	%LC
Leuprolide Prototype E - CU8	3.02	100.6%
Leuprolide Prototype E - CU9	2.64	88.1%
Leuprolide Prototype E - CU10	2.80	93.4%
Average:	2.79	92.9%
SD:	0.11	3.6%

[0217] The dissolution results for each batch are summarized in **FIGS. 4** and **5**. The results confirm acid resistance of all batches (reported at 0 minutes) and larger tablets dissolve at a slower rate. The tablets were stored refrigerated and shipped to the animal test site on ice. Extra tablets were returned for dose verification as summarized in **Table 5** and **FIG. 6**. The data indicate that the dissolution profiles and final percent dissolved (assays) were not significantly affected by time or shipping. The test articles were stable for the duration of the study.

Table 5. Prototype Tablet Dose Verification / Assay Stability

	Prototype Tablet A (ULB-231/035)	Prototype Tablet B (ULB-231/036)	Prototype Tablet C (ULB-231/037)	Prototype Tablet D (ULB-231/038)
Leuprolide/tablet at release	2.88 mg	0.96 mg	2.69 mg	2.85 mg
Leuprolide/tablet after dosing	2.91 mg	0.95 mg	2.68 mg	2.84 mg

In Vivo Studies

[0218] This study evaluated the pharmacokinetics of leuprolide in dogs following a single subcutaneous (SC) dose (0.01 mg/kg) and single oral doses of enteric-coated tablets containing either 1 mg or 3 mg amounts of leuprolide with various amounts of excipients. The active excipients evaluated were lauroyl-L-carnitine (LLC) and citric acid. The parameters examined were ratios of citric acid to LLC and the absolute amount of citric acid. An unformulated tablet (no citric acid, no LLC) was included as a control.

MATERIALS AND METHODS

Drug Substance

[0219] A 2.0 gram quantity of Leuprolide Acetate, GMP quality, was purchased and received from PolyPeptide Group.

Reference Standard

[0220] Approximately 60 mg of Leuprolide Acetate was used to establish a 1 mg/mL aqueous reference standard.

Analytical Development

[0221] A commercially available ELISA kit was qualified for measuring concentrations of Leuprolide in plasma samples. A rapid HPLC method was developed to measure leuprolide content in assay, content uniformity and dissolution (by USP<711>) samples of the tablet prototype test articles.

[0222] Each prototype was evaluated by dosing a single tablet in beagle dogs. Six dogs were dosed for prototypes A, B, C, E and G and three dogs were dosed for prototype D. [*plus 3 dogs for SQ = 24 dogs total*] Plasma samples were collected over a 24 hour period, with time points: pre-dose, 0.5, 1, 1.33, 1.66, 2, 2.33, 2.66, 3, 3.33, 3.66, 4, 6, 8, 12 and 24 hours. [*16 samples/dog × 21 dogs = 336 samples*]

Animals

[0223] Adult beagle dogs weighing approximately 8 to 16 kg were used in the study. Primary enclosures were specified in the USDA Welfare Act (9 CFR Parts 1, 2, and 3) and as described in the Guide for the Care and Use of Laboratory Animals (National Academy Press, Washington, S.C., 1996). A 12-hour light/12-hour dark photoperiod was maintained. Room temperature was set to be maintained at approximately 20 + 5°C. Relative humidity was monitored, but not controlled. Animal room and pen cleaning were performed according to testing facility (Sinclair) standard operating procedures (SOPs).

[0224] Purina® Dog Chow Canine Diet was provided once daily in amounts (~250 g) appropriate for the size and age of the animals. Tap water was available ad libitum via automatic watering device or water bowls. Animals were fasted overnight prior to drug administration and fed six hours after dosing.

Doses and Route of Administration

[0225] Subcutaneous doses of leuprolide were administered as a bolus injection into beagle dogs at a dose volume of 0.1 mL/kg. For a 10 kg dog, this would result in a dose of 0.1 mg. Oral dosing of tablets was accomplished by administering them to the back of the dog's mouth followed with 1.0 mL/kg of water.

Study Design and Pharmacokinetic Sample Collection

[0226] Adult beagle dogs were each dosed with tablet prototypes A, B, C, E or G. During a subsequent phase, three dogs were dosed with the SC formulation.

[0227] Prior to the study, the dogs were fasted overnight before administration of the test articles, but were allowed free access to water. On the following day, a pre-dose blood sample of about 2 mL was collected from each animal. Subsequently, each group of animals was given a single SC injection or tablet containing leuprolide blended in the specified formulation. The dogs were fed 6 hours after dosing.

[0228] After SC administration of the drug (0.01 mg/kg), 2 mL blood samples were collected from the brachial vein at 0.17, 0.33, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours post-dose. After oral administration, 2 mL blood samples were collected from the brachial vein at 0.5, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 6, 8, 12 and 24 hours post administration.

Pharmacokinetic Software

[0229] The pharmacokinetic (PK) profile of leuprolide was determined using plasma assay data. Plasma concentration-time data for individual subjects were analyzed by non-compartmental methods using the actual blood draw times, estimating the area under the curve (AUC) with the trapezoidal rule. Microsoft® Excel 2010 was used for all calculations. Section 0 provides a list of the PK parameters that were determined from the plasma concentration-time data.

Pharmacokinetic Data

[0230] The following PK metrics were estimated on the basis of non-compartmental analysis of plasma concentration-time course data using nominal blood sampling times:

- T_{lag} - the time of the first measurable plasma concentration value;
- T_{max} - the time to reach maximum plasma concentration;
- $T_{1/2}$ - the time necessary for the concentration of drug in the plasma to decrease by one-half.
- C_{max} - the maximum observed plasma concentration (in picograms per milliliter).

- $AUC_{(0-24hr)}$ - the area under the plasma concentration versus time curve from time zero to the time of the last measurable plasma concentration.

AUC (pg/mL * hr)

$$= \sum_0^t \left(\frac{(Cp_2 + Cp_1)}{2} \times (t_2 - t_1) \right)$$

. The calculated AUCs were then corrected for the actual dose given based on assay data and the subject body weight (mg/kg). The values were corrected for actual dose based on assay and body weight of the individual dog;

- %F - absolute bioavailability (Fraction absorbed relative to intravenous administration) was calculated from the mean subcutaneous response, using normalized AUC. The bioavailability of leuprolide by subcutaneous injection is comparable to that by intravenous administration. Bioavailability was calculated using the mg/kg-corrected AUCs [(hr * pg/mL)/(mg/kg)]:

$$\%F = \frac{AUC^{PO}}{AUC^{IV}} \times 100\%$$

[0231] All PK parameters were summarized using descriptive statistics (average and percent coefficient of variation [%CV]) for each treatment. Data from all individual dogs were included in the analyses.

[0232] A summary of the PK results is provided in **Table 6A** and **6B**.

Table 6A. Summary of Pharmacokinetic Results

Dosage Form	Tlag (hrs.)		Tmax (hrs.)		T1/2 (hrs.)	
	Avg.	CV	Avg.	CV	Avg.	CV
A: 500 mg CA, 50 mg LLC, 3mg Leuprolide (n=6)	2.5	93%	3	60%	1.56	15%
B: 500 mg CA, 50 mg LLC, 1mg Leuprolide (n=6)	0.81	35%	1.81	29%	2.13	38%
C: 250 mg CA, 50 mg LLC, 3mg Leuprolide (n=6)	1.72	35%	2.33	36%	1.41	22%
D: Unformulated 3mg Leuprolide (n=6)	1.18	16%	1.5	16%	1.39	35%
E: 250 mg CA, 50 mg LLC, 3mg Leuprolide SLOW (n=6)	1.89	41%	2.51	35%	1.58	19%
G: 250 mg CA, 50 mg LLC, 3mg Leuprolide FAST (n=6)	1.64	76%	2.22	84%	1.9	32%
SC: 0.1 mg Leuprolide (n=3)	0.17	17%	0.94	59%	1.72	16%

Table 6B. Summary of Pharmacokinetic Results

Dosage Form	Cmax (pg/mL)/(mg/kg)		AUC(pg/mL* hr.)/(mg/kg)		%F		
	Avg.	CV	Avg.	CV	Avg.	Median	CV
A: 500 mg CA, 50 mg LLC, 3mg Leuprolide (n=6)	58907	55%	164499	56%	6.10%	6.80%	56%
B: 500 mg CA, 50 mg LLC, 1mg Leuprolide (n=6)	45661	61%	140215	53%	5.20%	5.80%	53%
C: 250 mg CA, 50 mg LLC, 3mg Leuprolide (n=6)	101786	68%	200111	68%	7.40%	5.00%	68%
D: Unformulated 3mg Leuprolide (n=6)	7677	93%	15625	87%	0.60%		87%
E: 250 mg CA, 50 mg LLC, 3mg Leuprolide SLOW (n=6)	130942	63%	262777	56%	9.80%	10.60%	56%
G: 250 mg CA, 50 mg LLC, 3mg Leuprolide FAST (n=6)	87552	57%	238811	83%	8.90%	6.60%	83%
SC: 0.1 mg Leuprolide (n=3)	1081540	33%	2686192	21%	100%		21%

Subcutaneous (SC) Administration of Leuprolide

[0233] The entire time-concentration plot is provided in FIG. 7 on a linear scale and is duplicated in FIG. 8 using a semi-log scale.

3 mg Leuprolide Tablets with 500 mg Citric Acid and 50 mg LLC (Prototype A)

[0234] Six dogs were dosed with single units of the enhanced formulation prototype A (3 mg strength, enteric coated, 500 mg of citric acid and 50 mg of LLC). The entire time-concentration plot is provided (FIG. 9) on a linear scale and is duplicated in using a semi-log scale (FIG. 10). The data indicate a 10-fold increase in bioavailability relative to the non-enhanced formulation (prototype D).

1 mg Leuprolide Tablets with 500 mg Citric Acid and 50 mg LLC (Prototype B)

[0235] Six dogs were dosed with single units of the enhanced formulation prototype B (1 mg

strength, enteric coated, 500 mg of citric acid and 50 mg of LLC). The entire time-concentration plot is provided in (FIG. 11) on a linear scale and is duplicated using a semi-log scale in (FIG. 12). Prototype B was identical in formulation to prototype A with the exception of strength. The data indicated that the PK response was linear with respect to dose in the 1 mg to 3 mg range.

3 mg Leuprolide Tablets with 250 mg Citric Acid and 50 mg LLC (Prototype C)

[0236] Six dogs were dosed with individual units of the enhanced 3 mg leuprolide Prototype C tablets (3 mg strength, enteric coated, 250 mg of citric acid and 50 mg of LLC). The entire time-concentration plot is provided in (FIG. 13) on a linear scale and is duplicated in (FIG. 14) using a semi-log scale. Prototype C tablets differ from prototype A in that there is half the amount of citric acid (only 250 mg) and that the tablet size is substantially smaller. The mean bioavailability for prototype C was 5.6% with a 46% CV which is consistent with the results for prototype A.

3 mg Non-Enhanced Leuprolide Tablet (Prototype D)

[0237] Three dogs were dosed with the non-enhanced 3 mg leuprolide tablets (enteric coated, but without citric acid or LLC). The entire time-concentration plot is provided in (FIG. 15) on a linear scale and is duplicated in (FIG. 16) using a semi-log scale.

Slower Dissolving Tablet with 250 mg Citric Acid and 50 mg LLC (Prototype E)

[0238] Six dogs were dosed with single units of the enhanced formulation prototype E (3 mg strength, 250 mg of CA and 50 mg of LLC, 19 mg/cm² IR, 15 mg/cm² EC). The entire time-concentration plot is provided in (FIG. 17) on a linear scale and is duplicated in (FIG. 18) using a semi-log scale.

Faster Dissolving Tablet with 250 mg Citric Acid and 50 mg LLC (Prototype G)

[0239] Six dogs were dosed with single units of the enhanced formulation prototype E (3 mg strength, 250 mg of CA and 50 mg of LLC, 11 mg/cm² IR, 5 mg/cm² EC). The entire time-concentration plot is provided in (FIG. 19) on a linear scale and is duplicated in (FIG. 20).

[0240] A 250 mg citric acid formulation (Prototypes C, E and G) may be favored over a 500 mg citric acid formulation (Prototypes A and B) for a number of reasons. However, as illustrated in the results from Prototype C, that formulation did show moderately higher variability than its

500 mg citric acid counterparts (Prototypes A and B). The smaller sized tablet (Prototype C) showed median absorption levels similar to or slightly less than the larger tablets (Prototypes A and B) containing more citric acid, but often with one or two very high values which in-turn skew the averages higher than other tablets tested. The present study was undertaken to elucidate the effect, if any, of deliberate variations of the dissolution profile on absorption of tablets which are otherwise similar to prototype C.

[0241] FIG. 21 shows a linear time-concentration curve after oral administration of various leuprolide tablets of the present disclosure to beagle dogs. The tablets that showed the shortest lag time (T_{lag}) before opening in the neutral medium, *in-vitro*, (prototype G, see Table 6A) also showed the earliest average times of first measurable response and maximum concentration in the dogs. Likewise, the tablets which showed the longest lag time (T_{lag}) *in-vitro* (prototype E, see Table 6A), showed the longest average times of first measurable response and maximum concentration in the dogs.

[0242] The effects of T_{lag} and T_{max} on absorption are illustrated in FIG. 22 and FIG. 23. In FIG. 22, the response of C_{max} vs. T_{max} is shown. For both the formulations containing 500 mg CA/50 mg LLC (prototypes A and B, "leuprolide 500/50") and those containing 250 mg CA/50 mg LLC (prototypes C, E and G, "leuprolide 250/50"), there is an increase in C_{max} as T_{max} increases. FIG. 23 shows the dependence of C_{max} on both T_{lag} and T_{max} . In this bubble plot, the size of the bubble corresponds to the magnitude of C_{max} (also labeled on the data points). The data demonstrate that, for each formulation, an increase in T_{lag} , T_{max} , or both T_{lag} and T_{max} , results in increased absorption.

[0243] One of the formulation principles prior to this study was dosage forms (e.g. tablets) which dissolved as rapidly as possible after passage through the stomach to achieve a highly localized bolus concentration of API and absorption enhancers. That principle was derived, in part, from the literature, where it is expected that dissolution of the drug in the duodenum would result in the highest absorption and that variability would be reduced as a consequence of those higher overall bioavailabilities. The data in the present study, however, showed an unexpected and surprising trend in that the tablet which was slowest to open and dissolve (prototype E) showed the greatest average leuprolide absorption with the most precise individual absorptions. While the rapidly dissolving formulation (Prototype G) did show the highest individual absorption of the leuprolide (23.0% F), the average and median %F values were lower and less precise, when compared to Prototype E. The results suggest that the added coating material, and thus longer lag before dissolution, might moderate the extreme high and low absorption values commonly observed with the more lightly coated and therefore more rapidly dissolving tablets.

[0244] The results indicated that the dissolution profiles of the tablets can be manipulated to show measureable differences in the pharmacokinetic responses in dogs. Specifically, the data demonstrated that the greatest enteric coat film layer thickness (15 mg/cm², or approximately 10% weight gain) resulted in higher average bioavailability with improved precision when

compared to prototypes with relatively less coating. Bioavailabilities between 9-11% with CVs in the 50-60% can be achieved.

[0245] It is believed that mixtures of Eudragit® L 30 D-55 (an enteric coat which dissolves at pH 5.5 and above) available from Evonik Laboratories and Eudragit® FS 30 D (an enteric coat which dissolves at pH 7.4 and above) available from Evonik Laboratories, for example at a ratio of at least 75:25 mixture of Eudragit® FS 30: Eudragit® L 30 D-55 D, can delay an onset of dissolution further down the small intestine compared to at least one example discussed above (e.g., but not limited to, prototype E). The resulting delayed dissolution should be comparable to a tablet coated with more than 15 mg/cm² layer of Eudragit® L 30 D-55.

[0246] A tablet of the present disclosure may include a reduced amount (e.g., between about 0.1% to about 99% reduction or between about 1% to about 99% reduction) of the tablet disintegrant compared with, e.g., but not limited to, the examples described herein. Alternatively, a tablet of the present disclosure may not include a tablet disintegrant.

[0247] A tablet of the present disclosure may include a HPC/HPMC filler and/or other viscous or low solubility additive, to result in slowing the disintegration of the tablet core after the coating film layers dissolve.

[0248] Alternatively, a tablet of the present disclosure may include both (1) a mixture of Eudragit® L 30 D-55 and Eudragit® FS 30 D and (2) a reduced amount of tablet disintegrant and/or a viscous additive (e.g., but not limited to, a HPMC filler).

Example 2: Modified core

Materials and Methods:

[0249] Tablets containing a peptide, triptorelin, were manufactured as described in **Table 7**. Triptorelin is a decapeptide (pGlu-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-Gly-NH₂), synthetic analogue of gonadotropin-releasing hormone (GnRH) agonist. The tablets were manufactured with and without disintegrant (Kollidon CL), with or without hydroxypropyl cellulose (HPC), HPMC (hydroxypropyl methyl cellulose) or chitosan.

[0250] Several formulations of a tablet containing triptorelin as a model peptide API, a pH-lowering agent, and an absorption enhancer were manufactured. The tablet cores varied in the type and amount of filler/binder (microcrystalline cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, or chitosan), with or without a super-disintegrant (Kollidon CL), in order to vary the rate of release of the peptide API and enhancing agents. A slower release rate from the dosage form is expected to cause a delay in T_{max}. Furthermore, the tablets were

coated with an acid-resistant enteric coating, which varied in thickness and buffer capacity. Tablets with thick (10% w/w) enteric coats or enhanced buffer capacity (pH 2.3) are expected to open later in the gastrointestinal tract, and hence have a larger value of Tiag relative to tablets coated with 6% (w/w) enteric coat or decreased buffer capacity (pH 5.2-5.3). Also tested were tablets containing no enhancing excipients, and a tablet in which the permeation enhancer LLC was replaced with SDS (a surfactant with a higher critical micelle concentration (CMC) resulting in stronger surfactant properties).

Table 7

Component	Formulations							
	JSV-003-178	JSV-003-180	JSV-003-182	ULB-231-201	ULB-231-204	ULB-231-254	ULB-231-256	ELB-020-014
triptorelin † (mg)	4	4	4	4	4	4	4	4
LLC-C1 (mg)	50	50	0	50	50	50	50	0
SDS (mg)	0	0	0	0	0	0	0	50
Citric Acid DCF20 (mg)	250	250	0	250	250	250	250	250
Kollidon CL (% w/w)	0	3.5	3.5	0	0	0	0	3.5
Chitosan (% w/w)	0	0	0	40	0	40	0	0
HPC A4MP (% w/w)	23	0	0	0	17	0	17	0
HPMC E3 (% w/w)	0	0	0	0	6	0	6	0
enteric coat (% w/w)	6	10	10	6	6	6	6	6
enteric coat pH	2.3	2.3	2.3	5.3*	5.3*	5.2	5.2	5.2
† As triptorelin free base								
* After the dosing events, it was found that the enteric coat of these batches did not pass acid-stage dissolution, and the enteric coat showed substantial cracking when highlighted with a water-soluble dye								

Results:

[0251] The PK data summary is shown in Tables 8A and 8B.

Table 8A

Formulation	Description†	n	Tlag (h)		Tmax (h)		T½ (h)	
			Avg	CV in %	Avg	CV in %	Avg	CV in %
IV	0.1 mg/mL triptorelin in PBS	3	0.00	NC	0.00	NC	2.76	35
SC	0.1 mg/mL triptorelin in PBS	3	0.17	0	0.53	40	2.10	26
JSV-003-182	4 mg triptorelin/ 0 CA/0 LLC, 10% EC (neat)	3	2.67	NC	4.00	NC	1.44	NC
JSV-003-180	4 mg triptorelin/ 250 CA/50 LLC, 10% EC (neat)	5	1.33	20	1.58	26	1.70	17
JSV-003-178	4 mg triptorelin/ 250 CA/50 LLC/MR, 6% EC (neat)	5	1.73	37	3.07	59	1.70	38
ULB-231-201*	4 mg triptorelin/ 250 CA/50 LLC/ chi tosan, 6% EC (pH 5.3)	6	0.67	39	2.06	51	2.23	20
ULB-231-204*	4 mg triptorelin/ 250 CA/50 LLC/MR, 6% EC (pH 5.3)	4	0.75	38	1.33	20	2.01	30
ULB-231-254	4 mg triptorelin/ 250 CA/50 LLC/ chi tosan, 6% EC (pH 5.2)	6	1.03	30	1.39	35	1.29	16
ULB-231-256	4 mg triptorelin/ 250 CA/50 LLC/MR, 6% EC (5.2)	4	1.17	61	2.39	40	1.78	28
ELB-020-014	4 mg triptorelin/ 250 CA/50 SDS, 6% EC (pH 5.2)	6	0.75	37	1.08	45	1.43	43

† PBS, phosphate-buffered saline; CA, citric acid; LLC, lauroyl-L-carnitine; EC, enteric coat; MR, modified release core (HPC/HPMC)

* After the dosing events, it was found that the enteric coat of these batches did not pass acid-stage dissolution, and the enteric coat showed substantial cracking when highlighted with a water-soluble dye

Table 8B

Formulation	Description†	n	Cmax (ng/mL)/ (mg/kg)		AUC (ng/mL*h)/ (mg/kg)		%F(0-24 h)	
			Avg	CV in %	Avg	CV in %	Avg	CV
IV	0.1 mg/mL triptorelin in PBS	3	5243	16	8827	29	100.00 %	29%
SC	0.1 mg/mL triptorelin in PBS	3	2039	12	5372	9	60.9%	9%
JSV-003-182	4 mg triptorelin/ 0 CA/0 LLC, 10% EC (neat)	3	1.3	173	4.0	173	0.05%	173%

Formulation	Description†	n	Cmax (ng/mL)/ (mg/kg)		AUC (ng/mL·h)/ (mg/kg)		%F(0-24 h)	
			Avg	CV in %	Avg	CV in %	Avg	CV
JSV-003-180	4 mg triptorelin/ 250 CA/50 LLC, 10% EC (neat)	5	31	37	48	34	0.55%	34%
JSV-003-178	4 mg triptorelin/ 250 CA/50 LLC/MR, 6% EC (neat)	5	48	91	114	81	1.29%	81%
ULB-231- 201*	4 mg triptorelin/ 250 CA/50 LLC/ chi tosan, 6% EC (pH 5.3)	6	18.7	133	51.2	139	0.58%	139%
ULB-231- 204*	4 mg triptorelin/ 250 CA/50 LLC/MR, 6% EC (pH 5.3)	4	7.6	117	19.2	90	0.22%	90%
ULB-231- 254	4 mg triptorelin/ 250 CA/50 LLC/ chi tosan, 6% EC (pH 5.2)	6	5.1	64	6.4	51	0.07%	51%
ULB-231- 256	4 mg triptorelin/ 250 CA/50 LLC/MR, 6% EC (5.2)	4	23.2	92	56.6	108	0.64%	108%
ELB-020- 014	4 mg triptorelin/ 250 CA/50 SDS, 6% EC (pH 5.2)	6	26.3	73	46.3	84	0.52%	84%

[0252] The average PK curves for the intravenous (IV) and subcutaneous (SC) doses are shown in FIG. 24.

[0253] The average curves for PO doses, corrected for T_{max} are shown in FIGS. 25A and 25B.

[0254] FIG. 26 shows the bioavailability vs. T_{max} . "Conventional" denotes a core containing disintegrant, "Modified Release" or "MR" cores contain HPC or HPMC (and do not contain disintegrant), "chitosan" cores contain medium-weight chitosan (and do not disintegrant). Permeation enhancers were either LLC (lauroyl-L-carnitine) or SDS (sodium dodecyl sulfate). Note that %F increases as T_{max} increases - contrary to the dosage forms with a conventional core and/or enteric coating having a faster, more immediate release.

[0255] FIG. 27 is a bubble plot representation of the data, showing the influence of T_{lag} and T_{max} on %F. The size of the bubble corresponds to the value of %F (also labeled on the data points).

[0256] The conventional tablet with LLC (JSV-003-180, see U.S Patent No. 8,377,863,) is the baseline comparison for all formulations containing LLC. This formulation contains a super-disintegrant; thus, the tablet core disintegrates in solution. In contrast, the MR cores (JSV-003-178, ULB-231-204, and ULB-231-256) and chitosan cores (ULB-231-201 and ULB-231-254) do not contain a super-disintegrant. These cores do not disintegrate in solution, but instead form a viscous hydrogel that slowly erodes.

[0257] The chitosan cores demonstrate the advantage of a delayed $T_{\max}$. The data for batch ULB-231-254 show a relatively early T_{lag} and $T_{\max}$ (vs. JSV-003-180), which results in poor bioavailability. However, despite having a slightly earlier T_{lag} (than the aforementioned batches), batch ULB-231-201 has a longer $T_{\max}$ than both ULB-231-254 and JSV-003-180. This results in an 8-fold increase in %F for ULB-231-201 vs. ULB-231-254.

[0258] The MR cores also show that longer T_{lag} and $T_{\max}$ result in increased %F. Batch ULB-231-204 has both T_{lag} and $T_{\max}$ sooner than JSV-003-180, and lower bioavailability. By increasing T_{lag} and $T_{\max}$, batch ULB-231-256, there is a 3-fold increase in %F over batch ULB-231-204. In batch JSV-003-178, both T_{lag} and $T_{\max}$ are again increased, resulting in an additional 2-fold increase in %F (vs. ULB-231-256), or an overall 6-fold increase vs. ULB-231-204, or an overall 2.3-fold increase over the conventional formulation JSV-003-180.

[0259] The conventional core with SDS (batch ELB-020-014, which contains a super-disintegrant) shows that, for relatively early T_{lag} and $T_{\max}$ (compared to "conventional/LLC" JSV-003-180), a much more potent surfactant (having a higher CMC) than LLC can be used to achieve a similar %F. In this case, the CMC for SDS is about 10 mM, compared to about 1.2 mM for LLC.

[0260] The data show, within a formulation and across different formulations, that the bioavailability of the peptide (e.g. triptorelin) can be modulated by controlling the T_{lag} and $T_{\max}$ of the dosage form. A longer T_{lag} can be achieved by increasing the thickness or buffer capacity of the enteric coat. A longer $T_{\max}$ can be achieved by increasing the viscosity of the tablet core through the use of viscous fillers (HPC, HPMC, chitosan) in the absence of a super-disintegrant. Together, longer T_{lag} and $T_{\max}$ results in greater systemic bioavailability, in general.

[0261] In addition, the data show that the fine-tuning of these parameters can further augment systemic bioavailability. For example, in the case of the "MR/LLC" formulations, an increase in T_{lag} achieved by increased enteric coat buffer capacity (JSV-003-178) increased bioavailability, despite only slightly increasing $T_{\max}$ (compared to the "MR/LLC" formulation, ULB-231-256). Both of these batches perform better than ULB-231-204, which has the shortest T_{lag} and $T_{\max}$ of the three.

[0262] In the case of the "conventional" tablet core ELB-020-014, where T_{lag} and T_{max} were relatively short compared to the conventional core JSV-003-180, bioavailability can be enhanced by using a permeation enhancer with a greater CMC. In this case, substitution of LLC with SDS was able to achieve comparable bioavailability, despite the small values of T_{lag} and T_{max} .

[0263] T_{max} can be increased by slowing the dissolution of the tablet core, which can be done a number of ways through the core formulation. For example, a core composed of HPC or HPMC without disintegrant ("MR") can take longer to completely dissolve than a conventional core.

[0264] Based on these data, it is believed that that a tablet containing a pharmaceutical active ingredient (e.g. peptide), pH-lowering agent, and permeation enhancer, systemic bioavailability can be increased through a combination of:

1. 1. Increasing the T_{lag} (the time delay between oral dose administration and the first measurable concentration of the API in systemic circulation).
2. 2. Increasing T_{max} - the time at which the maximum concentration of API (C_{max}) is in systemic circulation.
3. 3. Increasing the surfactant strength of the permeation enhancer.

[0265] Where (1) can be achieved by increasing the thickness or buffer capacity of the enteric coat, (2) can be achieved by increasing the viscosity of the tablet core, and (3) can be achieved by substituting a permeation enhancer for another with a higher CMC (e.g. of about 1.0 to about 40 mM).

Example 3

[0266] One of ordinary skill in the art would reasonable expect that additional active agents described herein (i.e. various peptides or their prodrugs, such as esters or salts) would achieve a targeted delivery and increased bioavailability when in administered in a dosage form as disclosed herein. Without being bound by the theory, it is believed that the further delaying T_{lag} and T_{max} , the further the bioavailability increases. This can be achieved by changing the composition of the enteric coat to include mixtures of the polymers listed in **Table 9** below.

Table 9

Polymer	Dissolution Properties
EUDRAGIT [®] L 30 D-55	Dissolution above pH 5.5
EUDRAGIT [®] L 100-55	
EUDRAGIT [®] L 100	Dissolution above pH 6.0

Polymer	Dissolution Properties
EUDRAGIT [®] L 12,5	Dissolution above pH 7.0
EUDRAGIT [®] S 100	
EUDRAGIT [®] S 12,5	
EUDRAGIT [®] FS 30 D	

[0267] Combinations of these polymers can result in different dissolution properties due to changes in the plasticity and dissolution pH of the mixtures. The pH of the intestine increases from ~5.5 in the duodenum to ~7 in the ileum, with intermediate values in the jejunum. Thus, T_{lag} can be increased by using an enteric coat that dissolves at a pH between 5.5 and 7, due to longer intestinal transit time prior to dissolution of the coat.

[0268] Selected Eudragit[®] compositions are known to dissolve at different pH values ranging from pH 5.5 up to pH 7. Depending on the selected Eudragit[®] compositions, such coatings are suitable to avoid the acidic environment of the stomach and duodenum and to maximize the initial dissolution at a pH >5.5 of duodenal and jejunal fluid.

REFERENCES CITED IN THE DESCRIPTION

Cited references

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

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- [WO02072075A](#) [0003]
- [US8377863B](#) [0256]

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- Preformulation in Solid Dosage Form DevelopmentCRC Press20080000 [0002]
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- Guide for the Care and Use of Laboratory AnimalsNational Academy Press19960000 [0223]

P a t e n t k r a v

5 1. Fast oral sammensætning med modificeret frigivelse, hvor sammensætningen er en tablet, omfattende en kerne og fra 5 mg/cm² til 25 mg/cm² af en enterisk coating, hvor:

(a) kernen omfatter:

(i) en effektiv mængde af aktiv farmaceutisk ingrediens, hvor den aktive farmaceutiske ingrediens er et peptid på 500 Da til 10.000 Da,
10 (ii) et pH-sænkende middel, der er udvalgt blandt citronsyre, vinsyre og en kombination deraf,

(iii) en absorptionsforstærker, der omfatter et kationisk overfladeaktivt middel, et anionisk overfladeaktivt middel eller en kombination deraf, hvor absorptionsforstærkeren har en kritisk micellekoncentration på fra 1,0 mM til 40 mM,
15 (iv) et fyldstof, der omfatter en hydrogeldannende polymer, som er udvalgt blandt hydroxypropylcellulose (HPC), hydroxypropylmethylcellulose (HPMC) eller en kombination deraf, hvor en 2%-opløsning af den hydrogeldannende polymer har en viskositet mellem 3.000 og 120.000 cP ved 20°C, og eventuelt (v) et farmaceutisk acceptabelt desintegreringsmiddel, der er til stede i mindre end 0,01 vægt-% af tabletten; og

20 (b) den enteriske belægning omgiver kernen,
hvor sammensætningen tilvejebringer en farmakokinetisk profil for det aktive middel med en T_{lag} , der er større end 1,0 h og mindre end 16 h efter administration, og en T_{max} , der er større end ($T_{lag} + 0,5$ h) og mindre end 20 h efter administration ved fastende tilstand.

25

2. Sammensætning ifølge krav 1, der yderligere omfatter en vandopløselig barriere under den enteriske coating, og eventuelt hvor den vandopløselige barriere er i en mængde fra ca. 6 til ca. 15 vægt%.

- 3.** Sammensætning ifølge krav 1, hvor absorptionsforstærkeren har en kritisk micellekoncentration på fra 1,0 mM til 15 mM.
- 5 **4.** Sammensætning ifølge krav 1, hvor peptidet er en af leuprolid, insulin, vasopressin, calcitonin, calcitoninen-relateret peptid, parathyreoideahormon, desmopressin, gonadotropin-frigivende hormon (GnRH), luteiniserende hormon-frigivende faktor, adrenokorticototropin, enkephalin, glucagon-lignende peptid-1, 2,6-dimethyltyrosin-D-arginin-phenylalanin-lysinamid og triptorelin.
- 10 **5.** Sammensætning ifølge krav 1, hvor det kationiske overfladeaktive middel omfatter en acylcarnitin, og/eller hvor det anioniske overfladeaktive middel omfatter natriumdodecylsulfat.
- 15 **6.** Sammensætning ifølge krav 1, hvor det pH-sænkende middel er i form af coatede syrepartikler.
- 20 **7.** Sammensætning ifølge krav 1 omfattende fra ca. 50 mg til ca. 500 mg citronsyre.
- 25 **8.** Sammensætning ifølge krav 1, hvor den farmakokinetiske frigivelsesprofil er målrettet frigivelse af den farmaceutisk aktive bestanddel til jejunum, ileum eller jejunum og ileum.
- 25 **9.** Sammensætning ifølge krav 1, hvor sammensætningen er udformet således, at i det væsentlige ingen aktiv farmaceutisk ingrediens frigives i maven, tolvfingertarmen eller maven og tolvfingertarmen efter administration.

DRAWINGS

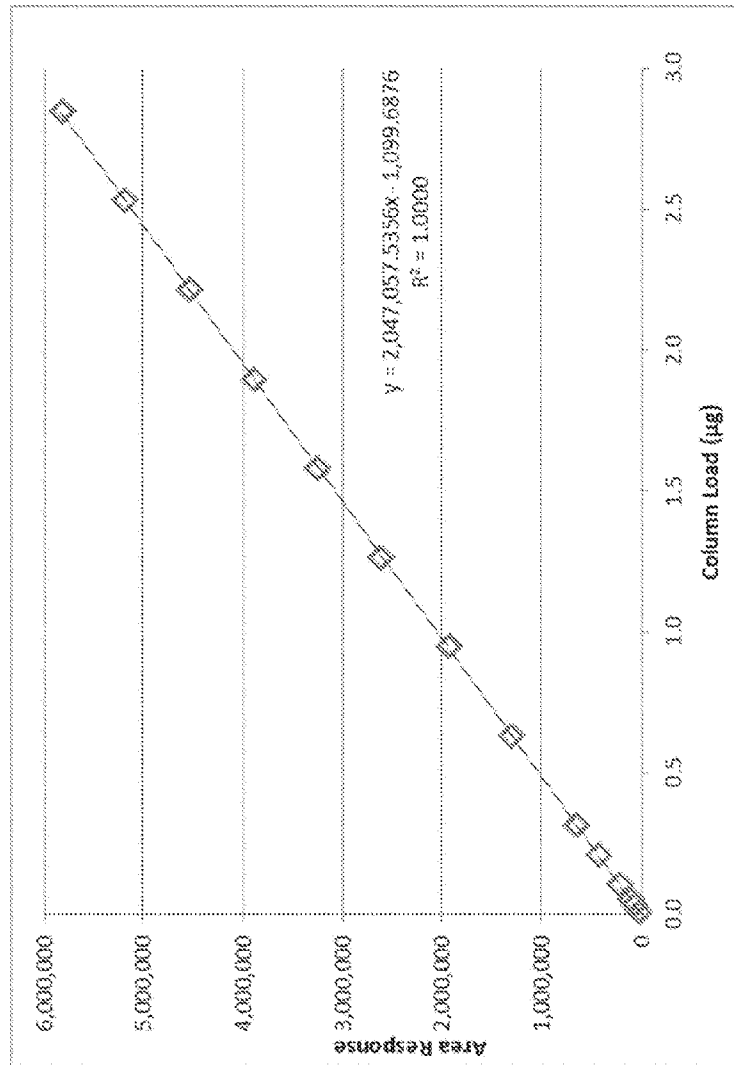
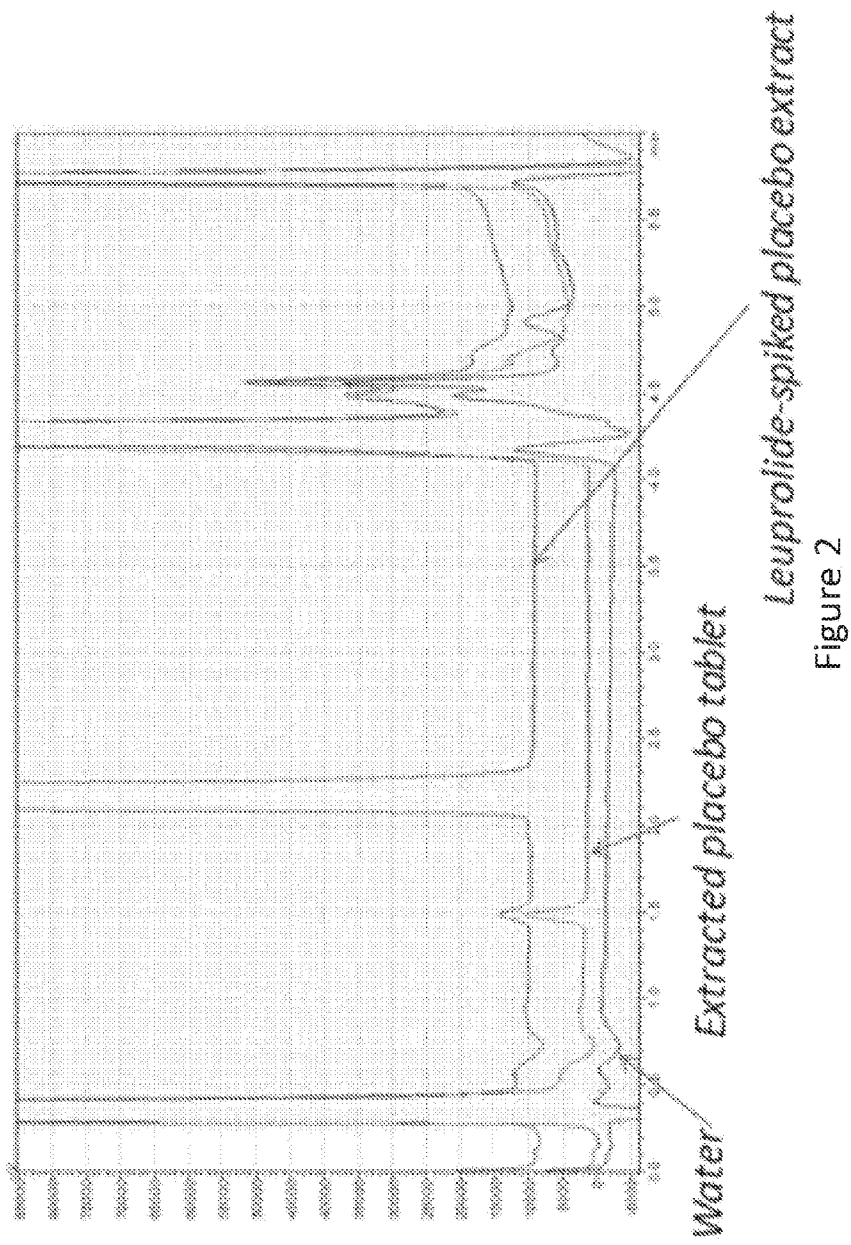


Figure 1



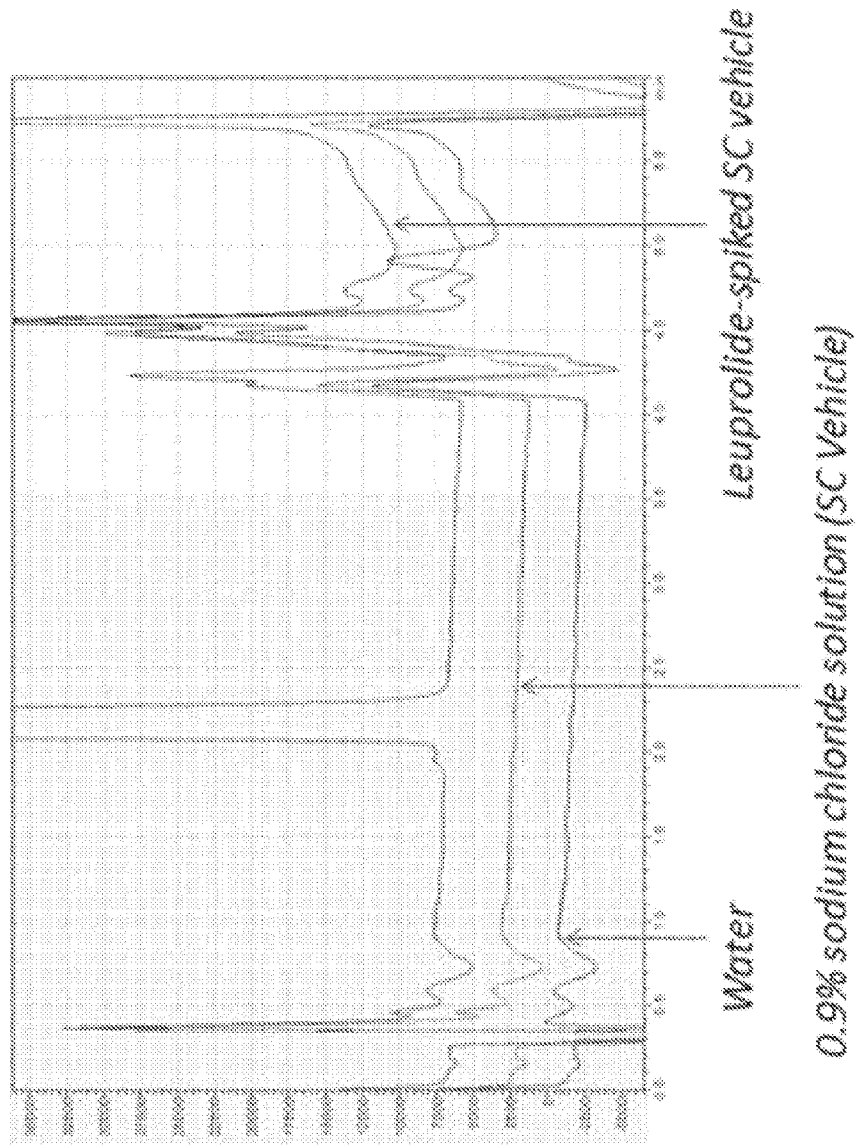


Figure 3

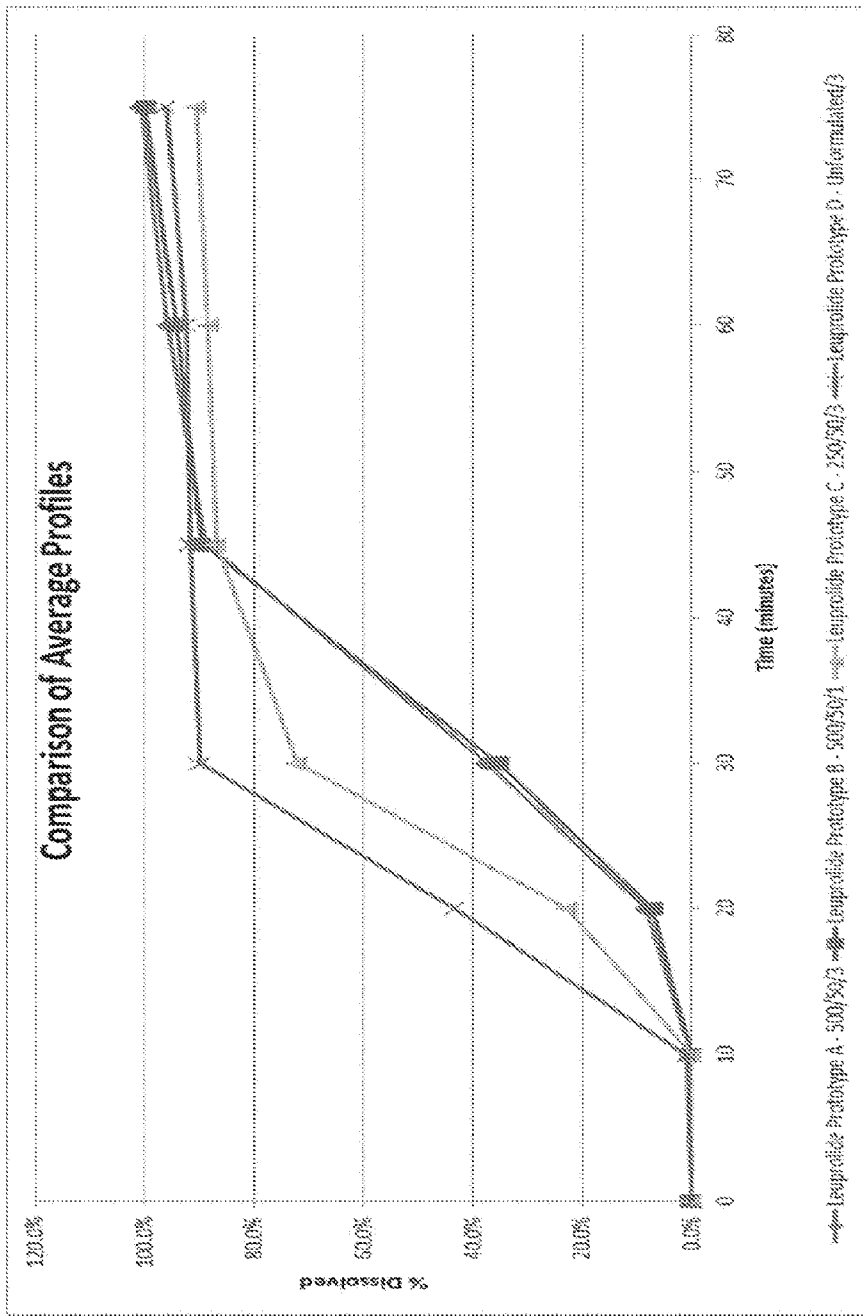


Figure 4

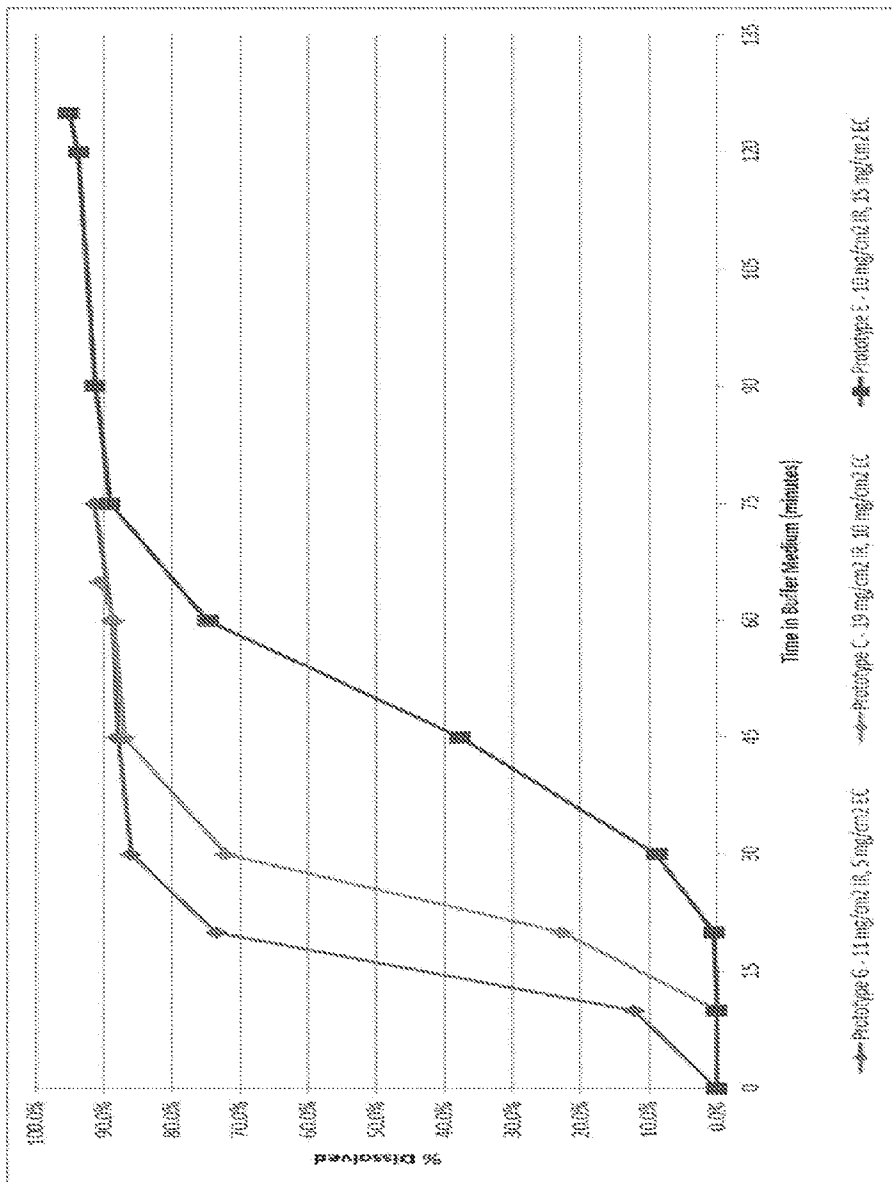


Figure 5

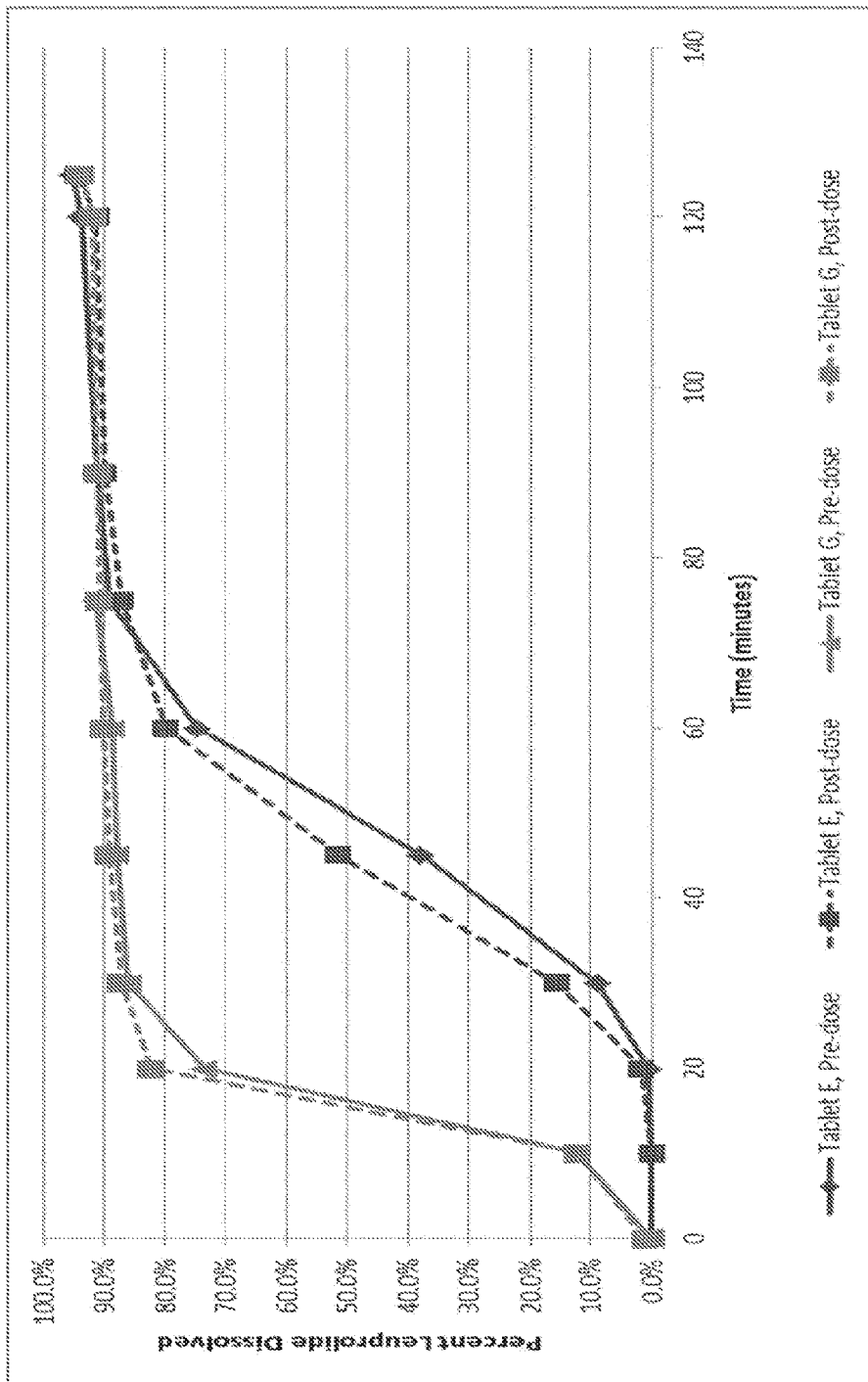


Figure 6

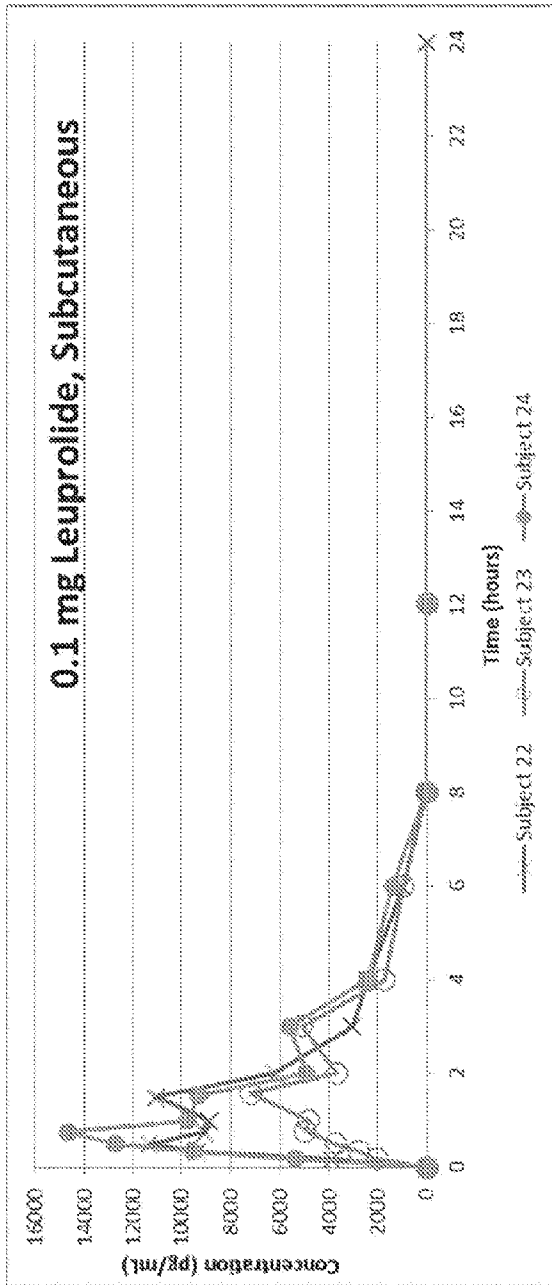


Figure 7

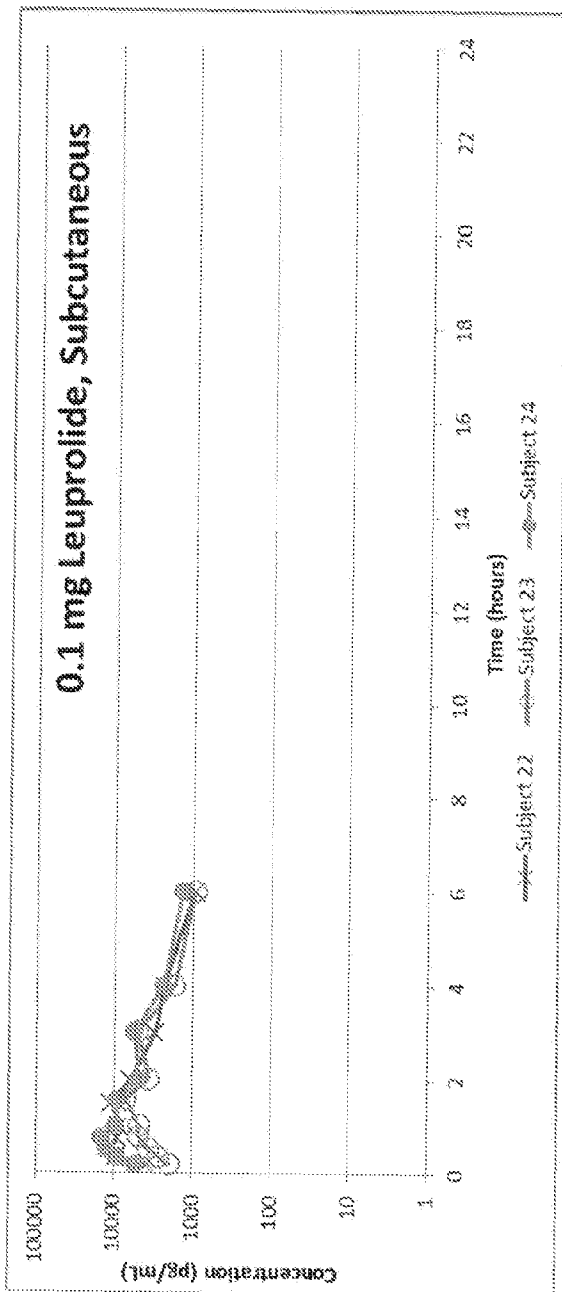


Figure 8

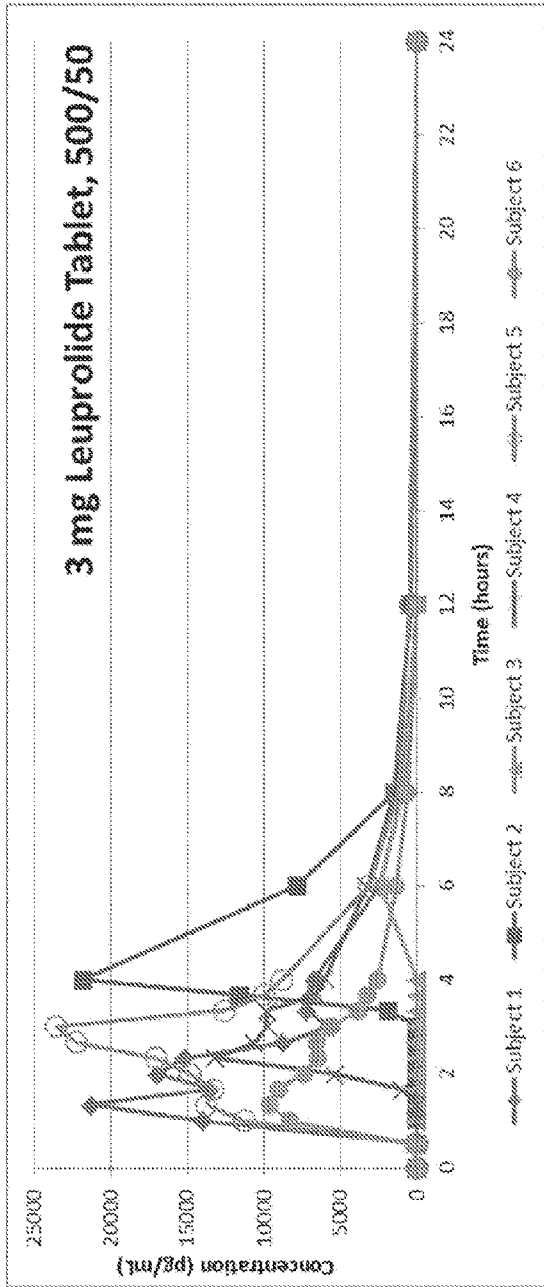


Figure 9

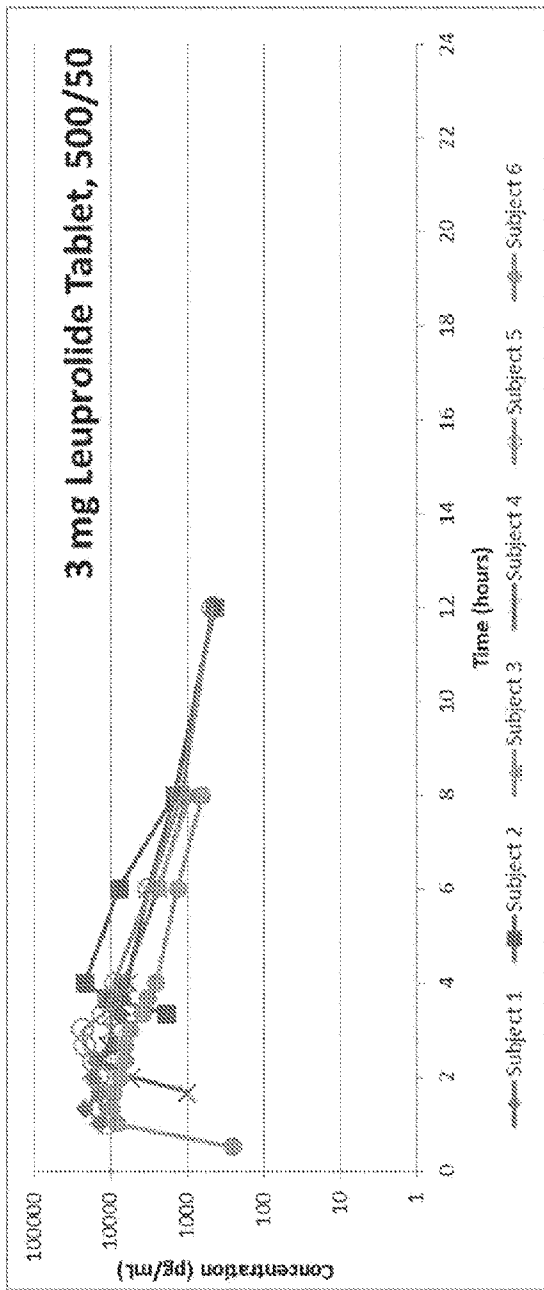


Figure 10

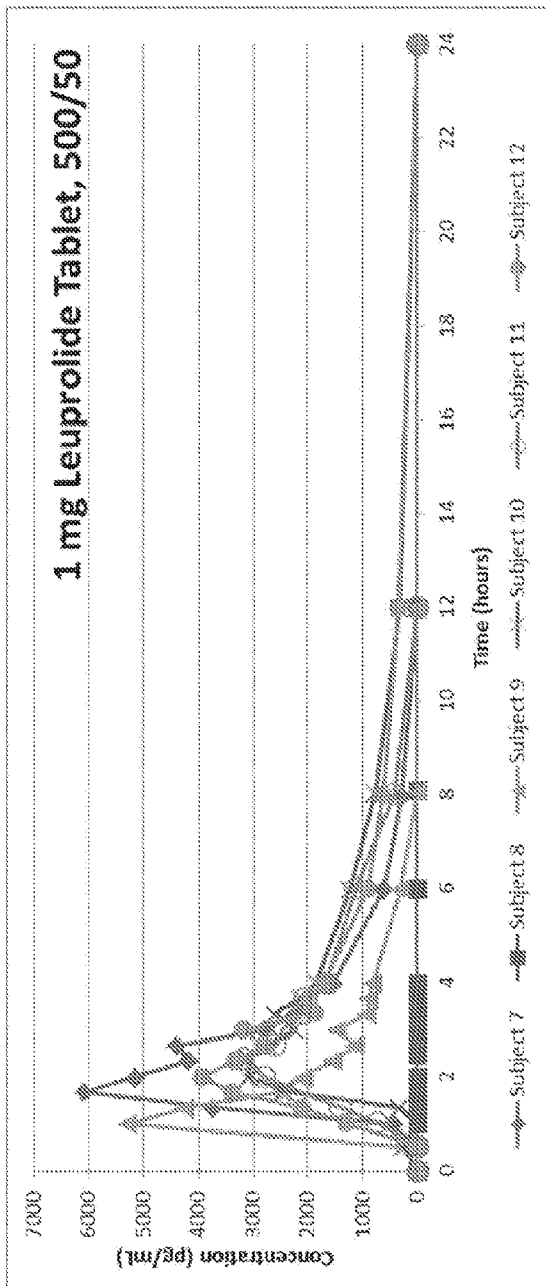


Figure 11

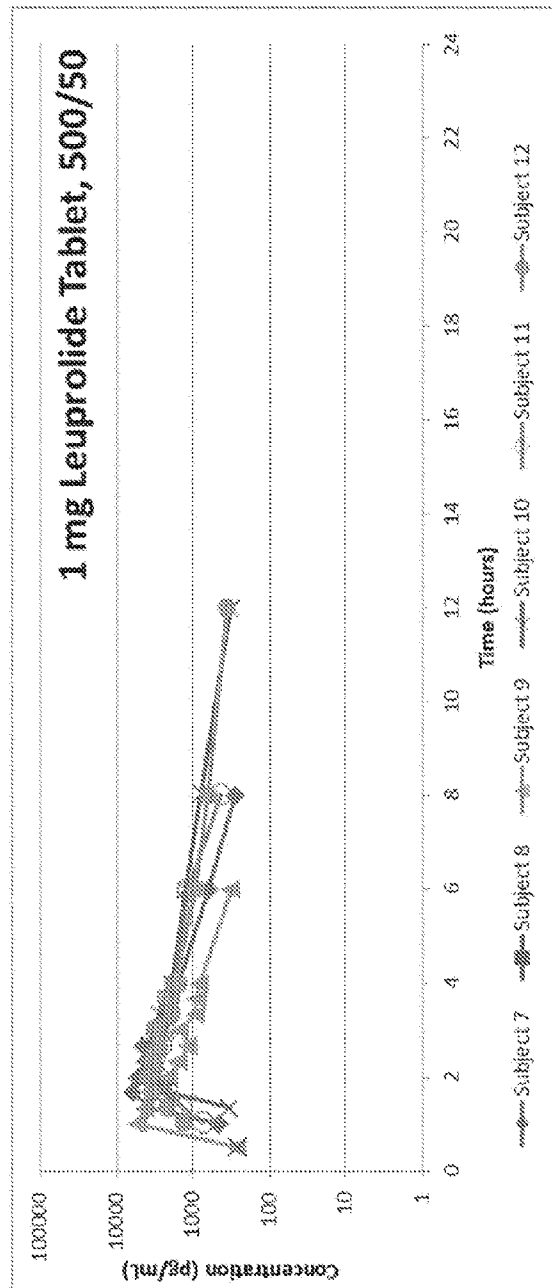


Figure 12

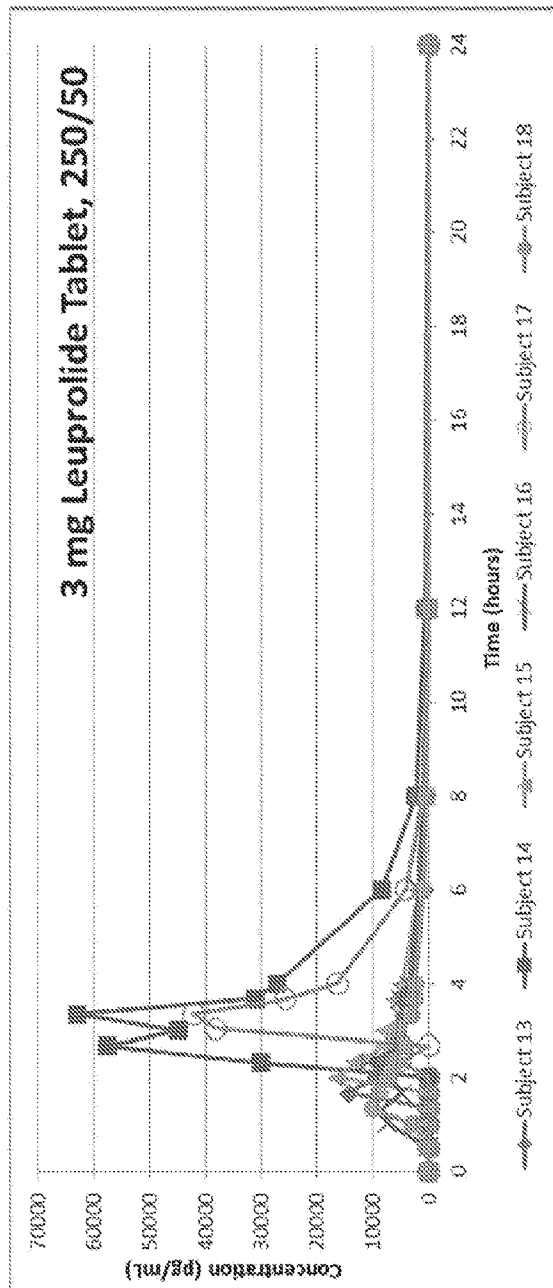


Figure 13

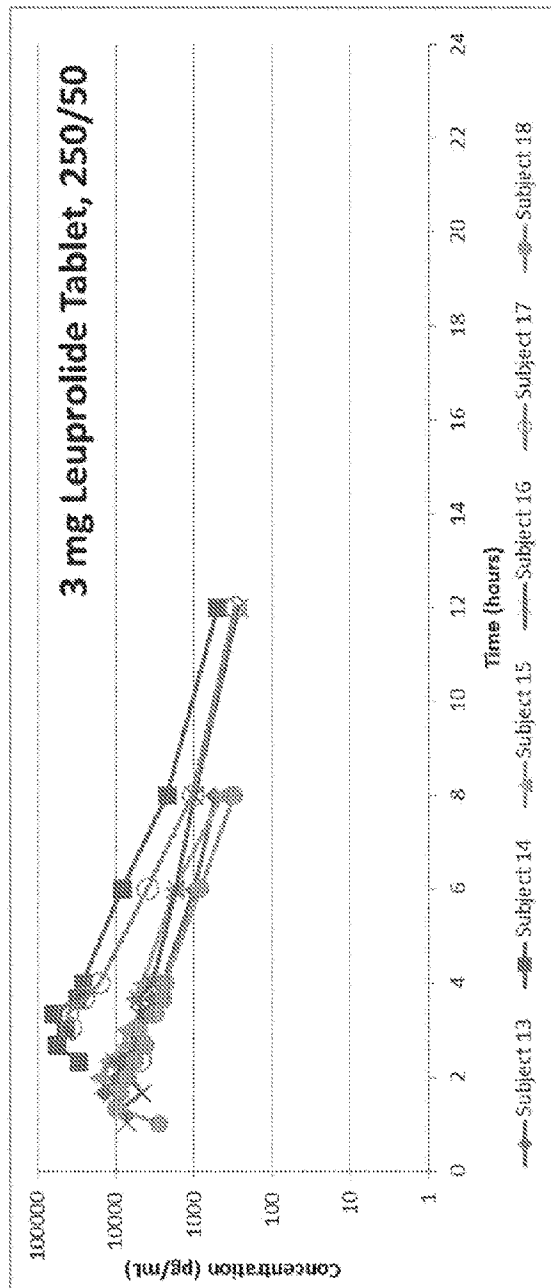


Figure 14

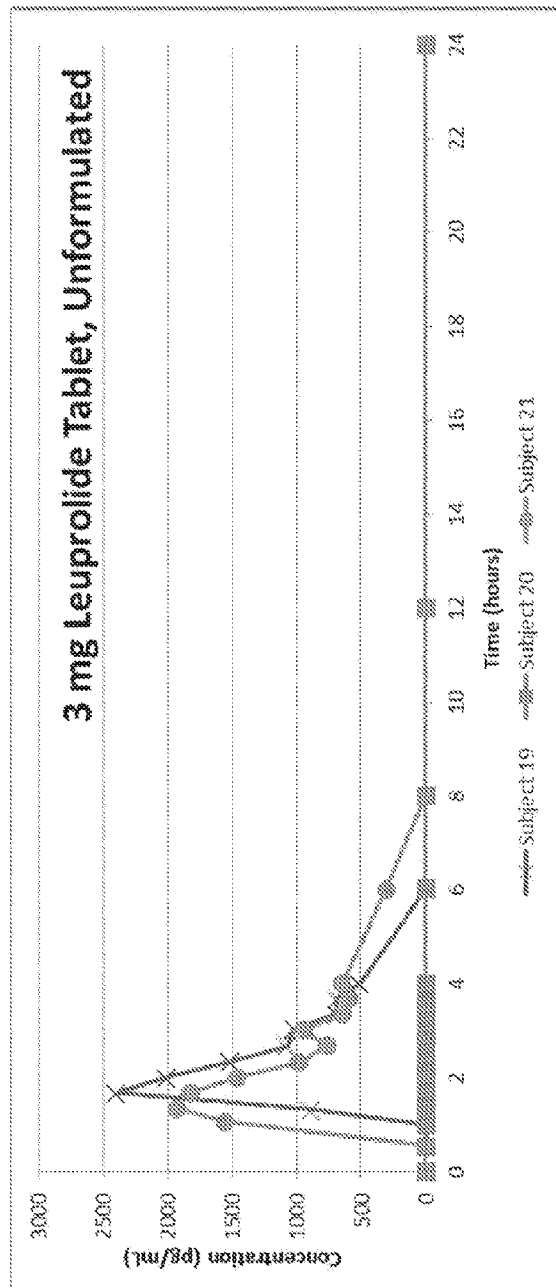


Figure 15

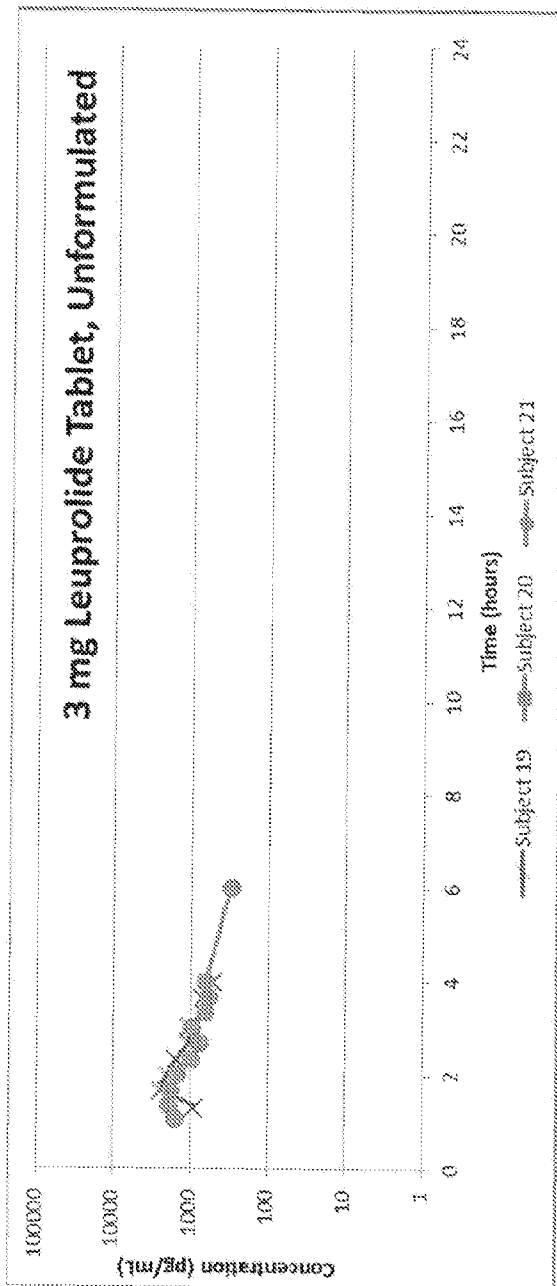


Figure 16

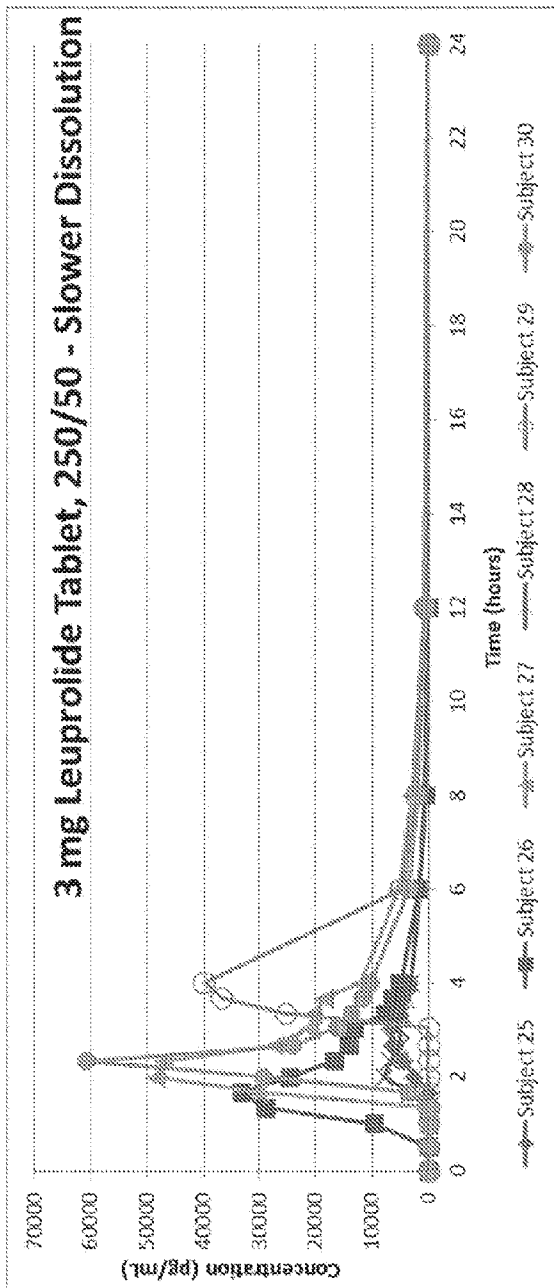


Figure 17

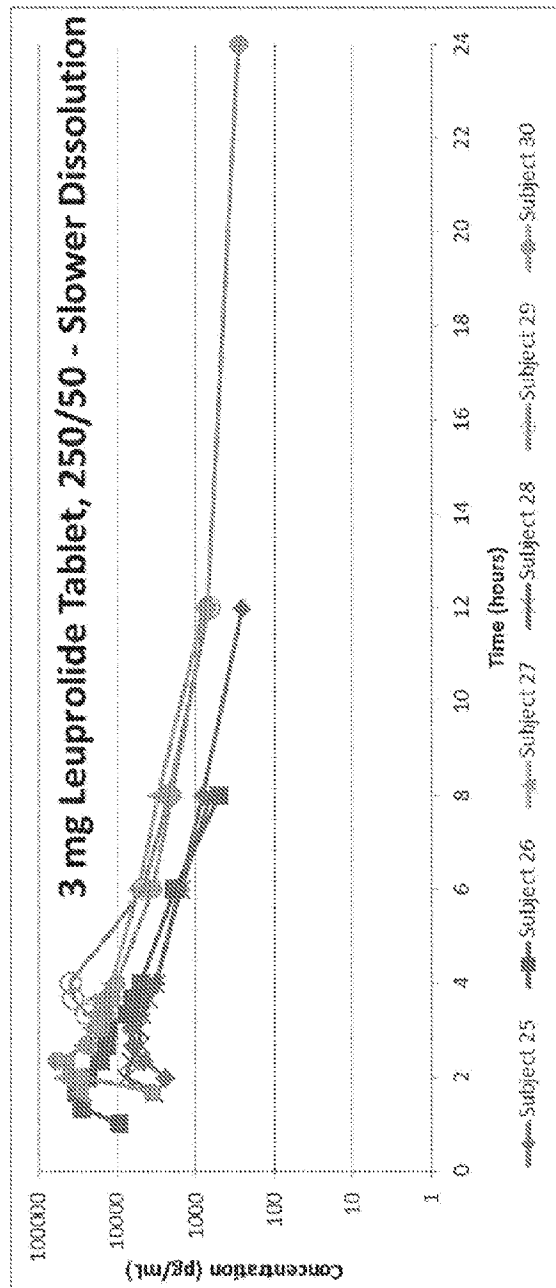


Figure 18

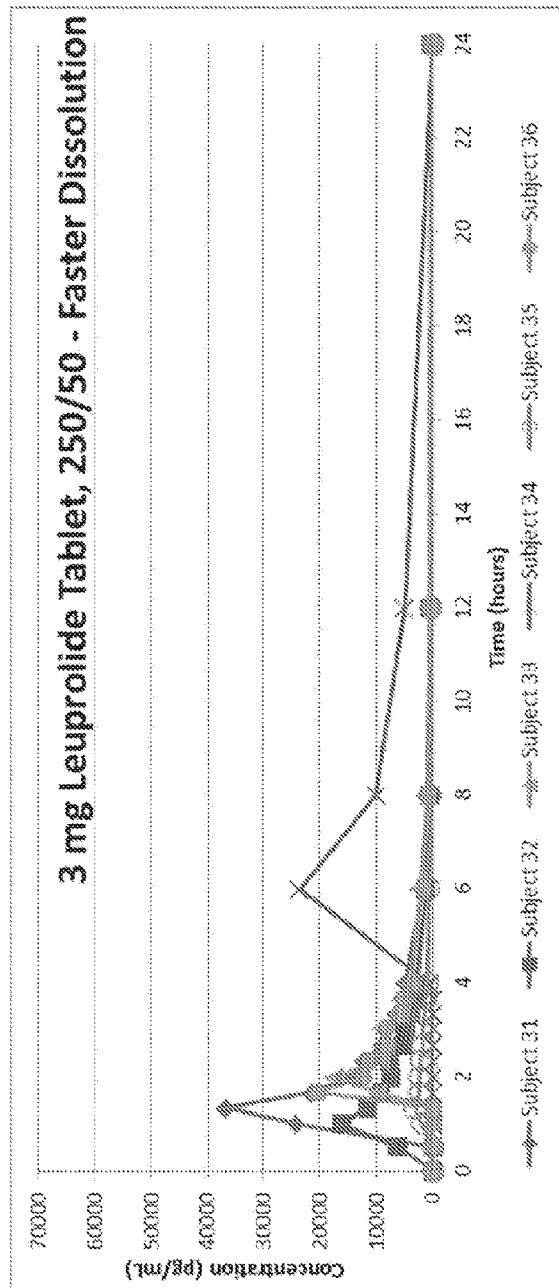


Figure 19

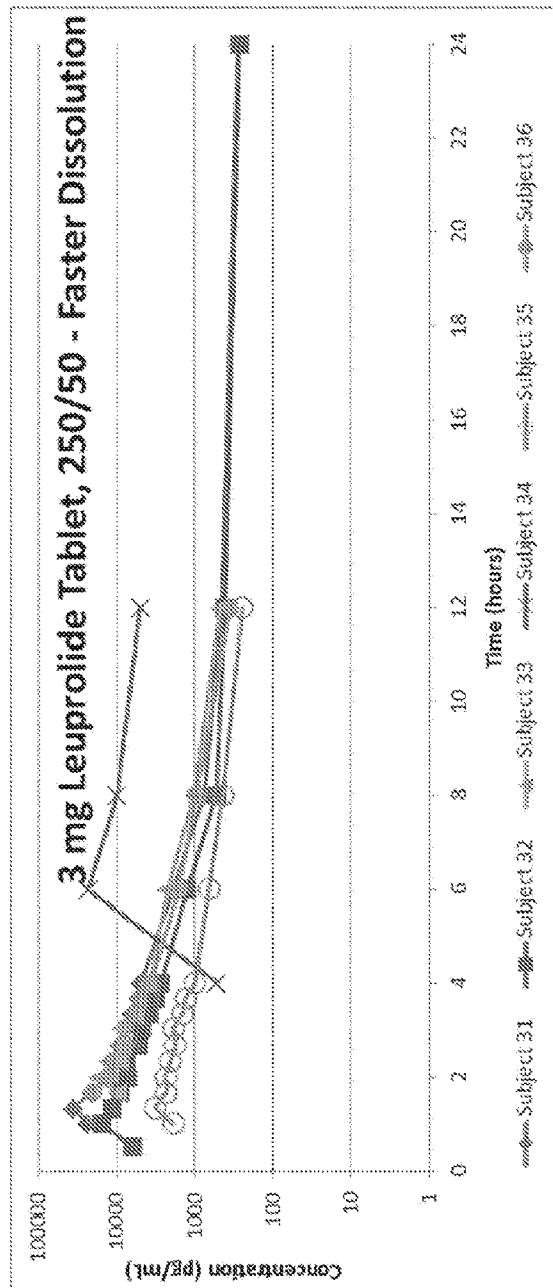


Figure 20

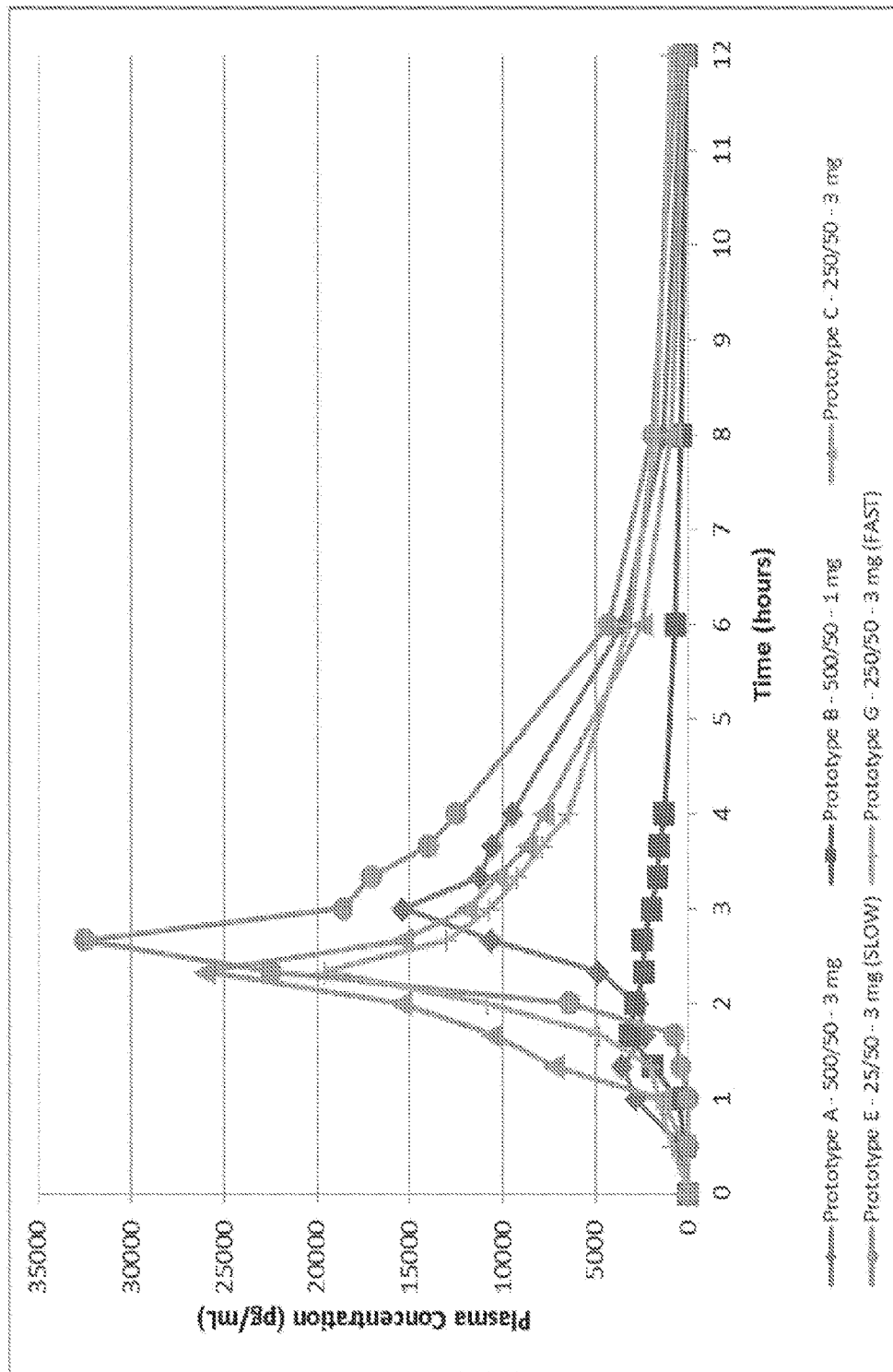


Figure 21

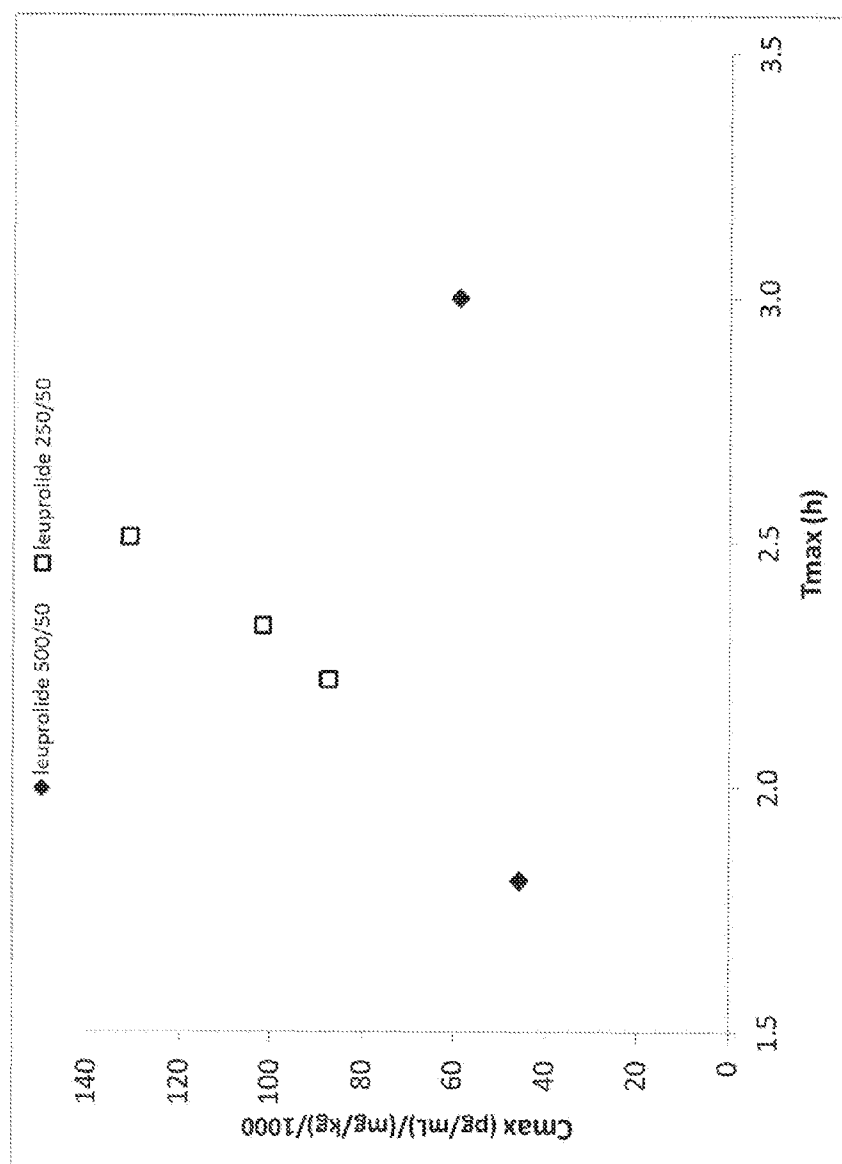


Figure 22

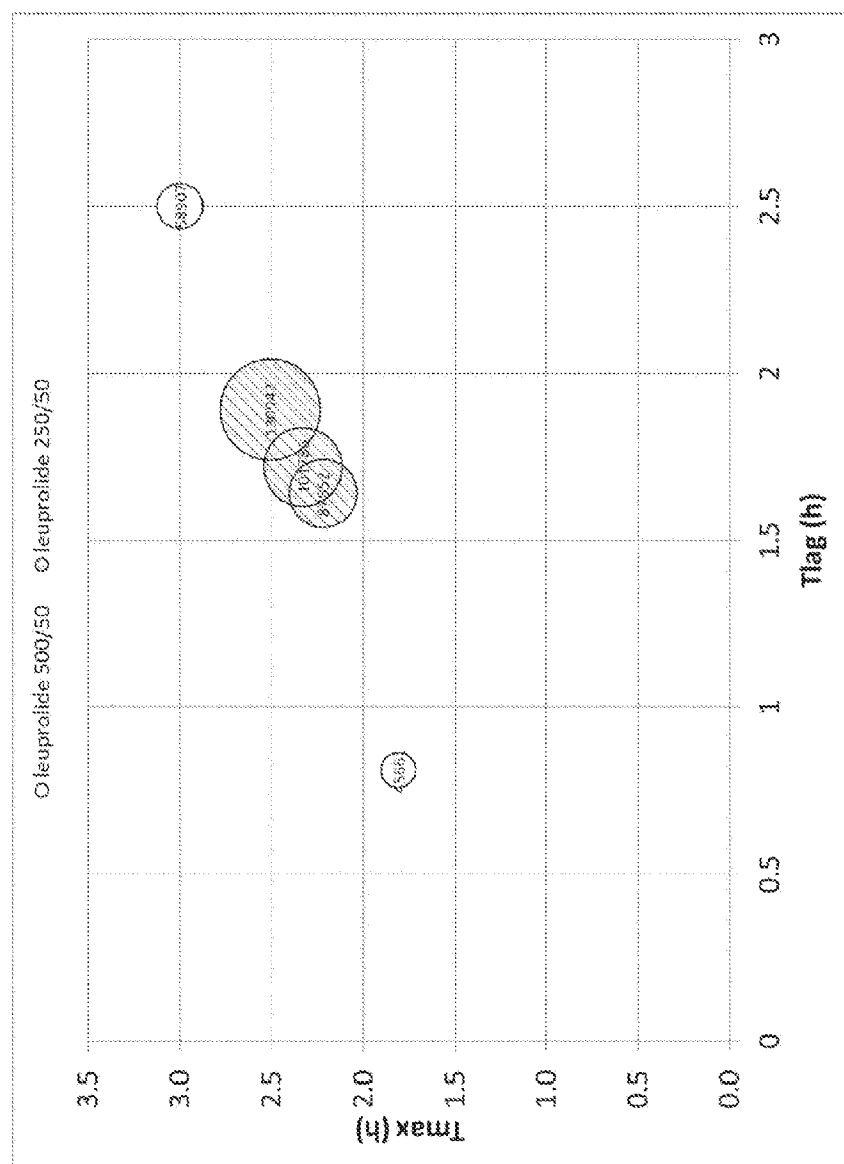


Figure 23

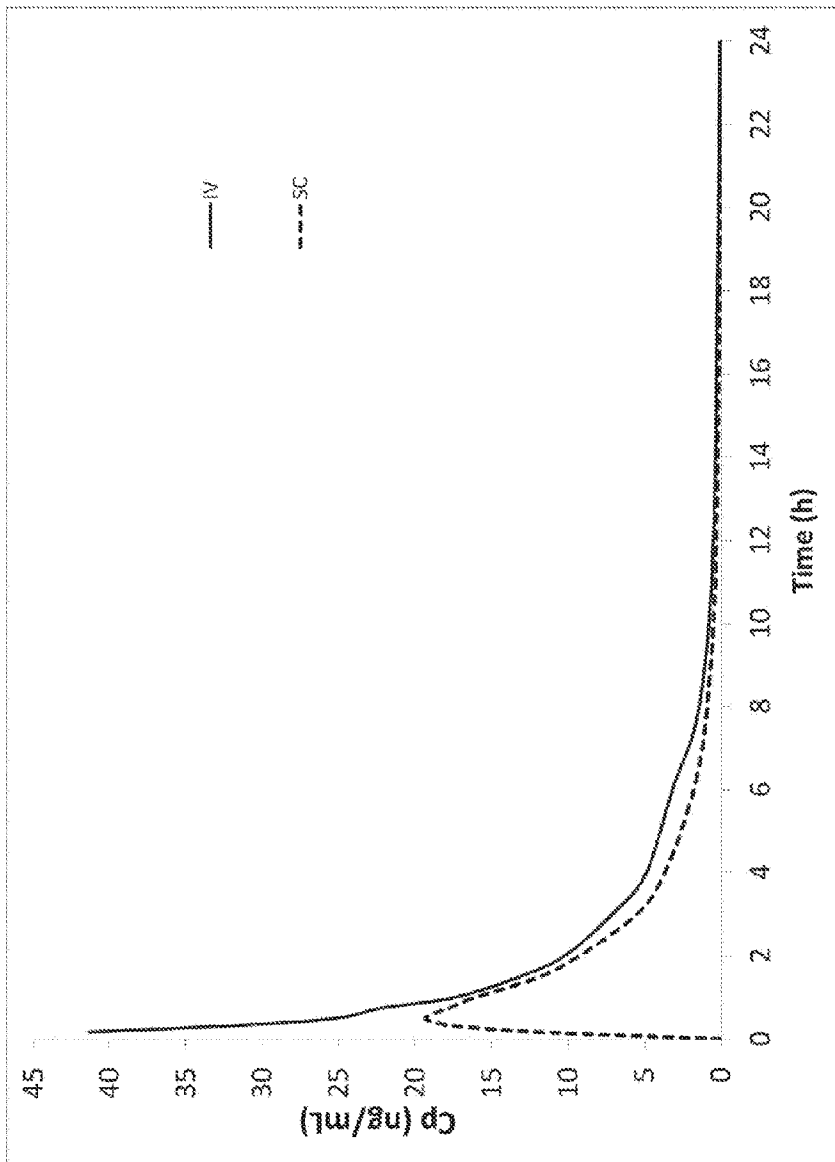


Figure 24

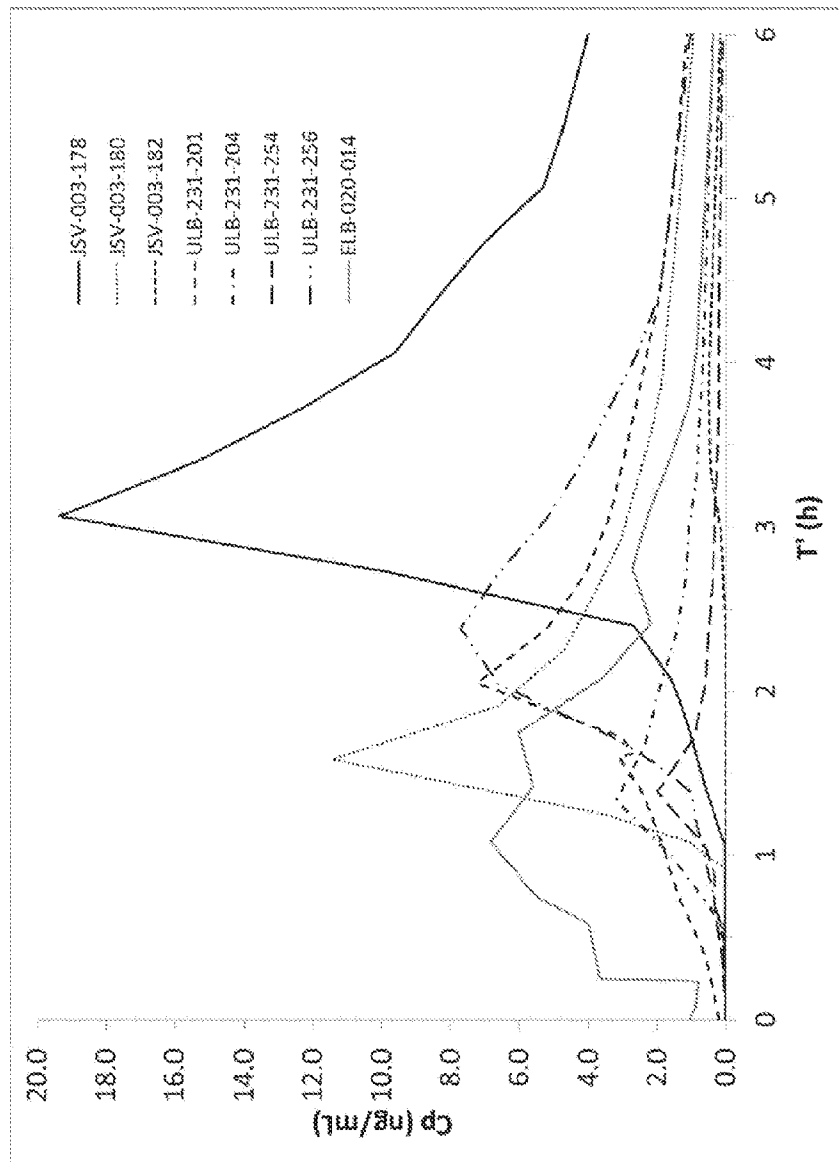


Figure 25A

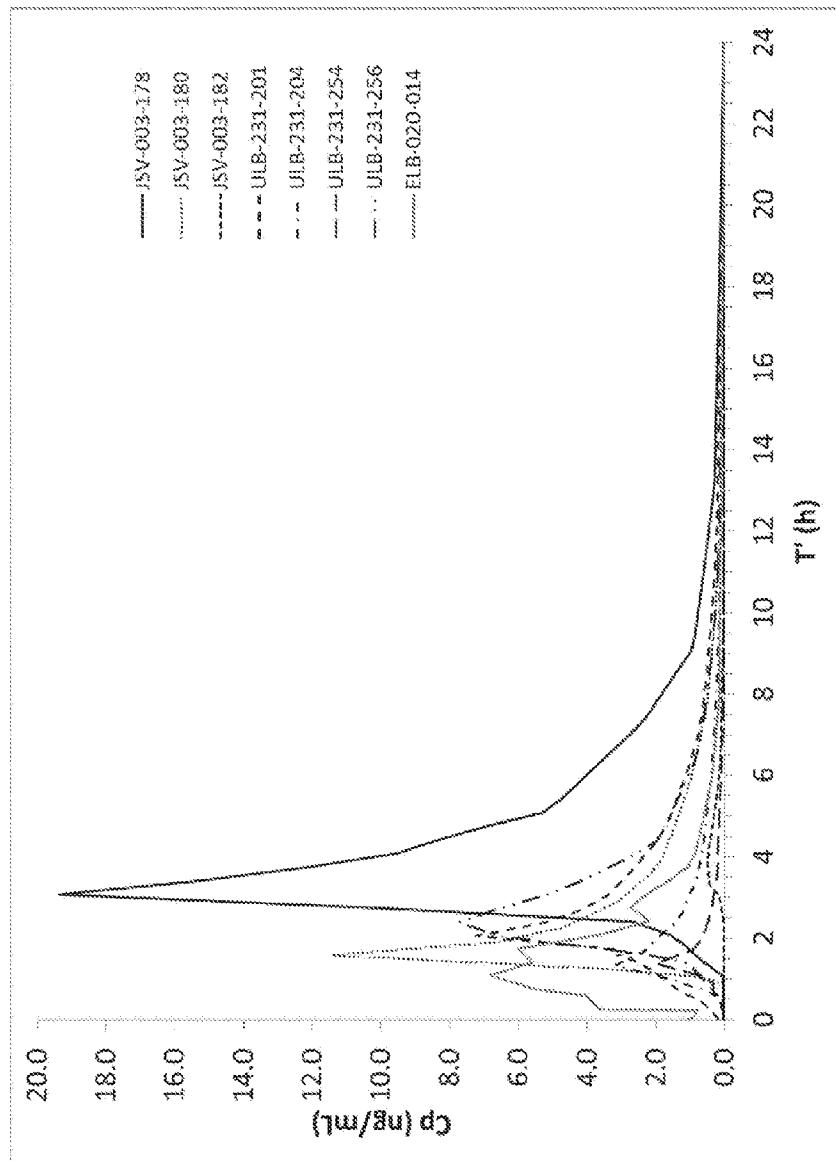


Figure 25B

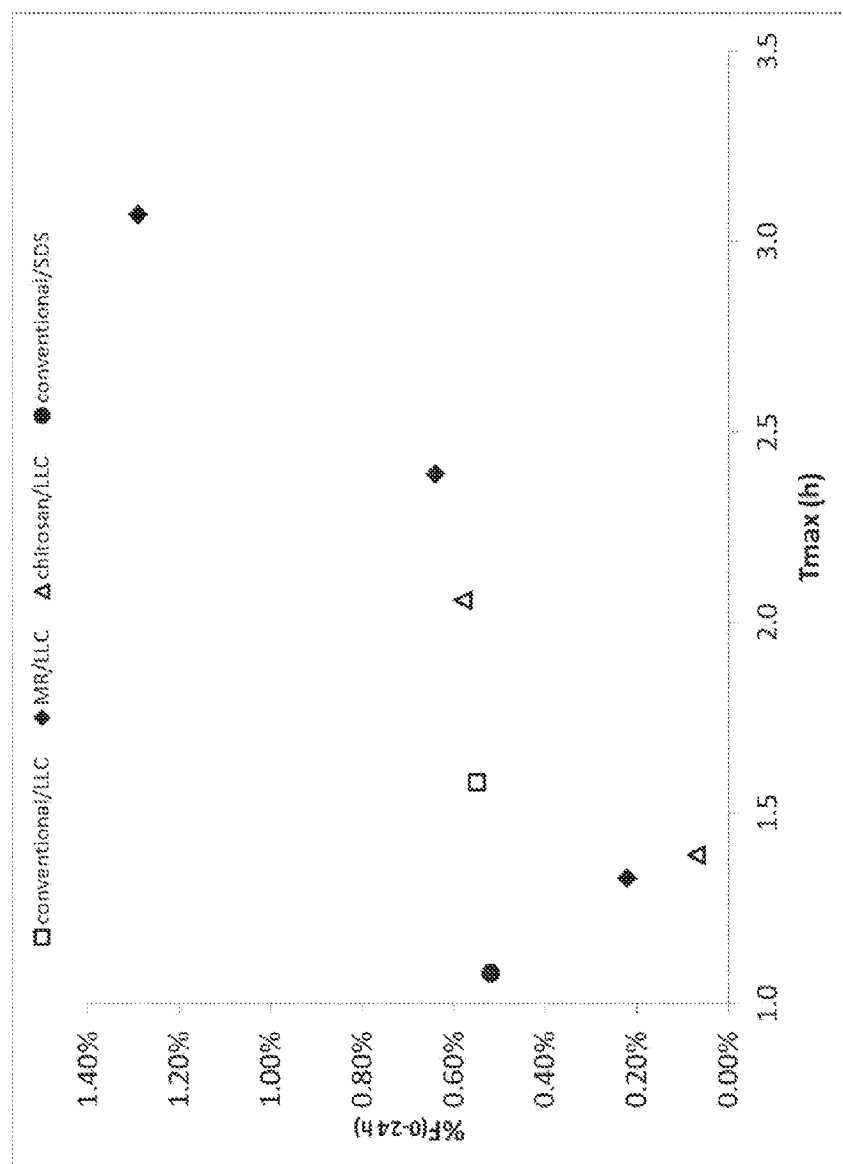


Figure 26

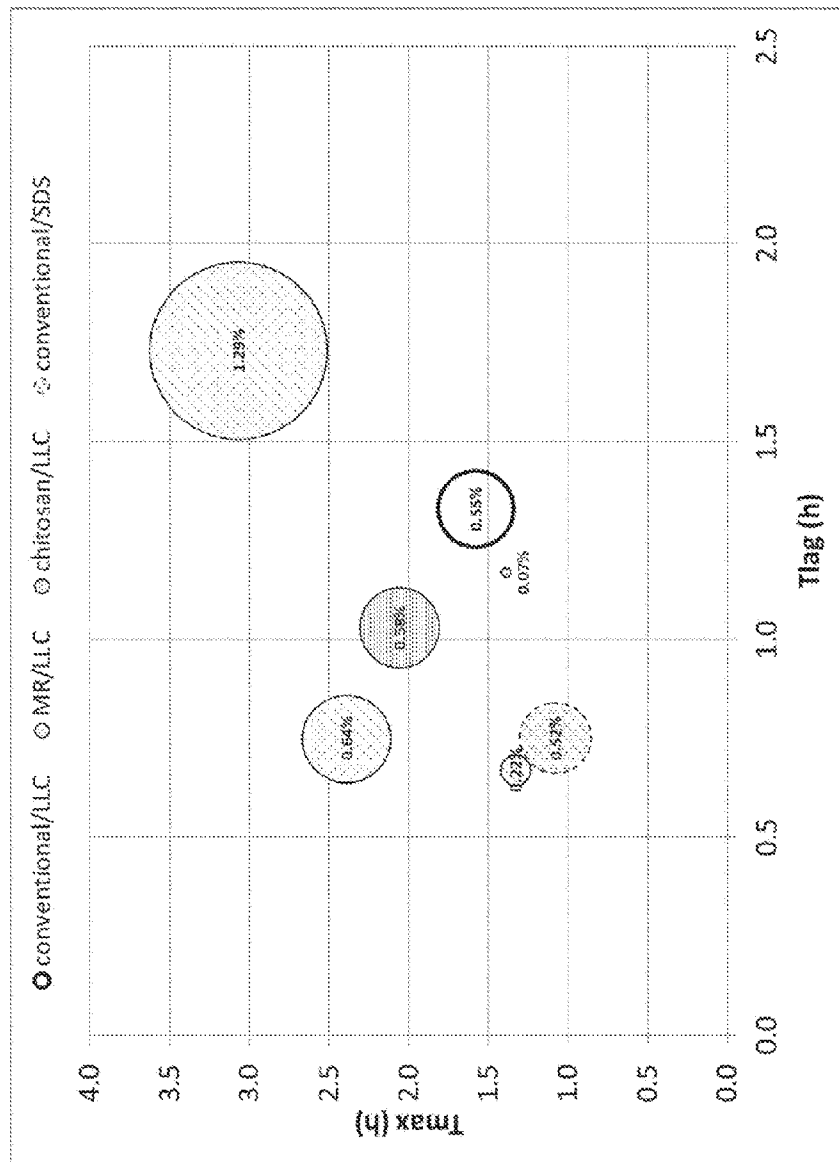


Figure 27