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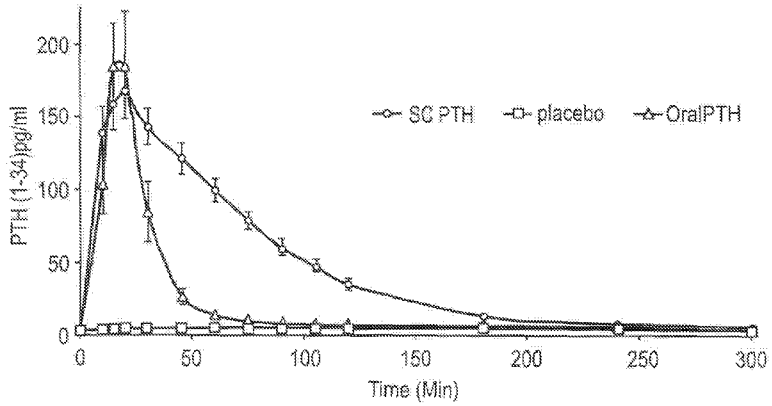

FIG. 3

(57) Abstract: A pharmaceutical composition comprising a therapeutically active agent and SNAC (sodium 8-N-(2-hydroxybenzoyl)aminocaprylate) is provided herein. The composition is formulated for oral administration and is such that the SNAC is active in enhancing absorption of the therapeutically active agent for no more than 60 minutes, and/or such that absorption of the therapeutically active agent following oral administration of the composition is characterized by a ratio of AUC to Cmax which is 60 minutes or lower and/or by a Tmax which is 60 minutes or lower. Further disclosed herein are uses and methods utilizing the compositions described herein for treating a condition treatable by oral administration of a therapeutically active agent in a subject in need thereof.

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FORMULATIONS FOR ORAL ADMINISTRATION OF ACTIVE AGENTS WITH CONTROLLED ABSORPTION PROFILE

FIELD AND BACKGROUND OF THE INVENTION

The present invention, in some embodiments thereof, relates to drug delivery, and more particularly, but not exclusively, to formulations and/or systems for oral administration of therapeutically active agents.

Oral administration of peptide and/or protein pharmaceuticals is problematic due to degradation of peptides and/or proteins in the digestive system and poor absorption of large molecules.

U.S. Patent Application Publication No. 2007/0087957 describes compositions for oral administration of a protein, the compositions comprising a protein and an omega-3 fatty acid, as well as the use of such compositions for oral administration of insulin.

Qi & Ping [*J Microencapsulation* 2004, 21:37-45] describe administration of enteric microspheres containing insulin with SNAC (sodium 8-N-(2-hydroxybenzoyl)aminocaprylate). The enteric microspheres are for protecting the insulin from digestive enzymes of the stomach and small intestine, and the SNAC is for enhancing absorption.

U.S. Patent Application Publication No. 2011/0142800 describes compositions for oral administration of a protein, comprising a protein having a molecular weight of up to 100,000 Da, a protease inhibitor, and an absorption enhancer, such as SNAC, N-(10-[2-hydroxybenzoyl]amino)decanoic acid (SNAD), 8-[N-(2-hydroxy-4-methoxybenzoyl)amino]caprylic acid (4-MOAC), 8-[N-(2-hydroxy-5-chlorobenzoyl)amino]caprylic acid (5-CNAC) and 4-[(4-chloro-2-hydroxy-benzoyl)amino]butanoic acid (4-CNAB) and sodium salts thereof.

U.S. Patent No. 8,110,547 describes compositions for buccal administration of parathyroid hormone (PTH). The composition comprises PTH or a fragment or analog thereof, as well as a delivery agent such as 4-MOAC, SNAC, SNAD, 5-CNAC and 4-CNAB.

Parathyroid hormone (PTH) is secreted by the parathyroid gland as a polypeptide containing 84 amino acids. PTH regulates serum calcium levels by enhancing release of

calcium from bones (bone resorption), and by enhancing absorption of calcium in the intestines.

Teriparatide is a recombinant form of the first 34 amino acids of human PTH (PTH (1-34)), and is used for treatment of osteoporosis. Administration is by subcutaneous injection once per day at a dose of 20 μg [Riek & Towler, *Mo Med* 2011, 108:118-123].

PTH (including PTH (1-34)) has been reported to enhance bone growth provided that it is administered intermittently, with circulating levels returning to control levels within 3 hours [Martin, *J Bone Metab* 2014, 21:8-20]. In contrast, prolonged elevated PTH levels deplete bones by enhancing bone resorption.

Additional background art includes Qi et al. [*Acta Pharm Sinica* 2004, 39:844-848]; International Patent Application Publications WO 00/50386, WO 01/32130, WO 01/32596, WO 03/045306 and WO 2007/121471; Japanese Patent Application Nos. 2005281231 and 2006111558; and U.S. Patent Application Publication Nos. 2006/0234913 and 2013/0224300.

SUMMARY OF THE INVENTION

According to an aspect of some embodiments of the invention, there is provided a pharmaceutical composition comprising a therapeutically active agent, and SNAC (sodium 8-N-(2-hydroxybenzoyl)aminocaprylate), the composition being formulated such that absorption of the therapeutically active agent following oral administration of the composition is characterized by a ratio of AUC to Cmax which is 60 minutes or lower and/or by a Tmax which is 60 minutes or lower.

According to an aspect of some embodiments of the invention, there is provided a pharmaceutical composition comprising a therapeutically active agent, and SNAC (sodium 8-N-(2-hydroxybenzoyl)aminocaprylate), the composition being formulated for oral administration and being such that the SNAC is active in enhancing absorption of the therapeutically active agent for no more than 60 minutes.

According to an aspect of some embodiments of the invention, there is provided a use of a composition described herein in the preparation of a medicament for use in the treatment of a condition treatable by oral administration of the therapeutically active agent in a subject in need thereof.

According to an aspect of some embodiments of the invention, there is provided a method of treating a condition treatable by oral administration of a therapeutically active agent in a subject in need thereof, the method comprising orally administering to the subject a composition described herein.

According to some embodiments of the invention, the ratio of AUC to Cmax is 30 minutes or lower.

According to some embodiments of the invention, the Tmax is 30 minutes or lower.

According to some embodiments of the invention, the SNAC is active in enhancing absorption of the therapeutically active agent for no more than 30 minutes.

According to some embodiments of the invention, the composition further comprises at least one protease inhibitor.

According to some embodiments of the invention, the at least one protease inhibitor comprises at least one trypsin inhibitor.

According to some embodiments of the invention, the at least one trypsin inhibitor is selected from the group consisting of lima bean trypsin inhibitor, aprotinin, soybean trypsin inhibitor and ovomucoid trypsin inhibitor.

According to some embodiments of the invention, the at least one trypsin inhibitor comprises soybean trypsin inhibitor.

According to some embodiments of the invention, the composition further comprises a lubricant.

According to some embodiments of the invention, the lubricant is magnesium stearate.

According to some embodiments of the invention, the composition is soluble in gastric fluid.

According to some embodiments of the invention, the composition dissolves in gastric fluid in no more than 60 minutes.

According to some embodiments of the invention, the composition is formulated as a tablet.

According to some embodiments of the invention, at least 90 weight percents of the tablet consists of ingredients selected from the group consisting of the therapeutically active agent, SNAC, and at least one protease inhibitor.

According to some embodiments of the invention, at least 50 weight percents of the composition consists of SNAC.

According to some embodiments of the invention, the composition comprises at least 50 mg of SNAC.

According to some embodiments of the invention, a bioavailability of the therapeutically active agent is in a range of from 0.05 to 50 %.

According to some embodiments of the invention, a bioavailability of the therapeutically active agent is in a range of from 0.2 to 5 %.

According to some embodiments of the invention, the therapeutically active agent has a molecular weight in a range of 0.5 kDa to 100 kDa.

According to some embodiments of the invention, the therapeutically active agent is a polypeptide.

According to some embodiments of the invention, the polypeptide is selected from the group consisting of parathyroid hormone and a fragment thereof.

According to some embodiments of the invention, the polypeptide comprises teriparatide.

According to some embodiments of the invention, an amount of the therapeutically active agent is in a range of from 100 to 3000 μg.

According to some embodiments of the invention, the composition is for use in the treatment of a condition treatable by oral administration of the therapeutically active agent in a subject in need thereof.

According to some embodiments of the invention, the treatment described herein comprises enhancing absorption of the therapeutically active agent for a controlled period of time, such that a ratio of AUC to Cmax is 60 minutes or lower and/or such that a Tmax is 60 minutes or lower.

According to some embodiments of the invention, the ratio of AUC to Cmax is 30 minutes or lower.

According to some embodiments of the invention, the treatment comprises enhancing absorption of the therapeutically active agent for no more than 60 minutes after the oral administration.

According to some embodiments of the invention, the treatment comprises enhancing absorption of the therapeutically active agent for no more than 30 minutes after the oral administration.

According to some embodiments of the invention, the treatment comprises enhancing absorption of the therapeutically active agent for a controlled period of time, such that a Tmax upon oral administration is no more than 30 minutes.

According to some embodiments of the invention, the method comprises enhancing absorption of the therapeutically active agent for a controlled period of time, such that a ratio of AUC to Cmax is 60 minutes or lower and/or such that a Tmax is 60 minutes or lower.

According to some embodiments of the invention, the ratio of AUC to Cmax is 30 minutes or lower.

According to some embodiments of the invention, the method comprises enhancing absorption of the therapeutically active agent for no more than 60 minutes after the oral administration.

According to some embodiments of the invention, the treatment comprises enhancing absorption of the therapeutically active agent for no more than 30 minutes after the oral administration.

According to some embodiments of the invention, the method comprises enhancing absorption of the therapeutically active agent for a controlled period of time, such that a Tmax upon oral administration is no more than 30 minutes.

Unless otherwise defined, all technical and/or scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments of the invention, exemplary methods and/or materials are described below. In case of conflict, the patent specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and are not intended to be necessarily limiting.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

Some embodiments of the invention are herein described, by way of example only, with reference to the accompanying drawings. With specific reference now to the

drawings in detail, it is stressed that the particulars shown are by way of example and for purposes of illustrative discussion of embodiments of the invention. In this regard, the description taken with the drawings makes apparent to those skilled in the art how embodiments of the invention may be practiced.

In the drawings:

FIGs. 1A-1C are graphs showing plasma concentrations of parathyroid hormone(1-34) as a function of time after oral administration of a tablet according to some embodiments of the invention; each of FIGs. 1A-1C present data for a different subject, and each subject was administered a tablet on two separate occasions (two weeks apart);

FIG. 2 is a bar graph showing maximal plasma concentrations (Cmax) of parathyroid hormone(1-34) as a function of time after oral administration of 200, 400, 680, 1400 or 1800 μg teriparatide according to some embodiments of the invention, and after subcutaneous administration of 20 μg teriparatide;

FIG. 3 is a graph showing plasma concentrations of parathyroid hormone(1-34) as a function of time after oral administration of 1800 μg teriparatide according to some embodiments of the invention, after subcutaneous administration of 20 μg teriparatide, or after administration of a placebo; and

FIG. 4 is a graph showing plasma concentrations of cAMP as a function of time after oral administration of 680 μg teriparatide according to some embodiments of the invention, or after subcutaneous administration of 20 μg teriparatide.

DESCRIPTION OF SPECIFIC EMBODIMENTS OF THE INVENTION

The present invention, in some embodiments thereof, relates to drug delivery, and more particularly, but not exclusively, to formulations and/or systems for oral administration of therapeutically active agents.

While investigating the enhancement of absorption of therapeutically active agents by SNAC (sodium 8-N-(2-hydroxybenzoyl)aminocaprylate) upon oral administration, the present inventors have uncovered that certain compositions comprising SNAC result in pharmacokinetic profiles characterized by rapid increase in levels of absorbed agent, followed almost immediately by a rapid decrease in levels of absorbed agent. The inventors have determined that such pharmacokinetic profiles are

associated with enhancement of absorption by SNAC for a brief period of time, followed by a decrease in absorption upon rapid inactivation of the SNAC due to protonation of SNAC (e.g., conversion of the carboxylate salt to a carboxylic acid). The present inventors have envisioned that oral administration of such compositions would be particularly useful for treating a variety of conditions in which oral administration has heretofore been unsuitable, because administration of typical oral formulations is associated with insufficient absorption and/or by gradual absorption over a lengthy period of time.

Before explaining at least one embodiment of the invention in detail, it is to be understood that the invention is not necessarily limited in its application to the details set forth in the following description or exemplified by the Examples. The invention is capable of other embodiments or of being practiced or carried out in various ways.

Referring now to the drawings, FIGs. 1A-1C show that oral administration of exemplary compositions according to some embodiments of the present invention, results in an increase in plasma levels of a polypeptide therapeutic agent (teriparatide), followed almost immediately by a rapid decrease in plasma levels of the agent. FIG. 2 shows that the plasma levels of the agent are proportional to the orally administered dose. FIG. 3 shows that the time during which the orally administered agent is absorbed into the blood is considerably shorter than when the agent is administered subcutaneously. FIG. 4 shows that the absorbed agent exhibits a biological effect.

These results indicate that oral administration of compositions as described herein is both an effective and convenient route for administering a therapeutically active agent, as well as being associated with a characteristic pharmacokinetic profile.

According to an aspect of some embodiments of the invention, there is provided a pharmaceutical composition comprising a therapeutically active agent, and SNAC (sodium 8-N-(2-hydroxybenzoyl)aminocaprylate).

In some embodiments, the composition is formulated such that absorption of the therapeutically active agent following oral administration of the composition is characterized by a ratio of AUC to Cmax which is 60 minutes or lower.

In some embodiments, the ratio of AUC to Cmax is 50 minutes or lower.

In some embodiments, the ratio of AUC to Cmax is 40 minutes or lower.

In some embodiments, the ratio of AUC to Cmax is 30 minutes or lower.

In some embodiments, the ratio of AUC to Cmax is 20 minutes or lower.

In some embodiments, the ratio of AUC to Cmax is 15 minutes or lower.

In some embodiments, the ratio of AUC to Cmax is 10 minutes or lower.

As used herein, the phrase "pharmaceutical composition" (also referred to herein, for brevity, as "composition") refers to a preparation of one or more therapeutically active agent described herein with other chemical components such as SNAC, and optionally additional ingredients such as described herein. The purpose of a pharmaceutical composition is to facilitate administration of the therapeutically active agent.

Herein the term "therapeutically active agent" refers to the ingredient accountable for a therapeutic effect, as opposed, for example, to enhancement of absorption of the therapeutically active agent, which is effected by SNAC.

As used herein the term "AUC" refers to the area under a curve which represents levels of the therapeutically active agent in the blood (e.g., plasma levels) as a function of time following administration, and can be determined by measuring plasma levels of the therapeutically active agent at various time points following administration, as exemplified herein.

As used herein the term "Cmax" refers to the maximal concentration of the therapeutically active agent in the blood (e.g., plasma levels), and can be determined by measuring levels of the therapeutically active agent at various time points following administration, as exemplified herein.

When the therapeutically active agent is present to some degree in the blood prior to administration (e.g., when the therapeutically active agent is naturally present in the body), the area under the baseline levels are excluded from the AUC and Cmax (e.g., by subtracting the baseline level from the measured levels at each time point), such that the AUC and Cmax each represent an aspect of the increase above baseline levels which occurs following administration. The baseline can be determined by measuring levels prior to administration and/or by determining (e.g., by curve-fitting) the baseline to which levels decay after administration.

The ratio of AUC to Cmax (i.e., AUC divided by Cmax) will depend on the nature of the pharmacokinetic profile of the composition, particularly on the shape of the curve which represents levels of the therapeutically active agent in the blood (e.g.,

plasma levels) as a function of time following administration. Pharmacokinetic profiles characterized by a sharp increase and decrease within a brief period of time will tend to have a relatively low ratio of AUC to Cmax, whereas pharmacokinetic profiles characterized by a more gradual increase and decrease over a broader period of time will tend to have a relatively high ratio of AUC to Cmax.

Without being bound by any particular theory, it is believed that a ratio of AUC to Cmax which is 60 minutes or lower, as described herein, is associated with a relatively sharp increase and decrease of levels of therapeutically active agent in the blood.

The ratio of AUC to Cmax is optionally calculated based on data from multiple administrations of the composition. In such cases, a ratio of AUC to Cmax is preferably calculated for each administration, and then the ratios calculated for each administration may be averaged.

Without being bound by any particular theory, it is believed that averaging data (e.g., measured blood levels of a therapeutically active agent) from different administrations of the therapeutically active agent will frequently result in a broader curve, and larger ratio of AUC to Cmax, than that which is observed after a single administration. Hence, a ratio of AUC to Cmax calculated for averaged data (as opposed to an average of ratios calculated for each administration, as described hereinabove) is a less accurate indicator of the effect of the composition following administration.

In some embodiments, the composition is formulated for oral administration and is such that the SNAC is active in enhancing absorption of the therapeutically active agent for no more than 60 minutes. In some embodiments, the SNAC is active in enhancing absorption of the therapeutically active agent for 50 minutes or lower. In some embodiments, the SNAC is active in enhancing absorption of the therapeutically active agent for 40 minutes or lower. In some embodiments, the SNAC is active in enhancing absorption of the therapeutically active agent for 30 minutes or lower. In some embodiments, the SNAC is active in enhancing absorption of the therapeutically active agent for 20 minutes or lower. In some embodiments, the SNAC is active in enhancing absorption of the therapeutically active agent for 15 minutes or lower. In

some embodiments, the SNAC is active in enhancing absorption of the therapeutically active agent for 10 minutes or lower.

Herein, the phrase "enhancing absorption" refers to causing an increase of at least 10 % in levels (e.g., plasma levels) of absorbed agent.

The enhancement of absorption by SNAC may be determined, for example, by comparing a pharmacokinetic profile of the composition with a pharmacokinetic profile of an equivalent composition which lacks SNAC (e.g., being identical in all aspects except for the absence of SNAC). The time period during which the composition with SNAC results in an increase of absorbed therapeutically active agent, in comparison to an equivalent composition without SNAC, is the time during which SNAC is active in enhancing absorption of the therapeutically active agent. It is to be appreciated that the time during which SNAC is active in enhancing absorption of the therapeutically active agent (e.g., a time of 60 minutes or lower, as described herein) does not necessarily begin immediately upon administration.

In some embodiments, the composition is formulated such that absorption of the therapeutically active agent following oral administration of the composition is characterized by a Tmax of no more than 60 minutes. In some embodiments, the Tmax is no more than 50 minutes. In some embodiments, the Tmax is no more than 40 minutes. In some embodiments, the Tmax is no more than 30 minutes. In some embodiments, the Tmax is no more than 25 minutes. In some embodiments, the Tmax is no more than 20 minutes. In some embodiments, the Tmax is no more than 15 minutes. In some embodiments, the Tmax is no more than 10 minutes. In some embodiments, the Tmax is no more than 5 minutes.

As used herein the term "Tmax" refers to the duration of time between administration and when maximal concentration of the therapeutically active agent in the blood (e.g., plasma levels) occurs.

In some embodiments of any of the embodiments described herein, the composition is soluble in gastric fluid. In some embodiments, the composition dissolves in gastric fluid in no more than 60 minutes. In some embodiments, the composition dissolves in gastric fluid in no more than 50 minutes. In some embodiments, the composition dissolves in gastric fluid in no more than 40 minutes. In some embodiments, the composition dissolves in gastric fluid in no more than 30 minutes. In

some embodiments, the composition dissolves in gastric fluid in no more than 20 minutes. In some embodiments, the composition dissolves in gastric fluid in no more than 15 minutes. In some embodiments, the composition dissolves in gastric fluid in no more than 10 minutes. In some embodiments, the composition dissolves in gastric fluid in no more than 5 minutes.

Herein, the phrases "soluble in gastric fluid", "dissolves in gastric fluid" and the like refer to solubility in simulated gastric fluid without pepsin, at pH 2.0, under conditions according to USP 23 Apparatus 2 (paddle) (e.g., 800 ml volume, 50 rotations per minute). Dissolution is indicated by absence of visible composition at the bottom of the fluid. However, visible material suspended in the liquid is not excluded by the terms "soluble" and "dissolution". The phrase "soluble in gastric fluid" refers herein to dissolution within a period of 6 hours.

Without being bound by any particular theory, it is believed that dissolution, and particularly relatively rapid dissolution, in gastric fluid facilitates rapid absorption of a therapeutically active agent, because both the therapeutically active agent and the SNAC which can enhance absorption of the therapeutically active agent become available in the stomach soon after oral administration (e.g., prior to passage of the composition to the intestines). It is further believed that dissolution, and particularly relatively rapid dissolution, in gastric fluid facilitates control over the time during which a therapeutically active agent is absorbed, because the SNAC can be inactivated upon exposure to acidic conditions of the stomach due to protonation of SNAC (e.g., conversion of the carboxylate salt to a carboxylic acid), such that soon after full dissolution of the composition in the stomach, little or no SNAC remains capable of enhancing absorption of a therapeutically active agent.

In some embodiments of any of the embodiments described herein, the composition further comprises at least one protease inhibitor.

Herein throughout, the term "protease inhibitor" refers to a compound which reduces a proteolytic activity of a protease, for example, a proteolytic activity which inactivates a therapeutically active agent described herein. The term "protease inhibitor" encompasses, for example, both large molecules (e.g., proteins) and small molecules, as well as both naturally occurring compounds and synthetic compounds.

In some embodiments of any of the embodiments described herein, the at least one protease inhibitor comprises at least one trypsin inhibitor. In some embodiments, the at least one protease inhibitor consists essentially of one or more trypsin inhibitor(s).

Examples of trypsin inhibitors which may be utilized in any one of the embodiments described herein include, without limitation, lima bean trypsin inhibitor, aprotinin, soybean trypsin inhibitor, ovomucoid trypsin inhibitor and any combination thereof. In some embodiments, the at least one trypsin inhibitor comprises soybean trypsin inhibitor (SBTI). In some embodiments, the at least one trypsin inhibitor (an optionally the at least one protease inhibitor) consists essentially of SBTI.

In some embodiments of any of the embodiments described herein, the at least one protease inhibitor comprises at least one serpin. In some embodiments, the at least one protease inhibitor consists essentially of one or more serpin(s).

Examples of serpins which may be utilized in any one of the embodiments described herein, include, without limitation, alpha 1-antitrypsin, antitrypsin-related protein, alpha 1-antichymotrypsin, kallistatin, protein C inhibitor, cortisol binding globulin, thyroxine-binding globulin, angiotensinogen, centerin, protein Z-related protease inhibitor, vaspin, monocyte/neutrophil elastase inhibitor, plasminogen activator inhibitor-2, squamous cell carcinoma antigen-1 (SCCA-1), squamous cell carcinoma antigen-2 (SCCA-2), maspin, proteinase inhibitor 6 (PI-6), megsin, serpin B8 (PI-8), serpin B9 (PI-9), bomapin, yukopin, hurpin/headpin, antithrombin, heparin cofactor II, plasminogen activator inhibitor 1, glia-derived nexin, pigment epithelium derived factor, alpha 2-antiplasmin, complement 1-inhibitor, 47 kDa heat shock protein (HSP47), neuroserpin and pancpin.

In some embodiments of any of the embodiments described herein, the at least one protease inhibitor comprises at least one cysteine protease inhibitor. In some embodiments, the at least one protease inhibitor consists essentially of one or more cysteine protease inhibitor(s).

Examples of cysteine protease inhibitors which may be utilized in any one of the embodiments described herein include, without limitation, type 1 cystatins, type 2 cystatins, human cystatins C, D, S, SN, and SA, cystatin E/M, cystatin F, and type 3 cystatins (including kininogens).

In some embodiments of any of the embodiments described herein, the at least one protease inhibitor comprises at least one threonine protease inhibitor. In some embodiments, the at least one protease inhibitor consists essentially of one or more threonine protease inhibitor(s).

Examples of threonine protease inhibitors which may be utilized in any one of the embodiments described herein include, without limitation, bortezomib, MLN-519, ER-807446 and TMC-95A.

In some embodiments of any of the embodiments described herein, the at least one protease inhibitor comprises at least one aspartic protease inhibitor. In some embodiments, the at least one protease inhibitor consists essentially of one or more aspartic protease inhibitor(s).

Examples of aspartic protease inhibitors which may be utilized in any one of the embodiments described herein, include, without limitation, α_2-macroglobulin, pepstatin A, aspartic protease inhibitor 11, aspartic protease inhibitor 1, aspartic protease inhibitor 2, aspartic protease inhibitor 3, aspartic protease inhibitor 4, aspartic protease inhibitor 5, aspartic protease inhibitor 6, aspartic protease inhibitor 7, aspartic protease inhibitor 8, aspartic protease inhibitor 9, pepsin inhibitor Dit33, and protease A inhibitor 3.

In some embodiments of any of the embodiments described herein, the at least one protease inhibitor comprises at least one metalloprotease inhibitor. In some embodiments, the at least one protease inhibitor consists essentially of one or more metalloprotease inhibitor(s).

Examples of metalloprotease inhibitors which may be utilized in any one of the embodiments described herein, include, without limitation, angiotensin-1-converting enzyme inhibitory peptide, antihemorrhagic factor BJ46a, beta-casein, proteinase inhibitor CeKI, venom metalloproteinase inhibitor DM43, carboxypeptidase A inhibitor, smpI, IMPI, alkaline proteinase, latexin, carboxypeptidase inhibitor, antihemorrhagic factor HSF, testican-3, SPOCK3, TIMP1, metalloproteinase inhibitor 1, metalloproteinase inhibitor 2, TIMP2, metalloproteinase inhibitor 3, TIMP3, metalloproteinase inhibitor 4, TIMP4, putative metalloproteinase inhibitor tag-225, tissue inhibitor of metalloprotease, WAP, kazal inhibitor, immunoglobulin, and kunitz and NTR domain-containing protein 1.

Examples of protease inhibitors which may be utilized in any one of the embodiments described herein also include, without limitation, AEBSF-HCl, ε-aminocaproic acid, α1-antichymotypsin, antipain, antithrombin III, α1-antitrypsin, APMSF (4-amidinophenyl-methane sulfonyl-fluoride), sprotinin, benzamidine, chymostatin, DFP (diisopropylfluoro-phosphate), leupeptin, 4-(2-Aminoethyl)-benzenesulfonyl fluoride hydrochloride, PMSF (phenylmethyl sulfonyl fluoride), TLCK (1-chloro-3-tosylamido-7-amino-2-heptanone), TPCK (1-chloro-3-tosylamido-4-phenyl-2-butanone), pentamidine isothionate, pepstatin, guanidium, α2-macroglobulin, a chelating agent of zinc, and iodoacetate.

In some embodiments of any one of the embodiments described herein, the amount of a protease inhibitor in a unit dosage form described herein is at least about 0.1 mg. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is at least about 0.2 mg. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is at least about 0.3 mg. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is at least about 0.4 mg. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is at least about 0.6 mg. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is at least about 0.8 mg. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is at least about 1 mg. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is at least about 1.5 mg. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is at least about 2 mg. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is at least about 2.5 mg. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is at least about 3 mg. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is at least about 5 mg. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is at least about 7 mg. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is at least about 10 mg. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is at least about 12 mg. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is at least about 15

mg. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is at least about 20 mg. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is at least about 30 mg. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is at least about 50 mg. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is at least about 70 mg. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is at least about 100 mg.

In some embodiments of any one of the embodiments described herein, the amount of a protease inhibitor in a unit dosage form described herein is in a range of from 0.1 to 1 mg. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is in a range of from 0.2 to 1 mg. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is in a range of from 0.3 to 1 mg. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is in a range of from 0.5 to 1 mg.

In some embodiments of any one of the embodiments described herein, the amount of a protease inhibitor in a unit dosage form described herein is in a range of from 0.1 to 2 mg. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is in a range of from 0.2 to 2 mg. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is in a range of from 0.3 to 2 mg. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is in a range of from 0.5 to 2 mg. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is in a range of from 1 to 2 mg.

In some embodiments of any one of the embodiments described herein, the amount of a protease inhibitor in a unit dosage form described herein is in a range of from 1 to 10 mg. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is in a range of from 2 to 10 mg. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is in a range of from 3 to 10 mg. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is in a range of from 5 to 10 mg.

In some embodiments of any one of the embodiments described herein, the amount of a protease inhibitor in a unit dosage form described herein is in a range of from 1 to 20 mg. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is in a range of from 2 to 20 mg. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is in a range of from 3 to 20 mg. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is in a range of from 5 to 20 mg. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is in a range of from 10 to 20 mg.

In some embodiments of any one of the embodiments described herein, the amount of a protease inhibitor in a unit dosage form described herein is in a range of from 10 to 100 mg. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is in a range of from 20 to 100 mg. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is in a range of from 30 to 100 mg. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is in a range of from 50 to 100 mg.

In some embodiments of any one of the embodiments described herein, the amount of a protease inhibitor in a unit dosage form described herein is in a range of from 10 to 200 mg. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is in a range of from 20 to 200 mg. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is in a range of from 30 to 200 mg. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is in a range of from 50 to 200 mg. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is in a range of from 100 to 200 mg.

In some embodiments of any one of the embodiments described herein, the amount of a protease inhibitor in a unit dosage form described herein is at least about 10 kallikrein inactivator units (k.i.u.). In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is at least about 12 k.i.u. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is at least about 15 k.i.u. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is at least about 20 k.i.u. In some embodiments, the

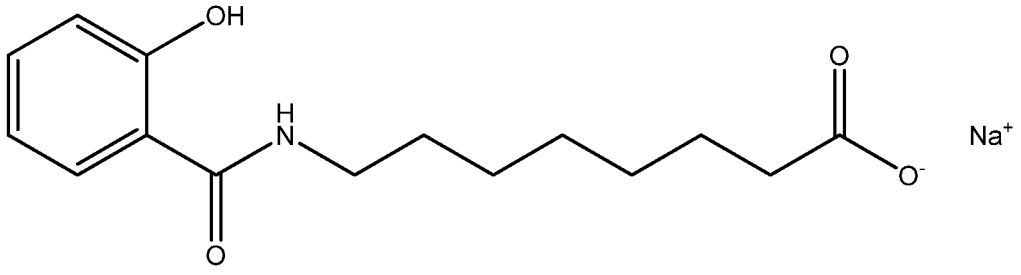
amount of a protease inhibitor in a unit dosage form described herein is at least about 30 k.i.u. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is at least about 40 k.i.u. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is at least about 50 k.i.u. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is at least about 70 k.i.u. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is at least about 100 k.i.u. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is at least about 150 k.i.u. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is at least about 200 k.i.u. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is at least about 300 k.i.u. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is at least about 500 k.i.u. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is at least about 700 k.i.u. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is at least about 1000 k.i.u. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is at least about 1500 k.i.u. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is at least about 3000 k.i.u. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is at least about 4000 k.i.u. In some embodiments, the amount of a protease inhibitor in a unit dosage form described herein is at least about 5000 k.i.u.

Herein and in the art, a "kallikrein inactivating unit" (k.i.u) refers to an amount of protease inhibitor that has the ability to inhibit 2 units of kallikrein by 50 % (e.g., in aqueous solution at an optimal pH and solution volume for activity of the protease inhibitor).

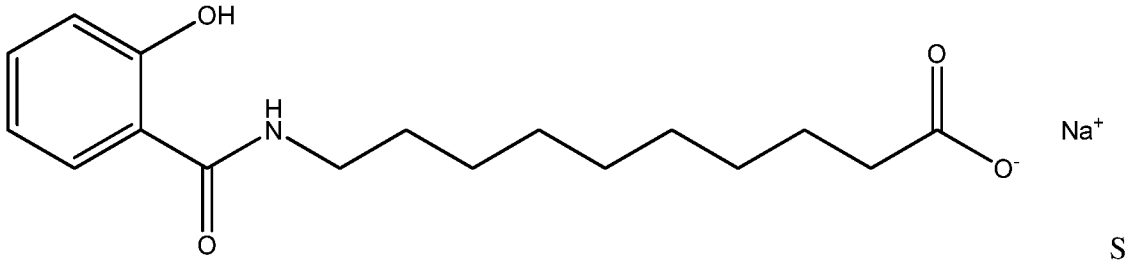
In some embodiments of any one of the embodiments described herein, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 1:1 to 5:1 (protease inhibitor: therapeutically active agent). In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 5:1 to 10:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 10:1 to 20:1. In some embodiments, a weight ratio of protease

inhibitor to therapeutically active agent is in a range of from 20:1 to 30:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 30:1 to 40:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 40:1 to 50:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 50:1 to 75:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 75:1 to 100:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 100:1 to 200:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 200:1 to 300:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 300:1 to 400:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 400:1 to 500:1. In some embodiments, the protease inhibitor is soybean trypsin inhibitor.

In some embodiments of any one of the embodiments described herein, the SNAC may optionally be replaced with a similar compound, such as SNAD (sodium 10-N-(2-hydroxybenzoyl)aminodecanoic acid). As shown below, the structure of SNAD differs from that of SNAC only in the length of the fatty acid moiety.



SNAC



NAD

In some embodiments of any one of the embodiments described herein, the SNAC may optionally be replaced with a similar compound, wherein the caprylic acid moiety of SNAC is replaced by another fatty acid moiety at least 6 carbon atoms in length, for example, from 6 to 20 carbon atoms in length, optionally from 6 to 18 carbon atoms in length, optionally from 6 to 16 carbon atoms in length, optionally from 6 to 14 carbon atoms in length, optionally from 6 to 12 carbon atoms in length and optionally from 6 to 10 carbon atoms in length. The fatty acid moiety may be saturated (e.g., as are caprylic acid in SNAC and decanoic acid in SNAD) or unsaturated (i.e., comprising at least one unsaturated carbon-carbon bond).

In some embodiments of any one of the embodiments described herein, a concentration of SNAC in a composition described herein is in a range of from 2.5 to 99.4 weight percents. In some of the aforementioned embodiments, the concentration of SNAC is in a range of from 2.5 to 10 weight percents. In some of the aforementioned embodiments, the concentration of SNAC is in a range of from 8 to 15 weight percents. In some of the aforementioned embodiments, the concentration of SNAC is in a range of from 10 to 20 weight percents. In some of the aforementioned embodiments, the concentration of SNAC is in a range of from 15 to 30 weight percents. In some of the aforementioned embodiments, the concentration of SNAC is in a range of from 20 to 40 weight percents. In some of the aforementioned embodiments, the concentration of SNAC is in a range of from 30 to 50 weight percents. In some of the aforementioned embodiments, the concentration of SNAC is in a range of from 40 to 60 weight percents. In some of the aforementioned embodiments, the concentration of SNAC is in a range of from 50 to 70 weight percents. In some of the aforementioned embodiments, the concentration of SNAC is in a range of from 2.5 to 10 weight percents. In some of the aforementioned embodiments, the concentration of SNAC is in a range of from 2.5 to 10 weight percents. In some of the aforementioned embodiments, the concentration of SNAC is in a range of from 70 to 99.4 weight percents.

In some embodiments of any one of the embodiments described herein, a weight ratio of SNAC to the therapeutically active agent is in a range of from 5:1 to 10:1 (SNAC: therapeutically active agent). In some embodiments, the ratio is about 7.5:1. In some embodiments, the composition further comprises a protease inhibitor. In some of the aforementioned embodiments wherein the composition comprises a protease

inhibitor, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 1:1 to 5:1 (protease inhibitor: therapeutically active agent), optionally about 3:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 5:1 to 10:1, optionally about 7.5:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 10:1 to 20:1, optionally about 15:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 20:1 to 30:1, optionally about 25:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 30:1 to 40:1, optionally about 35:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 40:1 to 50:1, optionally about 45:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 50:1 to 75:1, optionally about 62.5:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 75:1 to 100:1, optionally about 87.5:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 100:1 to 200:1, optionally about 150:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 200:1 to 300:1, optionally about 250:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 300:1 to 400:1, optionally about 350:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 400:1 to 500:1, optionally about 450:1. In some embodiments, the protease inhibitor is soybean trypsin inhibitor.

In some embodiments of any one of the embodiments described herein, a weight ratio of SNAC to therapeutically active agent is in a range of from 10:1 to 20:1 (SNAC: therapeutically active agent). In some embodiments, the ratio is about 15:1. In some embodiments, the composition further comprises a protease inhibitor. In some of the aforementioned embodiments wherein the composition comprises a protease inhibitor, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 1:1 to 5:1 (protease inhibitor: therapeutically active agent), optionally about 3:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 5:1 to 10:1, optionally about 7.5:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 10:1 to 20:1,

optionally about 15:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 20:1 to 30:1, optionally about 25:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 30:1 to 40:1, optionally about 35:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 40:1 to 50:1, optionally about 45:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 50:1 to 75:1, optionally about 62.5:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 75:1 to 100:1, optionally about 87.5:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 100:1 to 200:1, optionally about 150:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 200:1 to 300:1, optionally about 250:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 300:1 to 400:1, optionally about 350:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 400:1 to 500:1, optionally about 450:1. In some embodiments, the protease inhibitor is soybean trypsin inhibitor.

In some embodiments of any one of the embodiments described herein, a weight ratio of SNAC to therapeutically active agent is in a range of from 20:1 to 30:1 (SNAC: therapeutically active agent). In some embodiments, the ratio is about 25:1. In some embodiments, the composition further comprises a protease inhibitor. In some of the aforementioned embodiments wherein the composition comprises a protease inhibitor, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 1:1 to 5:1 (protease inhibitor: therapeutically active agent), optionally about 3:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 5:1 to 10:1, optionally about 7.5:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 10:1 to 20:1, optionally about 15:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 20:1 to 30:1, optionally about 25:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 30:1 to 40:1, optionally about 35:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 40:1 to

50:1, optionally about 45:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 50:1 to 75:1, optionally about 62.5:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 75:1 to 100:1, optionally about 87.5:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 100:1 to 200:1, optionally about 150:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 200:1 to 300:1, optionally about 250:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 300:1 to 400:1, optionally about 350:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 400:1 to 500:1, optionally about 450:1. In some embodiments, the protease inhibitor is soybean trypsin inhibitor.

In some embodiments of any one of the embodiments described herein, a weight ratio of SNAC to therapeutically active agent is in a range of from 30:1 to 50:1 (SNAC: therapeutically active agent). In some embodiments, the ratio is about 40:1. In some embodiments, the composition further comprises a protease inhibitor. In some of the aforementioned embodiments wherein the composition comprises a protease inhibitor, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 1:1 to 5:1 (protease inhibitor: therapeutically active agent), optionally about 3:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 5:1 to 10:1, optionally about 7.5:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 10:1 to 20:1, optionally about 15:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 20:1 to 30:1, optionally about 25:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 30:1 to 40:1, optionally about 35:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 40:1 to 50:1, optionally about 45:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 50:1 to 75:1, optionally about 62.5:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 75:1 to 100:1, optionally about 87.5:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from

100:1 to 200:1, optionally about 150:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 200:1 to 300:1, optionally about 250:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 300:1 to 400:1, optionally about 350:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 400:1 to 500:1, optionally about 450:1. In some embodiments, the protease inhibitor is soybean trypsin inhibitor.

In some embodiments of any one of the embodiments described herein, a weight ratio of SNAC to therapeutically active agent is in a range of from 50:1 to 100:1 (SNAC: therapeutically active agent). In some embodiments, the ratio is about 75:1. In some embodiments, the composition further comprises a protease inhibitor. In some of the aforementioned embodiments wherein the composition comprises a protease inhibitor, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 1:1 to 5:1 (protease inhibitor: therapeutically active agent), optionally about 3:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 5:1 to 10:1, optionally about 7.5:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 10:1 to 20:1, optionally about 15:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 20:1 to 30:1, optionally about 25:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 30:1 to 40:1, optionally about 35:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 40:1 to 50:1, optionally about 45:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 50:1 to 75:1, optionally about 62.5:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 75:1 to 100:1, optionally about 87.5:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 100:1 to 200:1, optionally about 150:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 200:1 to 300:1, optionally about 250:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 300:1 to 400:1, optionally about 350:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent

is in a range of from 400:1 to 500:1, optionally about 450:1. In some embodiments, the protease inhibitor is soybean trypsin inhibitor.

In some embodiments of any one of the embodiments described herein, a weight ratio of SNAC to therapeutically active agent is in a range of from 100:1 to 200:1 (SNAC: therapeutically active agent). In some embodiments, the ratio is about 150:1. In some embodiments, the composition further comprises a protease inhibitor. In some of the aforementioned embodiments wherein the composition comprises a protease inhibitor, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 1:1 to 5:1 (protease inhibitor: therapeutically active agent), optionally about 3:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 5:1 to 10:1, optionally about 7.5:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 10:1 to 20:1, optionally about 15:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 20:1 to 30:1, optionally about 25:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 30:1 to 40:1, optionally about 35:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 40:1 to 50:1, optionally about 45:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 50:1 to 75:1, optionally about 62.5:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 75:1 to 100:1, optionally about 87.5:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 100:1 to 200:1, optionally about 150:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 200:1 to 300:1, optionally about 250:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 300:1 to 400:1, optionally about 350:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 400:1 to 500:1, optionally about 450:1. In some embodiments, the protease inhibitor is soybean trypsin inhibitor.

In some embodiments of any one of the embodiments described herein, a weight ratio of SNAC to therapeutically active agent is in a range of from 200:1 to 300:1 (SNAC: therapeutically active agent). In some embodiments, the ratio is about 250:1.

In some embodiments, the composition further comprises a protease inhibitor. In some of the aforementioned embodiments wherein the composition comprises a protease inhibitor, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 1:1 to 5:1 (protease inhibitor: therapeutically active agent), optionally about 3:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 5:1 to 10:1, optionally about 7.5:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 10:1 to 20:1, optionally about 15:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 20:1 to 30:1, optionally about 25:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 30:1 to 40:1, optionally about 35:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 40:1 to 50:1, optionally about 45:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 50:1 to 75:1, optionally about 62.5:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 75:1 to 100:1, optionally about 87.5:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 100:1 to 200:1, optionally about 150:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 200:1 to 300:1, optionally about 250:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 300:1 to 400:1, optionally about 350:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 400:1 to 500:1, optionally about 450:1. In some embodiments, the protease inhibitor is soybean trypsin inhibitor.

In some embodiments of any one of the embodiments described herein, a weight ratio of SNAC to therapeutically active agent is in a range of from 300:1 to 500:1 (SNAC: therapeutically active agent). In some embodiments, the ratio is about 400:1. In some embodiments, the composition further comprises a protease inhibitor. In some of the aforementioned embodiments wherein the composition comprises a protease inhibitor, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 1:1 to 5:1 (protease inhibitor: therapeutically active agent), optionally about 3:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent

is in a range of from 5:1 to 10:1, optionally about 7.5:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 10:1 to 20:1, optionally about 15:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 20:1 to 30:1, optionally about 25:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 30:1 to 40:1, optionally about 35:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 40:1 to 50:1, optionally about 45:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 50:1 to 75:1, optionally about 62.5:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 75:1 to 100:1, optionally about 87.5:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 100:1 to 200:1, optionally about 150:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 200:1 to 300:1, optionally about 250:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 300:1 to 400:1, optionally about 350:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 400:1 to 500:1, optionally about 450:1. In some embodiments, the protease inhibitor is soybean trypsin inhibitor.

In some embodiments of any one of the embodiments described herein, a weight ratio of SNAC to therapeutically active agent is in a range of from 500:1 to 1000:1 (SNAC: therapeutically active agent). In some embodiments, the ratio is about 750:1. In some embodiments, the composition further comprises a protease inhibitor. In some of the aforementioned embodiments wherein the composition comprises a protease inhibitor, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 1:1 to 5:1 (protease inhibitor: therapeutically active agent), optionally about 3:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 5:1 to 10:1, optionally about 7.5:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 10:1 to 20:1, optionally about 15:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 20:1 to 30:1, optionally about 25:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is

in a range of from 30:1 to 40:1, optionally about 35:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 40:1 to 50:1, optionally about 45:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 50:1 to 75:1, optionally about 62.5:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 75:1 to 100:1, optionally about 87.5:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 100:1 to 200:1, optionally about 150:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 200:1 to 300:1, optionally about 250:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 300:1 to 400:1, optionally about 350:1. In some embodiments, a weight ratio of protease inhibitor to therapeutically active agent is in a range of from 400:1 to 500:1, optionally about 450:1. In some embodiments, the protease inhibitor is soybean trypsin inhibitor.

In some embodiments of any one of the embodiments described herein, the amount of SNAC in a unit dosage form described herein is at least about 0.1 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is at least about 0.2 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is at least about 0.3 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is at least about 0.4 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is at least about 0.6 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is at least about 0.8 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is at least about 1 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is at least about 1.5 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is at least about 2 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is at least about 2.5 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is at least about 3 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is at least about 5 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is at least about 7 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is at least

about 10 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is at least about 12 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is at least about 15 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is at least about 20 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is at least about 30 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is at least about 50 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is at least about 70 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is at least about 100 mg. In some embodiments, the amount of therapeutically active agent is in accordance with any one of the ratios of SNAC to therapeutically active agent described herein. In some embodiments, the composition further comprises at least one protease inhibitor in an amount which is in accordance with any one of the ratios of protease inhibitor to therapeutically active agent described herein.

In some embodiments of any one of the embodiments described herein, the amount of SNAC in a unit dosage form described herein is in a range of from 0.1 to 1 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 0.2 to 1 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 0.3 to 1 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 0.5 to 1 mg.

In some embodiments of any one of the embodiments described herein, the amount of SNAC in a unit dosage form described herein is in a range of from 0.1 to 2 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 0.2 to 2 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 0.3 to 2 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 0.5 to 2 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 1 to 2 mg.

In some embodiments of any one of the embodiments described herein, the amount of SNAC in a unit dosage form described herein is in a range of from 1 to 10 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein

is in a range of from 2 to 10 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 3 to 10 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 5 to 10 mg.

In some embodiments of any one of the embodiments described herein, the amount of SNAC in a unit dosage form described herein is in a range of from 1 to 20 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 2 to 20 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 3 to 20 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 5 to 20 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 10 to 20 mg.

In some embodiments of any one of the embodiments described herein, the amount of SNAC in a unit dosage form described herein is in a range of from 10 to 100 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 20 to 100 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 30 to 100 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 50 to 100 mg.

In some embodiments of any one of the embodiments described herein, the amount of SNAC in a unit dosage form described herein is in a range of from 10 to 200 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 20 to 200 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 30 to 200 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 50 to 200 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 100 to 200 mg.

In some embodiments of any one of the embodiments described herein, the amount of SNAC in a unit dosage form described herein is in a range of from 10 to 500 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 20 to 500 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 30 to 500 mg. In some

embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 50 to 500 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 100 to 500 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 200 to 500 mg.

In some embodiments of any one of the embodiments described herein, the amount of SNAC in a unit dosage form described herein is in a range of from 10 to 1000 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 20 to 1000 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 30 to 1000 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 50 to 1000 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 100 to 1000 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 200 to 1000 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 500 to 1000 mg.

In some embodiments of any one of the embodiments described herein, the amount of SNAC in a unit dosage form described herein is in a range of from 10 to 1000 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 20 to 1000 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 30 to 1000 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 50 to 1000 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 100 to 1000 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 200 to 1000 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 500 to 1000 mg.

In some embodiments of any one of the embodiments described herein, the amount of SNAC in a unit dosage form described herein is in a range of from 10 to 2000 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 20 to 2000 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 30 to 2000 mg. In some

embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 50 to 2000 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 100 to 2000 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 200 to 2000 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 500 to 2000 mg. In some embodiments, the amount of SNAC in a unit dosage form described herein is in a range of from 1000 to 2000 mg.

In some embodiments of any one of the embodiments described herein, a unit dosage form described herein comprises at least 50 μg of therapeutically active agent. In some embodiments, the composition comprises at least 100 μg of therapeutically active agent. In some embodiments, the composition comprises at least 200 μg of therapeutically active agent. In some embodiments, the composition comprises at least 500 μg of therapeutically active agent. In some embodiments, the amount of SNAC is in accordance with any one of the ratios of SNAC to therapeutically active agent described herein. In some embodiments, the composition further comprises at least one protease inhibitor in an amount which is in accordance with any one of the ratios of protease inhibitor to therapeutically active agent described herein.

In some embodiments of any one of the embodiments described herein, a unit dosage form described herein comprises 500 mg or less of therapeutically active agent. In some embodiments, the unit dosage form comprises 200 mg or less of therapeutically active agent. In some embodiments, the unit dosage form comprises 100 mg or less of therapeutically active agent. In some embodiments, the unit dosage form comprises 50 mg or less of therapeutically active agent. In some embodiments, the unit dosage form comprises 20 mg or less of therapeutically active agent. In some embodiments, the unit dosage form comprises 10 mg or less of therapeutically active agent. In some embodiments, the unit dosage form comprises 5 mg or less of therapeutically active agent. In some embodiments, the unit dosage form comprises 3 mg (3000 μg) or less of therapeutically active agent. In some embodiments, the unit dosage form comprises 2000 μg or less of therapeutically active agent. In some embodiments, the unit dosage form comprises 1000 μg or less of therapeutically active agent. In some embodiments, the amount of SNAC is in accordance with any one of the ratios of SNAC to therapeutically active agent described herein. In some embodiments, the composition

further comprises at least one protease inhibitor in an amount which is in accordance with any one of the ratios of protease inhibitor to therapeutically active agent described herein.

In some embodiments of any one of the embodiments described herein, the unit dosage form comprises from 100 μg to 500 mg of therapeutically active agent. In some embodiments, the unit dosage form comprises 100 μg to 200 mg of therapeutically active agent. In some embodiments, the unit dosage form comprises 100 μg to 100 mg of therapeutically active agent. In some embodiments, the unit dosage form comprises 100 μg to 50 mg of therapeutically active agent. In some embodiments, the unit dosage form comprises 100 μg to 20 mg of therapeutically active agent. In some embodiments, the unit dosage form comprises 100 μg to 10 mg of therapeutically active agent. In some embodiments, the unit dosage form comprises 100 μg to 5 mg of therapeutically active agent. In some embodiments, the unit dosage form comprises from 100 to 3000 μg of therapeutically active agent. In some embodiments, the unit dosage form comprises from 100 to 2000 μg of therapeutically active agent. In some embodiments, the unit dosage form comprises about 750 μg of therapeutically active agent. In some embodiments, the amount of SNAC is in accordance with any one of the ratios of SNAC to therapeutically active agent described herein. In some embodiments, the composition further comprises at least one protease inhibitor in an amount which is in accordance with any one of the ratios of protease inhibitor to therapeutically active agent described herein.

In some embodiments of any one of the embodiments described herein, the unit dosage form comprises from 200 μg to 500 mg of therapeutically active agent. In some embodiments, the unit dosage form comprises 200 μg to 200 mg of therapeutically active agent. In some embodiments, the unit dosage form comprises 200 μg to 100 mg of therapeutically active agent. In some embodiments, the unit dosage form comprises 200 μg to 50 mg of therapeutically active agent. In some embodiments, the unit dosage form comprises 200 μg to 20 mg of therapeutically active agent. In some embodiments, the unit dosage form comprises 200 μg to 10 mg of therapeutically active agent. In some embodiments, the unit dosage form comprises 200 μg to 5 mg of therapeutically active agent. In some embodiments, the unit dosage form comprises from 200 to 3000 μg of therapeutically active agent. In some embodiments, the unit dosage form

comprises from 200 to 2000 μg of therapeutically active agent. In some embodiments, the unit dosage form comprises from 500 to 1000 μg of therapeutically active agent. In some embodiments, the therapeutically active agent is a parathyroid hormone or a fragment thereof. In some embodiments, the therapeutically active agent is teriparatide. In some embodiments, the amount of SNAC is in accordance with any one of the ratios of SNAC to therapeutically active agent described herein. In some embodiments, the composition further comprises at least one protease inhibitor in an amount which is in accordance with any one of the ratios of protease inhibitor to therapeutically active agent described herein.

Compositions described herein are particularly suitable for controlling the absorption of therapeutically active agents whose absorption upon oral administration is limited, as absorption of such therapeutically active agents is particularly dependent on absorption enhancement activity of SNAC. Limited absorption of a therapeutically active agent may be, for example, due to a large molecular weight, strong hydrophilicity (e.g., which inhibits crossing of lipid membranes in the gastrointestinal tract), strong lipophilicity (e.g., which reduces dissolution and consequently diffusion in the gastrointestinal tract, inhibits permeation of hydrophilic layers such as intestinal mucus linings, and/or results in accumulation in lipid membranes), and/or degradation in the gastrointestinal tract (e.g., by proteolysis).

In some embodiments of any one of the embodiments described herein, the therapeutically active agent has a molecular weight of at least 0.5 kDa. In some embodiments, the molecular weight is in a range of from 0.5 to 150 kDa. In some embodiments, the molecular weight is in a range of from 0.5 to 100 kDa. In some embodiments, the molecular weight is in a range of from 0.5 to 75 kDa. In some embodiments, the molecular weight is in a range of from 0.5 to 50 kDa. In some embodiments, the molecular weight is in a range of from 0.5 to 30 kDa. In some embodiments, the molecular weight is in a range of from 0.5 to 20 kDa. In some embodiments, the molecular weight is in a range of from 0.5 to 10 kDa. In some embodiments, the molecular weight is in a range of from 0.5 to 7.5 kDa. In some embodiments, the molecular weight is in a range of from 0.5 to 5 kDa.

In some embodiments of any one of the embodiments described herein, the therapeutically active agent has a molecular weight of at least 1 kDa. In some

embodiments, the molecular weight is in a range of from 1 to 150 kDa. In some embodiments, the molecular weight is in a range of from 1 to 100 kDa. In some embodiments, the molecular weight is in a range of from 1 to 75 kDa. In some embodiments, the molecular weight is in a range of from 1 to 50 kDa. In some embodiments, the molecular weight is in a range of from 1 to 30 kDa. In some embodiments, the molecular weight is in a range of from 1 to 20 kDa. In some embodiments, the molecular weight is in a range of from 1 to 10 kDa. In some embodiments, the molecular weight is in a range of from 1 to 7.5 kDa. In some embodiments, the molecular weight is in a range of from 1 to 5 kDa.

In some embodiments of any one of the embodiments described herein, the therapeutically active agent has a molecular weight of at least 2 kDa. In some embodiments, the molecular weight is in a range of from 2 to 150 kDa. In some embodiments, the molecular weight is in a range of from 2 to 100 kDa. In some embodiments, the molecular weight is in a range of from 2 to 75 kDa. In some embodiments, the molecular weight is in a range of from 2 to 50 kDa. In some embodiments, the molecular weight is in a range of from 2 to 30 kDa. In some embodiments, the molecular weight is in a range of from 2 to 20 kDa. In some embodiments, the molecular weight is in a range of from 2 to 10 kDa. In some embodiments, the molecular weight is in a range of from 2 to 7.5 kDa. In some embodiments, the molecular weight is in a range of from 2 to 5 kDa.

In some embodiments of any one of the embodiments described herein, the therapeutically active agent has a molecular weight of at least 3 kDa. In some embodiments, the molecular weight is in a range of from 3 to 150 kDa. In some embodiments, the molecular weight is in a range of from 3 to 100 kDa. In some embodiments, the molecular weight is in a range of from 3 to 75 kDa. In some embodiments, the molecular weight is in a range of from 3 to 50 kDa. In some embodiments, the molecular weight is in a range of from 3 to 30 kDa. In some embodiments, the molecular weight is in a range of from 3 to 20 kDa. In some embodiments, the molecular weight is in a range of from 3 to 10 kDa. In some embodiments, the molecular weight is in a range of from 3 to 7.5 kDa. In some embodiments, the molecular weight is in a range of from 3 to 5 kDa.

In some embodiments of any one of the embodiments described herein, the therapeutically active agent has a molecular weight of at least 4 kDa. In some embodiments, the molecular weight is in a range of from 4 to 150 kDa. In some embodiments, the molecular weight is in a range of from 4 to 100 kDa. In some embodiments, the molecular weight is in a range of from 4 to 75 kDa. In some embodiments, the molecular weight is in a range of from 4 to 50 kDa. In some embodiments, the molecular weight is in a range of from 4 to 30 kDa. In some embodiments, the molecular weight is in a range of from 4 to 20 kDa. In some embodiments, the molecular weight is in a range of from 4 to 10 kDa. In some embodiments, the molecular weight is in a range of from 4 to 7.5 kDa. In some embodiments, the molecular weight is in a range of from 4 to 5 kDa.

In some embodiments of any one of the embodiments described herein, the therapeutically active agent has a molecular weight of at least 5 kDa. In some embodiments, the molecular weight is in a range of from 5 to 150 kDa. In some embodiments, the molecular weight is in a range of from 5 to 100 kDa. In some embodiments, the molecular weight is in a range of from 5 to 75 kDa. In some embodiments, the molecular weight is in a range of from 5 to 50 kDa. In some embodiments, the molecular weight is in a range of from 5 to 30 kDa. In some embodiments, the molecular weight is in a range of from 5 to 20 kDa. In some embodiments, the molecular weight is in a range of from 5 to 10 kDa. In some embodiments, the molecular weight is in a range of from 5 to 7.5 kDa.

In some embodiments of any one of the embodiments described herein, the therapeutically active agent has a molecular weight of at least 10 kDa. In some embodiments, the molecular weight is in a range of from 10 to 150 kDa. In some embodiments, the molecular weight is in a range of from 10 to 100 kDa. In some embodiments, the molecular weight is in a range of from 10 to 75 kDa. In some embodiments, the molecular weight is in a range of from 10 to 50 kDa. In some embodiments, the molecular weight is in a range of from 10 to 30 kDa. In some embodiments, the molecular weight is in a range of from 10 to 20 kDa.

In some embodiments of any one of the embodiments described herein, the therapeutically active agent has a molecular weight of at least 20 kDa. In some embodiments, the molecular weight is in a range of from 20 to 150 kDa. In some

embodiments, the molecular weight is in a range of from 20 to 100 kDa. In some embodiments, the molecular weight is in a range of from 20 to 75 kDa. In some embodiments, the molecular weight is in a range of from 20 to 50 kDa. In some embodiments, the molecular weight is in a range of from 20 to 30 kDa.

In some embodiments of any one of the embodiments described herein, the therapeutically active agent has a molecular weight of at least 50 kDa. In some embodiments, the molecular weight is in a range of from 50 to 150 kDa. In some embodiments, the molecular weight is in a range of from 50 to 100 kDa. In some embodiments, the molecular weight is in a range of from 50 to 75 kDa.

Without being bound by any particular theory, it is believed that agents having a relatively high molecular weight (e.g., at least 0.5 kDa, at least 1 kDa, at least 2 kDa, at least 3 kDa, at least 4 kDa) tend to be less efficiently absorbed upon oral administration than relatively small molecules (e.g., molecules having a molecular weight of less than 0.5 kDa, or less than 1 kDa) and therefore, their absorption is particularly susceptible to enhancement by SNAC activity.

In some embodiments of any one of the embodiments described herein, the therapeutically active agent is a hormone and/or cytokine (e.g., a hormone).

In some embodiments of any one of the embodiments described herein, the therapeutically active agent is a polypeptide. In some embodiments, the polypeptide is a polypeptide hormone and/or cytokine, or a fragment thereof (e.g., a fragment exhibiting an activity of the hormone and/or cytokine), or a homolog of a polypeptide hormone and/or cytokine or fragment thereof.

Examples of polypeptides which may be utilized (*per se* or as fragments thereof and/or homologs thereof) as therapeutically active agents according to embodiments of the invention include, without limitation, insulin, a glucagon, a parathyroid hormone, an interferon, a growth hormone, an erythropoietin, a calcitonin, an omentin, a motilin, a leptin, a peptide YY, a GLP-1 (glucagon-like peptide-1), a GLP-2 (glucagon-like peptide-2), granulocyte-colony stimulating factor (G-CSF), an antibody (e.g., monoclonal antibody), an interleukin, an erythropoietin, a vasopressin, a vasoactive intestinal peptide, a pituitary adenylate cyclase-activating peptide (PACAP), a blood clotting factor, an endomorphin (e.g., endomorphin-1, endomorphin-2), a TNF inhibitor (e.g., infliximab, adalimumab, certolizumab, golimumab, etanercept), disitertide,

octreotide (a somatotropin analog), davunetide, icatibant, glucocerebrosidase, a gonadotropin releasing hormone (GnRH), acyline (a GnRH antagonist), and a GLP-1 agonist such as exendin-4 (including exenatide and lixisenatide). Examples of growth hormones, include, without limitation, somatotropin (growth hormone 1), growth hormone 2, and growth factors (e.g., insulin-like growth factor 1 (IGF-1), fibroblast growth factor (FGF), ciliary neurotrophic factor).

Insulin, glucagon, parathyroid hormone, erythropoietin, calcitonin, motilin, leptin, peptide YY, GLP-1 (including derivatives thereof such as liraglutide, taspoglutide, albiglutide and dulaglutide), GLP-2, GnRH (including derivatives thereof such as leuprorelin, buserelin, histrelin, goserelin, deslorelin, nafarelin and triptorelin), vasopressin (including derivatives thereof such as desmopressin), vasoactive intestinal peptide (including aviptadil), pituitary adenylate cyclase-activating peptide (PACAP), growth hormones (including axokine, a homolog of a fragment of ciliary neurotrophic factor) and G-CSF are non-limiting examples of polypeptide hormones.

Interferons, interleukins, erythropoietin and analogs thereof (e.g., darbepoetin), omentin and G-CSF are non-limiting examples of polypeptide cytokines.

In some embodiments of any one of the embodiments described herein, the therapeutically active agent is parathyroid hormone (PTH) or a fragment thereof (e.g., a fragment exhibiting an activity of PTH). In some embodiments, the polypeptide is teriparatide (i.e., a PTH fragment having amino acid residues 1-34 of PTH).

Herein, the term "parathyroid hormone" or its abbreviation "PTH" encompasses parathyroid hormone (having a naturally occurring amino acid sequence, e.g., in humans) and homologs of the parathyroid hormone. A "fragment" of parathyroid hormone encompasses fragments of parathyroid hormone having a naturally occurring amino acid sequence (e.g., in humans) and homologs of such fragments.

Without being bound by any particular theory, it is believed that agents which are polypeptides tend to be poorly absorbed upon oral administration, for example, due to their polarity and/or relatively large molecular weight; and therefore, their absorption is particularly susceptible to enhancement by SNAC activity.

In some embodiments of any one of the embodiments described herein wherein the therapeutically active agents is a polypeptide, the composition further comprises at

least one protease inhibitor, for example, according to any one of the embodiments described herein relating to a protease inhibitor.

It has been reported that therapeutically active agents which exhibit more than one of the following criteria tend to be poorly absorbed upon oral administration (when administered alone), a phenomenon referred to in the art as "Lipinski's rule of 5":

(i) a total number of nitrogen-hydrogen bonds and oxygen hydrogen bonds (which are typically hydrogen bond donors) which is more than 5;

(ii) a total number of nitrogen and oxygen atoms (which are typically hydrogen bond acceptors) which is more than 5;

(iii) an octanol-water partition coefficient (log P) which is greater than 5; and/or

(iv) a molecular weight of at least 500 Da (0.5 kDa).

The abovementioned criteria (i) and (ii) are associated with hydrogen bonding and hydrophilicity; whereas criteria (iii) is associated with lipophilicity.

As described herein, therapeutically active agents poorly absorbed upon oral administration when administered alone are particularly suitable for being included in compositions described herein, in order to enhance their absorption.

In some embodiments of any one of the embodiments described herein, the therapeutically active agent meets at least one of the abovementioned criteria (i), (ii), (iii) and (iv). In some embodiments, the therapeutically active agent meets at least two of the abovementioned criteria (i), (ii), (iii) and (iv). In some embodiments, the therapeutically active agent meets at least three of the abovementioned criteria (i), (ii), (iii) and (iv). In some embodiments, the therapeutically active agent meets all four of the abovementioned criteria (i), (ii), (iii) and (iv).

In some embodiments of any one of the embodiments described herein, the therapeutically active agent has a molecular weight of at least 0.5 kDa, in accordance with any one of the embodiments described herein relating to a molecular weight of at least 0.5 kDa, and further meets at least one of the abovementioned criteria (i), (ii) and (iii). In some such embodiments, the therapeutically active agent meets at least two of the abovementioned criteria (i), (ii) and (iii).

Dihydroergotamine and fondaparinux are non-limiting examples of non-peptidic agents having a molecular weight of at least 0.5 kDa, which are poorly absorbed upon oral administration.

In some embodiments of any one of the embodiments described herein, the therapeutically active agent has a molecular weight of less than 0.5 kDa, and meets at least one of the abovementioned criteria (i), (ii) and (iii). In some such embodiments, the therapeutically active agent meets at least two of the abovementioned criteria (i), (ii) and (iii). In some such embodiments, the therapeutically active agent meets all three of the abovementioned criteria (i), (ii) and (iii).

In addition, ionic molecules tend to be poorly absorbed upon oral administration, generally due to a considerably reduced ability to cross lipid membranes. Whether a molecule is ionic or non-ionic often depends on pH, which varies according to location in the gastrointestinal tract. In general, it is believed that the more a therapeutically active agent is in ionic form in the gastrointestinal tract, the more likely it is to be poorly absorbed upon oral administration.

In some embodiments of any one of the embodiments described herein, the therapeutically active agent is ionic in an aqueous solution at a pH of 7.0.

In some embodiments of any one of the embodiments described herein, the therapeutically active agent is ionic in an aqueous solution at a pH of 6.0.

In some embodiments of any one of the embodiments described herein, the therapeutically active agent is ionic in an aqueous solution at a pH of 5.0.

In some embodiments of any one of the embodiments described herein, the therapeutically active agent is ionic in an aqueous solution at a pH of 4.0.

In some embodiments of any one of the embodiments described herein, the therapeutically active agent is ionic in an aqueous solution at a pH of 3.0.

In some embodiments of any one of the embodiments described herein, the therapeutically active agent is ionic in an aqueous solution at a pH of 2.0.

In some embodiments of any one of the embodiments described herein, the therapeutically active agent is ionic in an aqueous solution at a pH of 1.0.

Examples of such agents include, without limitation, compounds comprising at least one basic group (e.g., amine group) which is positively charged at a pH of 7.0 (or less).

Herein, a compound is considered "ionic" when it comprises at least one functional group which is charged in at least 50 % of the molecules in a population of molecules of the compound under designated conditions (e.g., in an aqueous solution at a designated pH value or range of pH values). The skilled person will be readily capable of determining whether a functional group is charged in at least 50 % of the molecules, for example, by determining a pKa value associated with the functional group. An ionic compound, as defined herein, may optionally have a net negative charge, optionally a net positive charge, and optionally an equal number of negatively charged functional groups and positively functional groups, resulting in no net charge.

In some embodiments of any one of the embodiments described herein, the therapeutically active agent is ionic in an aqueous solution at all pH values within a range of from 5.0 to 7.0. In some embodiments, the therapeutically active agent is ionic in an aqueous solution at all pH values within a range of from 5.0 to 8.0. In some embodiments, the therapeutically active agent is ionic in an aqueous solution at all pH values within a range of from 4.0 to 9.0. In some embodiments, the therapeutically active agent is ionic in an aqueous solution at all pH values within a range of from 3.0 to 10.0. In some embodiments, the therapeutically active agent is ionic in an aqueous solution at all pH values within a range of from 2.0 to 11.0.

In some embodiments of any one of the embodiments described herein, the therapeutically active agent is ionic at a pH value and/or range according to any one of the abovementioned embodiments, and further has a molecular weight of at least 0.5 kDa, in accordance with any one of the embodiments described herein relating to a molecular weight of at least 0.5 kDa. In some embodiments of any one of the embodiments described herein, the therapeutically active agent is ionic at a pH value and/or range according to any one of the abovementioned embodiments, and further has a molecular weight of less than 0.5 kDa.

Examples of ionic therapeutically active agents which tend to have a molecular weight of less than 0.5 kDa, and which tend to exhibit poor absorption upon oral administration, include, without limitation, bisphosphonates (e.g., for use in treating osteoporosis and related conditions) such as alendronate, clodronate, etidronate, ibandronate, neridronate, olpadronate, pamidronate, risedronate, tiludronate and zoledronate; and cromolyn (e.g., cromolyn sodium).

In some embodiments of any one of the embodiments described herein, the therapeutically active agent is a Class III agent according to the Biopharmaceutics Classification System (BCS), as provided by the U.S. FDA, that is, the therapeutically active agent is characterized by low permeability and high solubility.

In the context of the BCS, the phrase "low permeability" refers herein and in the art to absorption of less than 90 % of a given agent upon oral administration in humans (in the absence of SNAC), as determined by mass-balance determination and/or in comparison to an intravenous dose.

In some embodiments, absorption of a Class III therapeutically active agent is less than 50 % upon oral administration (in the absence of SNAC). In some embodiments, absorption is less than 20 % upon oral administration (in the absence of SNAC). In some embodiments, absorption is less than 10 % upon oral administration (in the absence of SNAC). In some embodiments, absorption is less than 5 % upon oral administration (in the absence of SNAC). In some embodiments, absorption is less than 2 % upon oral administration (in the absence of SNAC). In some embodiments, absorption is less than 1 % upon oral administration (in the absence of SNAC).

In the context of the BCS, the phrase "high solubility" refers herein and in the art to an amount of therapeutically active agent in an administered dose being soluble in 250 ml or less of water over a pH range of 1 to 7.5.

In some embodiments of any one of the embodiments described herein, a bioavailability of the therapeutically active agent upon oral administration of the composition is in a range of from 0.05 to 50 %. In some embodiments, the bioavailability is in a range of from 0.1 to 15 %. In some embodiments, the bioavailability is in a range of from 0.2 to 5 %. In some embodiments, the bioavailability is in a range of from 0.5 to 3 %.

Without being bound by any particular theory, it is believed that SNAC enhances the bioavailability of the therapeutically active agent considerably. It is further believed that enhancing absorption for a controlled period of time, in accordance with some of the embodiments described herein, results in a somewhat lower bioavailability than that which occurs upon enhancement of absorption for a time period which is not controlled.

In some embodiments of any one of the embodiments described herein, a bioavailability of the therapeutically active agent upon oral administration of the

composition is at least 50 % higher than (150 % of the level of) a bioavailability of the therapeutically active agent upon oral administration of an equivalent composition which lacks SNAC (e.g., being identical in all aspects except for the absence of SNAC). In some embodiments, the bioavailability is at least twice (200 % of the level of) the bioavailability upon oral administration of an equivalent composition which lacks SNAC. In some embodiments, the bioavailability is at least four-fold (400 % of the level of) the bioavailability upon oral administration of an equivalent composition which lacks SNAC. In some embodiments, the bioavailability is at least ten-fold (1000 % of the level of) the bioavailability upon oral administration of an equivalent composition which lacks SNAC. In some embodiments, the bioavailability is at least twenty-fold (2000 % of the level of) the bioavailability upon oral administration of an equivalent composition which lacks SNAC. In some embodiments, the bioavailability is at least fifty-fold (5000 % of the level of) the bioavailability upon oral administration of an equivalent composition which lacks SNAC.

In some embodiments of any one of the embodiments described herein, the therapeutically active agent is a natural or synthetic hormone and/or cytokine which is regulated *in vivo* by a negative feedback loop, such that continuous exposure to administered hormone may result in the body producing less of a hormone and/or cytokine similar or identical to the administered hormone and/or cytokine, thereby at least partially neutralizing a therapeutic effect of administering exogenous hormone and/or cytokine. In some embodiments, the negative feedback is associated with adverse effects of administration of exogenous hormone and/or cytokine *per se* (e.g., by parenteral administration).

Without being bound by any particular theory, it is believed that a pharmacokinetic profile of compositions described herein can decrease and even eliminate effects of negative feedback, by allowing levels of the therapeutically active agent to return to normal levels before a substantial (e.g., long-term) negative feedback effect is induced.

In some embodiments of any one of the embodiments described herein, the therapeutically active agent is a modulator of blood glucose levels.

In some embodiments, the therapeutically active agent reduces blood glucose levels, and may be used, for example, to treat hyperglycemia. Insulin and GLP-1 are non-limiting examples of such an agent.

In some embodiments, the therapeutically active agent increases blood glucose levels, and may be used, for example, to treat hypoglycemia. Glucagon is a non-limiting example of such an agent.

Without being bound by any particular theory, it is believed that a pharmacokinetic profile of compositions described herein is particularly useful for treating acute hyperglycemia and/or hypoglycemia, while decreasing and even eliminating a risk of overshoot, whereby treating hyperglycemia results in hypoglycemia, or treating hypoglycemia results in hyperglycemia.

In some embodiments of any one of the embodiments described herein, the therapeutically active agent is an agent characterized in that acute exposure to the agent results in a substantially different biological effect than does chronic exposure.

Herein, the phrase "substantially different biological effect" means that at least a portion of the effects differ in type rather than in magnitude. In some embodiments, opposite effects are exhibited by acute vs. chronic exposure.

Parathyroid hormone is an example of an agent characterized in that acute exposure to the agent results in a substantially different biological effect than does chronic exposure, as acute exposure causes a net enhancement of bone growth, whereas chronic exposure causes a net enhancement of bone resorption (effectively the opposite of enhancing bone growth). Enhancement of bone growth may optionally be used for treating, for example, osteoporosis.

Without being bound by any particular theory, it is believed that a pharmacokinetic profile of compositions described herein can provide particularly pronounced and/or consistent effects associated with acute exposure to an agent, for example, pronounced and consistent enhancement of bone growth by parathyroid hormone and similar agents.

In some embodiments of any one of the embodiments described herein, the therapeutically active agent is oxytocin or an analog thereof, and the composition is for inducing labor.

Without being bound by any particular theory, it is believed that a pharmacokinetic profile of compositions described herein can allow for induction of labor by a brief presence of oxytocin in the blood, while decreasing a risk of adverse effects of oxytocin (e.g., more painful labor) by decreasing the time period during which the administered oxytocin is in the blood.

In some embodiments of any one of the embodiments described herein, the composition is for use in the treatment of a condition treatable by oral administration of the therapeutically active agent (e.g., a condition described herein).

According to another aspect of embodiments of the invention, there is provided a use of a composition according to any one of the embodiments described herein in the preparation of a medicament for use in the treatment of a condition treatable by oral administration of the therapeutically active agent (e.g., a condition described herein).

According to another aspect of embodiments of the invention, there is provided a method of treating a condition treatable by oral administration of a therapeutically active agent in a subject in need thereof (e.g., a condition and therapeutically active agent described herein), the method comprising orally administering to the subject a composition which comprises the therapeutically active agent, according to any one of the embodiments described herein.

Conditions treatable by the compositions and methods as described herein depend on the therapeutically active agents included in the composition, and should be recognized by persons skilled in the art.

For example, when the therapeutically active agent is insulin or GLP-1, the condition treatable by the compositions and methods described herein can be hyperglycemia and/or a condition associated with hyperglycemia, for example, diabetes.

When the therapeutically active agent is glucagon, the condition treatable by the compositions and methods described herein can be hypoglycemia and/or a condition associated with hypoglycemia, for example, hyperinsulinemia, hormone deficiency and/or infection, toxicity and/or organ failure associated with hypoglycemia.

When the therapeutically active agent is PTH or a fragment thereof, the condition treatable by the compositions and methods described herein can be osteoporosis, a bone fracture, a bone defect and/or a medical condition associated with a bone fracture and/or bone defect, for example, bone resorption (e.g., resorption of

alveolar bone associated with a missing tooth, bone resorption associated with inflammation) and/or a presence of an implant in a bone.

As used herein, the term "treatable" refers to an expected ability of an agent to treat a condition (as defined herein), based on knowledge available to a person of ordinary skill in the relevant medical art, for example, knowledge that the agent has been used to treat a condition and/or that the agent exhibits a biological effect which is beneficial for treating the condition.

In some embodiments of any one of the embodiments of the various aspects described herein, the treatment or method described herein is characterized in that it comprises enhancing absorption of the therapeutically active agent for a controlled period of time.

In some embodiments of any one of the embodiments described herein, enhancing absorption is for no more than 60 minutes after oral administration. In some embodiments, enhancing absorption is for no more than 50 minutes. In some embodiments, enhancing absorption is for no more than 40 minutes. In some embodiments, enhancing absorption is for no more than 30 minutes. In some embodiments, enhancing absorption is for no more than 20 minutes. In some embodiments, enhancing absorption is for no more than 15 minutes. In some embodiments, enhancing absorption is for no more than 10 minutes.

In some embodiments of any one of the embodiments described herein, the enhanced absorption for a controlled period of time is such that a ratio of AUC to Cmax (as defined herein) is 60 minutes or lower. In some embodiments, the ratio of AUC to Cmax is 50 minutes or lower. In some embodiments, the ratio of AUC to Cmax is 40 minutes or lower. In some embodiments, the ratio of AUC to Cmax is 30 minutes or lower. In some embodiments, the ratio of AUC to Cmax is 20 minutes or lower. In some embodiments, the ratio of AUC to Cmax is 15 minutes or lower. In some embodiments, the ratio of AUC to Cmax is 10 minutes or lower.

In some embodiments of any one of the embodiments described herein, the controlled period of time is such that a Tmax upon oral administration is no more than 60 minutes. In some embodiments, the Tmax is no more than 50 minutes. In some embodiments, the Tmax is no more than 40 minutes. In some embodiments, the Tmax is no more than 30 minutes. In some embodiments, the Tmax is no more than 25 minutes.

In some embodiments, the Tmax is no more than 20 minutes. In some embodiments, the Tmax is no more than 15 minutes. In some embodiments, the Tmax is no more than 10 minutes. In some embodiments, the Tmax is no more than 5 minutes.

Any formulation which provides desired pharmacokinetic parameters according to any of the respective embodiments described herein is suitable for use according to embodiments of the invention in the treatment of the indicated medical conditions, and is encompassed by the terms "pharmaceutical composition" and "medicament" recited herein.

Such formulations may include ingredients or combinations of ingredients known to a person skilled in the art as providing the desired pharmacokinetic parameters according to any of the respective embodiments described herein.

Any of the compositions and unit dosage forms described herein may optionally consist essentially of the ingredients described hereinabove (e.g., a therapeutically active agent, SNAC, and optionally at least one protease inhibitor), or alternatively, the composition further comprises suitable pharmaceutically acceptable carriers or excipients.

Hereinafter, the phrases "physiologically acceptable carrier" and "pharmaceutically acceptable carrier", which may be interchangeably used, refer to a carrier or a diluent that does not cause significant irritation to an organism and does not abrogate the biological activity and properties of the administered compound. An adjuvant is included under these phrases.

Herein the term "excipient" refers to an inert substance added to a pharmaceutical composition to further facilitate administration of an active ingredient. Examples, without limitation, of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils and polyethylene glycols.

The term "unit dosage form", as used herein, describes physically discrete units, each unit containing a predetermined quantity of one or more active ingredient(s) calculated to produce the desired therapeutic effect, in association with at least one pharmaceutically acceptable carrier, diluent, excipient, or combination thereof.

In some embodiments of any one of the embodiments described herein, the composition is formulated as a solid composition. In some embodiments, the composition is formulated as a tablet.

In some embodiments of any one of the embodiments described herein, the composition consists primarily of the combination of therapeutically active agent, SNAC, and optional at least one protease inhibitor described herein, that is, at least 50 weight percents of the composition consists of ingredients selected from the group consisting of a therapeutically active agent, SNAC and (optional) at least one protease inhibitor. In some embodiments, at least 60 weight percents of the composition consists of a therapeutically active agent, SNAC and (optional) at least one protease inhibitor. In some embodiments, at least 70 weight percents of the composition consists of a therapeutically active agent, SNAC and (optional) at least one protease inhibitor. In some embodiments, at least 80 weight percents of the composition consists of a therapeutically active agent, SNAC and (optional) at least one protease inhibitor. In some embodiments, at least 90 weight percents of the composition consists of a therapeutically active agent, SNAC and (optional) at least one protease inhibitor. In some embodiments, at least 95 weight percents of the composition consists of a therapeutically active agent, SNAC and (optional) at least one protease inhibitor. In some embodiments, at least 98 weight percents of the composition consists of a therapeutically active agent, SNAC and (optional) at least one protease inhibitor. In some embodiments, the composition is formulated as a tablet.

In some embodiments of any one of the embodiments described herein, at least 50 weight percents of the composition consists of SNAC. In some embodiments, at least 60 weight percents of composition consists of SNAC. In some embodiments, at least 70 weight percents of composition consists of SNAC. In some embodiments, at least 80 weight percents of composition consists of SNAC. In some embodiments, at least 90 weight percents of composition consists of SNAC.

Without being bound by any particular theory, it is believed that compositions having a large proportion of SNAC, which is a salt, tend to be readily soluble in aqueous solution, including in gastric fluid, as is desirable according to some embodiments of the invention.

Techniques for formulation and administration of drugs may be found in "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA, latest edition, which is incorporated herein by reference.

Pharmaceutical compositions of some embodiments of the invention may be manufactured by processes well known in the art, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

Pharmaceutical compositions for use in accordance with some embodiments of the invention thus may be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries, which facilitate processing of the active ingredients into preparations which, can be used pharmaceutically.

The pharmaceutical composition can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art as being suitable for oral administration. Such carriers optionally facilitate formulation of the pharmaceutical composition as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for oral ingestion by a patient. Pharmacological preparations for oral use can be made using a solid excipient, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries if desired, to obtain tablets or dragee cores.

Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose; and/or physiologically acceptable polymers such as polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate; and/or lubricants such as talc or magnesium stearate.

In some embodiments of any one of the embodiments described herein, the composition (e.g., formulated as a tablet) further comprises a lubricant. In some embodiments, the lubricant is included in a concentration of 5 weight percents or less, optionally 2 weight percents or less, and optionally about 1 weight percent. In some

embodiments, the composition (e.g., formulated as a tablet) consists essentially of the therapeutically active agent (as described herein), SNAC, lubricant and optionally at least one protease inhibitor (as described herein). In some embodiments, the lubricant is magnesium stearate.

Dragee cores are optionally provided with suitable coatings. For this purpose, concentrated sugar solutions may be used which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical compositions which can be used orally include push-fit capsules made of gelatin as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules may contain the active ingredients in admixture with filler such as lactose, binders such as starches, lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active ingredients may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added.

Pharmaceutical compositions suitable for use in context of some embodiments of the invention include compositions wherein the therapeutically active agent is contained in an amount effective to achieve the intended purpose. More specifically, the composition preferably comprises a therapeutically effective amount of therapeutically active agent, that is, an amount of therapeutically active agent effective to prevent, alleviate or ameliorate symptoms of a disorder or prolong the survival of the subject being treated. Furthermore, an amount of SNAC is preferably effective for enhancing absorption of the therapeutically active agent (e.g., in a manner described herein); and an amount of protease inhibitor is preferably effective for inhibiting degradation of the therapeutically active agent (e.g., a polypeptide agent) by a protease.

Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

For any preparation used in the methods of the invention, the therapeutically effective amount or dose can be estimated initially from *in vitro* and cell culture assays. For example, a dose can be formulated in animal models to achieve a desired

concentration or titer. Such information can be used to more accurately determine useful doses in humans.

Toxicity and therapeutic efficacy of the therapeutically active agent described herein can be determined by standard pharmaceutical procedures *in vitro*, in cell cultures or experimental animals. The data obtained from these *in vitro* and cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage may vary depending upon the dosage form employed and the route of administration utilized. The exact formulation and dosage can be chosen by the individual physician in view of the patient's condition. (See e.g., Fingl, et al., 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 p.1).

Dosage amount and interval may be adjusted individually to provide levels (e.g., plasma levels) of the therapeutically active agent sufficient to induce or suppress a biological effect (minimal effective concentration, MEC). The MEC will vary for each preparation, but can be estimated from *in vitro* data. Dosages necessary to achieve the MEC will depend on individual characteristics. Detection assays can be used to determine plasma concentrations.

Depending on the severity and responsiveness of the condition to be treated, dosing can be of a single or a plurality of administrations, with course of treatment lasting from several hours to several weeks or until cure is effected or diminution of the disease state is achieved.

The amount of a composition to be administered will, of course, be dependent on the subject being treated, the severity of the affliction, the manner of administration, the judgment of the prescribing physician, etc.

Compositions of some embodiments of the invention may, if desired, be presented in a pack or dispenser device, such as an FDA approved kit, which may contain one or more unit dosage forms containing the active ingredient. The pack may, for example, comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser may also be accommodated by a notice associated with the container in a form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the compositions or human or veterinary administration. Such notice, for example, may be

of labeling approved by the U.S. Food and Drug Administration for prescription drugs or of an approved product insert. Compositions comprising a preparation of the invention may also be prepared (e.g., as described herein), placed in an appropriate container, and labeled for treatment of an indicated condition, as is further detailed herein.

Herein, the term "polypeptide" refers to a polymer comprising at least 4 amino acid residues linked by peptide bonds or analogs thereof (as described herein below), and optionally only by peptide bonds *per se*. In some embodiments, the polypeptide comprises at least 10 amino acid residues or analogs thereof. In some embodiments, the polypeptide comprises at least 20 amino acid residues or analogs thereof. In some embodiments, the polypeptide comprises at least 30 amino acid residues or analogs thereof. In some embodiments, the polypeptide comprises at least 50 amino acid residues or analogs thereof. The term "polypeptide" encompasses native polypeptides (e.g., degradation products, synthetically synthesized polypeptides and/or recombinant polypeptides), including, without limitation, native proteins, fragments of native proteins and homologs of native proteins and/or fragments thereof; as well as peptidomimetics (typically, synthetically synthesized polypeptides) and peptoids and semipeptoids which are polypeptide analogs, which may have, for example, modifications rendering the polypeptides more stable while in a body or more capable of penetrating into cells. Such modifications include, but are not limited to N terminus modification, C terminus modification, peptide bond modification, backbone modifications, and residue modification. Methods for preparing peptidomimetic compounds are well known in the art and are specified, for example, in Quantitative Drug Design, C.A. Ramsden Gd., Chapter 17.2, F. Choplin Pergamon Press (1992), which is incorporated by reference as if fully set forth herein. Further details in this respect are provided herein below.

Peptide bonds (-CO-NH-) within the polypeptide may be substituted, for example, by N-methylated amide bonds (-N(CH_3)-CO-), ester bonds (-C(=O)-O-), ketomethylene bonds (-CO-CH_2-), sulfinylmethylene bonds (-S(=O)-CH_2-), α-aza bonds (-NH-N(R)-CO-), wherein R is any alkyl (e.g., methyl), amine bonds (-CH_2-NH-), sulfide bonds (-CH_2-S-), ethylene bonds (-CH_2-CH_2-), hydroxyethylene bonds (-CH(OH)-CH_2-), thioamide bonds (-CS-NH-), olefinic double bonds (-CH=CH-),

fluorinated olefinic double bonds (-CF=CH-), retro amide bonds (-NH-CO-), peptide derivatives (-N(R)-CH2-CO-), wherein R is the "normal" side chain, naturally present on the carbon atom.

These modifications can occur at any of the bonds along the polypeptide chain and even at several (2-3) bonds at the same time.

Natural aromatic amino acids, Trp, Tyr and Phe, may be substituted by non-natural aromatic amino acids such as 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic), naphthylalanine, ring-methylated derivatives of Phe, halogenated derivatives of Phe or O-methyl-Tyr.

The polypeptides of some embodiments of the invention (e.g., a therapeutically active agent and/or a protease inhibitor described herein) may also include one or more modified amino acids or one or more non-amino acid monomers (e.g. fatty acids, complex carbohydrates etc).

The term "amino acid" or "amino acids" is understood to include the 20 naturally occurring amino acids; those amino acids often modified post-translationally in vivo, including, for example, hydroxyproline, phosphoserine and phosphothreonine; and other unusual amino acids including, but not limited to, 2-aminoadipic acid, hydroxylysine, isodesmosine, nor-valine, nor-leucine and ornithine. Furthermore, the term "amino acid" includes both D- and L-amino acids.

Tables 1 and 2 below list naturally occurring amino acids (Table 1), and non-conventional or modified amino acids (e.g., synthetic, Table 2) which can be used with some embodiments of the invention.

Table 1

Amino Acid	***Three-Letter Abbreviation***	***One-letter Symbol***
Alanine	Ala	A
Arginine	Arg	R
Asparagine	Asn	N
Aspartic acid	Asp	D
Cysteine	Cys	C
Glutamine	Gln	Q
Glutamic Acid	Glu	E

Glycine	Gly	G
Histidine	His	H
Isoleucine	Ile	I
Leucine	Leu	L
Lysine	Lys	K
Methionine	Met	M
Phenylalanine	Phe	F
Proline	Pro	P
Serine	Ser	S
Threonine	Thr	T
Tryptophan	Trp	W
Tyrosine	Tyr	Y
Valine	Val	V
Any amino acid as above	Xaa	X

Table 2

Non-conventional amino acid	***Code***	***Non-conventional amino acid***	***Code***
ornithine	Orn	hydroxyproline	Hyp
α-aminobutyric acid	Abu	aminonorbornyl-carboxylate	Norb
D-alanine	Dala	aminocyclopropane-carboxylate	Cpro
D-arginine	Darg	N-(3-guanidinopropyl)glycine	Narg
D-asparagine	Dasn	N-(carbamylmethyl)glycine	Nasn
D-aspartic acid	Dasp	N-(carboxymethyl)glycine	Nasp
D-cysteine	Dcys	N-(thiomethyl)glycine	Ncys
D-glutamine	Dgln	N-(2-carbamylethyl)glycine	Ngln
D-glutamic acid	Dglu	N-(2-carboxyethyl)glycine	Nglu
D-histidine	Dhis	N-(imidazolylethyl)glycine	Nhis

D-isoleucine	Dile	N-(1-methylpropyl)glycine	Nile
D-leucine	Dleu	N-(2-methylpropyl)glycine	Nleu
D-lysine	Dlys	N-(4-aminobutyl)glycine	Nlys
D-methionine	Dmet	N-(2-methylthioethyl)glycine	Nmet
D-ornithine	Dorn	N-(3-aminopropyl)glycine	Norn
D-phenylalanine	Dphe	N-benzylglycine	Nphe
D-proline	Dpro	N-(hydroxymethyl)glycine	Nser
D-serine	Dser	N-(1-hydroxyethyl)glycine	Nthr
D-threonine	Dthr	N-(3-indolylethyl) glycine	Nhtrp
D-tryptophan	Dtrp	N-(*p*-hydroxyphenyl)glycine	Ntyr
D-tyrosine	Dtyr	N-(1-methylethyl)glycine	Nval
D-valine	Dval	N-methylglycine	Nmgly
D-N-methylalanine	Dnmala	L-N-methylalanine	Nmala
D-N-methylarginine	Dnmarg	L-N-methylarginine	Nmarg
D-N-methylasparagine	Dnmasn	L-N-methylasparagine	Nmasn
D-N-methylasparatate	Dnmasp	L-N-methylaspartic acid	Nmasp
D-N-methylcysteine	Dnmcys	L-N-methylcysteine	Nmcys
D-N-methylglutamine	Dnmgln	L-N-methylglutamine	Nmgln
D-N-methylglutamate	Dnmglu	L-N-methylglutamic acid	Nmglu
D-N-methylhistidine	Dnmhis	L-N-methylhistidine	Nmhis
D-N-methylisoleucine	Dnmile	L-N-methylisolleucine	Nmile
D-N-methylleucine	Dnmleu	L-N-methylleucine	Nmleu
D-N-methyllysine	Dnmlys	L-N-methyllysine	Nmlys
D-N-methylmethionine	Dnmmet	L-N-methylmethionine	Nmmet
D-N-methylornithine	Dnmorn	L-N-methylornithine	Nmorn
D-N-methylphenylalanine	Dnmphe	L-N-methylphenylalanine	Nmphe
D-N-methylproline	Dnmpro	L-N-methylproline	Nmpro
D-N-methylserine	Dnmser	L-N-methylserine	Nmser
D-N-methylthreonine	Dnmthr	L-N-methylthreonine	Nmthr
D-N-methyltryptophan	Dnmtrp	L-N-methyltryptophan	Nmtrp
D-N-methyltyrosine	Dnmtyr	L-N-methyltyrosine	Nmtyr

D-N-methylvaline	Dnmval	L-N-methylvaline	Nmval
L-norleucine	Nle	L-N-methylnorleucine	Nmnle
L-norvaline	Nva	L-N-methylnorvaline	Nmnva
L-ethylglycine	Etg	L-N-methyl-ethylglycine	Nmetg
L-t-butylglycine	Tbug	L-N-methyl-t-butylglycine	Nmtbug
L-homophenylalanine	Hphe	L-N-methyl-homophenylalanine	Nmhphe
α-naphthylalanine	Anap	N-methyl-α-naphthylalanine	Nmanap
penicillamine	Pen	N-methylpenicillamine	Nmpen
γ-aminobutyric acid	Gabu	N-methyl-γ-aminobutyrate	Nmgabu
cyclohexylalanine	Chexa	N-methyl-cyclohexylalanine	Nmchexa
cyclopentylalanine	Cpen	N-methyl-cyclopentylalanine	Nmcpen
α-amino-α-methylbutyrate	Aabu	N-methyl-α-amino-α-methylbutyrate	Nmaabu
α-aminoisobutyric acid	Aib	N-methyl-α-aminoisobutyrate	Nmaib
D-α-methylarginine	Dmarg	L-α-methylarginine	Marg
D-α-methylasparagine	Dmasn	L-α-methylasparagine	Masn
D-α-methylaspartate	Dmasp	L-α-methylaspartate	Masp
D-α-methylcysteine	Dmcys	L-α-methylcysteine	Mcys
D-α-methylglutamine	Dmgln	L-α-methylglutamine	Mgln
D-α-methyl glutamic acid	Dmglu	L-α-methylglutamate	Mglu
D-α-methylhistidine	Dmhis	L-α-methylhistidine	Mhis
D-α-methylisoleucine	Dmile	L-α-methylisoleucine	Mile
D-α-methylleucine	Dmleu	L-α-methylleucine	Mleu
D-α-methyllysine	Dmlys	L-α-methyllysine	Mlys
D-α-methylmethionine	Dmmet	L-α-methylmethionine	Mmet
D-α-methylornithine	Dmorn	L-α-methylornithine	Morn
D-α-methylphenylalanine	Dmphe	L-α-methylphenylalanine	Mphe
D-α-methylproline	Dmpro	L-α-methylproline	Mpro

D-α-methylserine	Dmser	L-α-methylserine	Mser
D-α-methylthreonine	Dmthr	L-α-methylthreonine	Mthr
D-α-methyltryptophan	Dmtrp	L-α-methyltryptophan	Mtrp
D-α-methyltyrosine	Dmtyr	L-α-methyltyrosine	Mtyr
D-α-methylvaline	Dmval	L-α-methylvaline	Mval
N-cyclobutylglycine	Ncbut	L-α-methylnorvaline	Mnva
N-cycloheptylglycine	Nchep	L-α-methylethylglycine	Metg
N-cyclohexylglycine	Nchex	L-α-methyl-*t*-butylglycine	Mtbug
N-cyclodecylglycine	Ncdec	L-α-methyl-homophenylalanine	Mhphe
N-cyclododecylglycine	Ncdod	α-methyl-α-naphthylalanine	Manap
N-cyclooctylglycine	Ncoct	α-methylpenicillamine	Mpen
N-cyclopropylglycine	Ncpro	α-methyl-γ-aminobutyrate	Mgabu
N-cycloundecylglycine	Ncund	α-methyl-cyclohexylalanine	Mchexa
N-(2-aminoethyl)glycine	Naeg	α-methyl-cyclopentylalanine	Mcpen
N-(2,2-diphenylethyl)glycine	Nbhm	N-(N-(2,2-diphenylethyl) carbamylmethyl-glycine	Nnbhm
N-(3,3-diphenylpropyl)glycine	Nbhe	N-(N-(3,3-diphenylpropyl) carbamylmethyl-glycine	Nnbhe
1-carboxy-1-(2,2-diphenyl ethylamino)cyclopropane	Nmbc	1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid	Tic
phosphoserine	pSer	phosphothreonine	pThr
phosphotyrosine	pTyr	O-methyl-tyrosine	
2-aminoadipic acid		hydroxylysine	

The polypeptides of some embodiments of the invention (e.g., a therapeutically active agent and/or a protease inhibitor described herein) are preferably utilized in a linear form, although it will be appreciated that in cases where cyclicization does not severely interfere with polypeptide characteristics, cyclic forms of the polypeptide can also be utilized.

In some embodiments of any one of the embodiments described herein, the polypeptide is water-soluble.

Herein, the term "water-soluble" refers to a compound having a solubility of at least 1 gram per liter in an aqueous solution at pH 7.

Water-soluble polypeptides preferably include one or more (non-natural or natural) polar amino acids, including but not limited to serine and threonine which are capable of increasing polypeptide water-solubility due to their hydroxyl-containing side chain. Optionally, a homolog of a polypeptide is selected so as to be more water-soluble than the parent polypeptide, for example, by replacing one or more amino acids in the polypeptide with polar amino acids.

The polypeptides of some embodiments of the invention (e.g., a therapeutically active agent and/or a protease inhibitor described herein) may be synthesized by any techniques that are known to those skilled in the art of peptide synthesis. For solid phase peptide synthesis, a summary of the many techniques may be found in J. M. Stewart and J. D. Young, Solid Phase Peptide Synthesis, W. H. Freeman Co. (San Francisco), 1963 and J. Meienhofer, Hormonal Proteins and Peptides, vol. 2, p. 46, Academic Press (New York), 1973. For classical solution synthesis see G. Schroder and K. Lupke, The Peptides, vol. 1, Academic Press (New York), 1965.

In general, these methods comprise the sequential addition of one or more amino acids or suitably protected amino acids to a growing polypeptide chain. Normally, either the amino or carboxyl group of the first amino acid is protected by a suitable protecting group. The protected or derivatized amino acid can then either be attached to an inert solid support or utilized in solution by adding the next amino acid in the sequence having the complimentary (amino or carboxyl) group suitably protected, under conditions suitable for forming the amide linkage. The protecting group is then removed from this newly added amino acid residue and the next amino acid (suitably protected) is then added, and so forth. After all the desired amino acids have been linked in the proper sequence, any remaining protecting groups (and any solid support) are removed sequentially or concurrently, to afford the final polypeptide compound. By simple modification of this general procedure, it is possible to add more than one amino acid at a time to a growing chain, for example, by coupling (under conditions which do not racemize chiral centers) a protected tripeptide with a properly protected dipeptide to

form, after deprotection, a pentapeptide and so forth. Further description of peptide synthesis is disclosed in U.S. Pat. No. 6,472,505.

A preferred method of preparing the polypeptide compounds of some embodiments of the invention (e.g., a therapeutically active agent and/or a protease inhibitor described herein) involves solid phase peptide synthesis.

Large scale polypeptide synthesis is described by Andersson et al. [*Biopolymers* 2000; 55:227-250].

Herein, a "homolog" of a given polypeptide refers to a polypeptide that exhibits at least 80 % homology, preferably at least 90 % homology, and more preferably at least 95 % homology, and more preferably at least 98 % homology to the given polypeptide. In some embodiments, a homolog of a given polypeptide further shares a therapeutic activity with the given polypeptide. The percentage of homology refers to the percentage of amino acid residues in a first polypeptide sequence which matches a corresponding residue of a second polypeptide sequence to which the first polypeptide is being compared. Generally, the polypeptides are aligned to give maximum homology. A variety of strategies are known in the art for performing comparisons of amino acid or nucleotide sequences in order to assess degrees of identity, including, for example, manual alignment, computer assisted sequence alignment and combinations thereof. A number of algorithms (which are generally computer implemented) for performing sequence alignment are widely available, or can be produced by one of skill in the art. Representative algorithms include, e.g., the local homology algorithm of Smith and Waterman (Adv. Appl. Math., 1981, 2: 482); the homology alignment algorithm of Needleman and Wunsch (J. Mol. Biol., 1970, 48: 443); the search for similarity method of Pearson and Lipman (Proc. Natl. Acad. Sci. (USA), 1988, 85: 2444); and/or by computerized implementations of these algorithms (e.g., GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package Release 7.0, Genetics Computer Group, 575 Science Dr., Madison, Wis.). Readily available computer programs incorporating such algorithms include, for example, BLASTN, BLASTP, Gapped BLAST, PILEUP, CLUSTALW etc. When utilizing BLAST and Gapped BLAST programs, default parameters of the respective programs may be used. Alternatively, the practitioner may use non-default parameters depending on his or her

experimental and/or other requirements (see for example, the Web site having URL www(dot)ncbi(dot)nlm(dot)nih(dot)gov).

It is expected that during the life of a patent maturing from this application many relevant therapeutically active agents and many relevant treatments of conditions by therapeutically active agents will be developed, and the scope of the phrases "therapeutically active agent" and "condition treatable by... therapeutically active agent" are intended to include all such new technologies *a priori*.

As used herein the term "about" refers to ± 10 %.

The terms "comprises", "comprising", "includes", "including", "having" and their conjugates mean "including but not limited to".

The term "consisting of" means "including and limited to".

The term "consisting essentially of" means that the composition, method or structure may include additional ingredients, steps and/or parts, but only if the additional ingredients, steps and/or parts do not materially alter the basic and novel characteristics of the claimed composition, method or structure.

The word "exemplary" is used herein to mean "serving as an example, instance or illustration". Any embodiment described as "exemplary" is not necessarily to be construed as preferred or advantageous over other embodiments and/or to exclude the incorporation of features from other embodiments.

The word "optionally" is used herein to mean "is provided in some embodiments and not provided in other embodiments". Any particular embodiment of the invention may include a plurality of "optional" features unless such features conflict.

As used herein, the singular form "a", "an" and "the" include plural references unless the context clearly dictates otherwise. For example, the term "a therapeutically active agent" may include a plurality of compounds, including mixtures thereof.

Throughout this application, various embodiments of this invention may be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the invention. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed subranges such as

from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 3, 4, 5, and 6. This applies regardless of the breadth of the range.

Whenever a numerical range is indicated herein, it is meant to include any cited numeral (fractional or integral) within the indicated range. The phrases “ranging/ranges between” a first indicate number and a second indicate number and “ranging/ranges from” a first indicate number “to” a second indicate number are used herein interchangeably and are meant to include the first and second indicated numbers and all the fractional and integral numerals therebetween.

As used herein the term "method" refers to manners, means, techniques and procedures for accomplishing a given task including, but not limited to, those manners, means, techniques and procedures either known to, or readily developed from known manners, means, techniques and procedures by practitioners of the chemical, pharmacological, biological, biochemical and medical arts.

As used herein, the term “treating” includes abrogating, substantially inhibiting, slowing or reversing the progression of a condition, substantially ameliorating clinical or aesthetical symptoms of a condition or substantially preventing the appearance of clinical or aesthetical symptoms of a condition.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination or as suitable in any other described embodiment of the invention. Certain features described in the context of various embodiments are not to be considered essential features of those embodiments, unless the embodiment is inoperative without those elements.

Various embodiments and aspects of the present invention as delineated hereinabove and as claimed in the claims section below find experimental support in the following examples.

EXAMPLES

Reference is now made to the following examples, which together with the above descriptions illustrate some embodiments of the invention in a non-limiting fashion.

MATERIALS

8-Aminocaprylic acid was obtained from Alfa-Aesar.

Magnesium stearate was obtained from Sigma-Aldrich.

O-acetylsalicyloyl chloride was obtained from Sigma-Aldrich.

Soybean trypsin inhibitor (SBTI) was obtained from Sigma-Aldrich.

Teriparatide was purchased from Bachem.

SNAC (sodium 8-N-(2-hydroxybenzoyl)aminocaprylate) was prepared by reacting O-acetylsalicyloyl chloride with 8-aminocaprylic acid.

EXAMPLE 1

Pharmacokinetic profile of orally administered parathyroid hormone (PTH)

Pharmacokinetic study design:

An open label comparative pharmacokinetic study was performed in healthy volunteers over the course of 3 months. Each volunteer received - in each of two visits – the same oral tablet containing 0.75 mg of teriparatide, a recombinant form of parathyroid hormone (1-34).

The formulation was composed of teriparatide (0.75 mg), SNAC (sodium 8-N-(2-hydroxybenzoyl) aminocaprylate), soybean trypsin inhibitor (SBTI) and a small amount of magnesium stearate.

Tablets were administered in the morning after an 8-hour overnight fast and immediately followed by 150 ml of water. At each visit a standard meal was provided 3 hours after drug administration. Patients did not eat or drink alcoholic or caffeinated beverages. There was a two weeks period between the visits.

To determine parathyroid hormone (1-34) (PTH(1-34)) concentrations, blood samples (4 ml each) were drawn via an indwelling catheter from the forearm vein at predetermined time points during each visit. The cannula was flushed with 1.5 ml normal saline after each sampling. In addition, to avoid sample dilution, 1 ml of blood was drawn and discarded before the next sample. The blood samples were taken at

following times: baseline (predose), 10 minutes, 15 minutes, 20 minutes, 30 minutes, 45 minutes, 60 minutes, 75 minutes, 90 minutes, 105 minutes, 2 hours, 3 hours, 4 hours and 5 hours post-administration. Each blood sample was collected into a single tube containing EDTA (ethylenediaminetetraacetic acid) and placed on ice. Within 15 minutes of blood collection, samples were centrifuged for 10 minutes at 4 °C (2500 rotations per minute) and the plasma was separated and divided into two or three aliquots. Each aliquot was transferred into appropriately labeled polypropylene tubes and stored at approximately -20 °C pending analysis. PTH(1-34) levels were measured using an IDS-iSYS automated assay for the measurement of intact PTH(1-34) in human plasma or serum. The results of the assay do not include levels of PTH(1-84) such as endogenous PTH.

Results:

As shown in Table 3 below and in FIGs. 1A-1C, the pharmacokinetic profile of the administered parathyroid hormone (1-34) was characterized by a sharp increase in plasma levels, followed by a rapid decrease, such that a peak concentration (Cmax) of parathyroid hormone (1-34) occurred within 20 minutes of administration. As further shown therein, the Cmax was relatively constant between different administrations in a given subject. As further shown in FIGs. 1A-1C, parathyroid hormone (1-34) levels returned to baseline levels within 60 minutes of tablet administration.

As further shown in FIGs. 1A-1C, particularly in FIGs. 1B and 1C, even slight variations in Tmax (e.g., from 10 to 20 minutes) result in different pharmacokinetic curves having little overlap, because the peaks in PTH plasma levels are so narrow.

Table 3: Pharmacokinetic data for three subjects following two oral administrations of teriparatide

Subject	Tmax after 1st administration (minutes)	Tmax after 2nd administration (minutes)	Cmax after 1st administration (picogram/ml)	Cmax after 2nd administration (picogram/ml)
A	15	20	195	283
B	10	20	124	116
C	10	20	35	36

This result indicates the importance of data from individual measurements, as opposed to averaged data from different measurements. Averaging values from different measurements, even different measurements in a single subject, would result in a broader and lower curve which does not accurately represent the rapidity of increase and decrease in plasma levels.

EXAMPLE 2

Phase I clinical trial of orally administered parathyroid hormone (PTH)

A Phase I clinical study of exemplary oral formulations comprising teriparatide (parathyroid hormone (1-34)) was conducted at the Hadassah Clinical Research Center. 42 healthy volunteers were included throughout the study.

The formulation was composed of teriparatide (200, 400, 680, 1400 or 1800 μg), SNAC (sodium 8-N-(2-hydroxybenzoyl) aminocaprylate), soybean trypsin inhibitor and magnesium stearate.

Tablets were administered in the morning after an 8-hour overnight fast and immediately followed by 150 ml of water. At each visit a standard meal was provided 3 hours after drug administration. Patients did not eat or drink alcoholic or caffeinated beverages.

To determine parathyroid hormone concentrations, blood samples (4 ml each) were drawn via an indwelling catheter from the forearm vein at predetermined time points. The cannula was flushed with 1.5 ml normal saline after each sampling. In addition, to avoid sample dilution, 1 ml of blood was drawn and discarded before the next sample. The blood samples were taken at following times: baseline (predose), 15 minutes, 30 minutes, 45 minutes, 60 minutes, 75 minutes, 90 minutes, 105 minutes, 2 hours, 3 hours, 4 hours and 5 hours post-administration. Each blood sample was collected into a single tube containing EDTA (ethylenediaminetetraacetic acid) and placed on ice. Within 15 minutes of blood collection, samples were centrifuged for 10 minutes at 4 °C (2500 rotations per minute) and the plasma was separated and divided into two or three aliquots. Each aliquot was transferred into appropriately labeled polypropylene tubes and stored at approximately -20 °C pending analysis. PTH(1-34) levels were measured using an IDS-iSYS automated assay for the measurement of intact PTH(1-34) in human plasma or serum.

Oral administration of teriparatide was performed as described hereinabove at doses of 200, 400, 680, 1400 or 1800 μg. The Cmax of PTH(1-34) for each orally administered dose was compared with the Cmax of PTH(1-34) for subcutaneous injection of 20 μg teriparatide.

As shown in FIG. 2, the Cmax of PTH(1-34) following oral administration was proportional to the dose, with oral administration of roughly 750 μg teriparatide providing a Cmax equivalent to that of subcutaneous administration of 20 μg teriparatide.

As shown in FIG. 3, oral administration of 1800 μg teriparatide and subcutaneous administration of 20 μg teriparatide were characterized by similar Cmax values, the primary difference in pharmacokinetic profile being that PTH levels declined considerably more rapidly following oral administration than after subcutaneous administration. It is to be appreciated that a pharmacokinetic profile for an individual administration is characterized by a narrower and higher curve than the curve shown in FIG. 3, because averaging data from different measurements results in a broader and lower curve, due to slight variations in Tmax (as discussed in Example 1).

In addition, plasma levels of cAMP, a known marker of PTH activity, were determined in order to confirm biological activity of administered PTH. cAMP plasma levels were measured following oral administration of 680 μg teriparatide or subcutaneous injection of 20 μg teriparatide, as described hereinabove.

As shown in FIG. 4, oral administration of 680 μg teriparatide and subcutaneous administration of 20 μg teriparatide increased plasma cAMP levels to a similar degree. This result confirms that the orally administered PTH exhibits biological activity.

These results indicate that oral administration of PTH results in biologically active increases in PTH levels, and for a briefer period of time than obtained by subcutaneous administration.

The brief period of increased PTH levels in the blood may be advantageous for enhancing bone growth, as chronic exposure to PTH has the opposite effect (enhancement of bone resorption) than intermittent exposure to PTH.

Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all

such alternatives, modifications and variations that fall within the spirit and broad scope of the appended claims.

All publications, patents and patent applications mentioned in this specification are herein incorporated in their entirety by reference into the specification, to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference. In addition, citation or identification of any reference in this application shall not be construed as an admission that such reference is available as prior art to the present invention. To the extent that section headings are used, they should not be construed as necessarily limiting.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising a therapeutically active agent, and SNAC (sodium 8-N-(2-hydroxybenzoyl)aminocaprylate), the composition being formulated such that absorption of said therapeutically active agent following oral administration of the composition is characterized by a ratio of AUC to Cmax which is 60 minutes or lower and/or by a Tmax which is 60 minutes or lower.

2. The composition of claim 1, wherein said ratio of AUC to Cmax is 30 minutes or lower.

3. The composition of claim 1, wherein said Tmax is 30 minutes or lower.

4. A pharmaceutical composition comprising a therapeutically active agent, and SNAC (sodium 8-N-(2-hydroxybenzoyl)aminocaprylate), the composition being formulated for oral administration and being such that said SNAC is active in enhancing absorption of the therapeutically active agent for no more than 60 minutes.

5. The composition of claim 4, wherein said SNAC is active in enhancing absorption of the therapeutically active agent for no more than 30 minutes.

6. The composition of any one of claims 1 to 5, further comprising at least one protease inhibitor.

7. The composition of claim 6, wherein said at least one protease inhibitor comprises at least one trypsin inhibitor.

8. The composition of claim 7, wherein said at least one trypsin inhibitor is selected from the group consisting of lima bean trypsin inhibitor, aprotinin, soybean trypsin inhibitor and ovomucoid trypsin inhibitor.

9. The composition of claim 7, wherein said at least one trypsin inhibitor comprises soybean trypsin inhibitor.

10. The composition of any one of claims 1 to 9, further comprising a lubricant.

11. The composition of claim 10, wherein said lubricant is magnesium stearate.

12. The composition of any one of claims 1 to 11, being soluble in gastric fluid.

13. The composition of claim 12, wherein the composition dissolves in said gastric fluid in no more than 60 minutes.

14. The composition of any one of claims 1 to 13, being formulated as a tablet.

15. The composition of claim 14, wherein at least 90 weight percents of said tablet consists of ingredients selected from the group consisting of said therapeutically active agent, SNAC, and at least one protease inhibitor.

16. The composition of any one of claims 1 to 15, wherein at least 50 weight percents of the composition consists of SNAC.

17. The composition of any one of claims 1 to 16, comprising at least 50 mg of SNAC.

18. The composition of any one of claims 1 to 17, wherein a bioavailability of said therapeutically active agent is in a range of from 0.05 to 50 %.

19. The composition of claim 18, wherein a bioavailability of said therapeutically active agent is in a range of from 0.2 to 5 %.

20. The composition of any one of claims 1 to 19, wherein said therapeutically active agent has a molecular weight in a range of 0.5 kDa to 100 kDa.

21. The composition of any one of claims 1 to 20, wherein said therapeutically active agent is a polypeptide.

22. The composition of claim 21, wherein said polypeptide is selected from the group consisting of parathyroid hormone and a fragment thereof.

23. The composition of claim 21, wherein said polypeptide comprises teriparatide.

24. The composition of any one of claims 20 to 23, wherein an amount of said therapeutically active agent is in a range of from 100 to 3000 μg.

25. The composition of any one of claims 1 to 24, for use in the treatment of a condition treatable by oral administration of said therapeutically active agent in a subject in need thereof.

26. Use of the composition of any one of claims 1 to 24, in the preparation of a medicament for use in the treatment of a condition treatable by oral administration of said therapeutically active agent in a subject in need thereof.

27. The composition of claim 25 or the use of claim 26, wherein said treatment comprises enhancing absorption of said therapeutically active agent for a controlled period of time, such that a ratio of AUC to Cmax is 60 minutes or lower and/or such that a Tmax is 60 minutes or lower.

28. The composition or use of claim 27, wherein said ratio of AUC to Cmax is 30 minutes or lower.

29. The composition of claim 25 or the use of claim 26, wherein said treatment comprises enhancing absorption of said therapeutically active agent for no more than 60 minutes after said oral administration.

30. The composition or use of claim 29, wherein said treatment comprises enhancing absorption of said therapeutically active agent for no more than 30 minutes after said oral administration.

31. The composition of claim 25 or the use of claim 26, wherein said treatment comprises enhancing absorption of said therapeutically active agent for a controlled period of time, such that a Tmax upon said oral administration is no more than 30 minutes.

32. A method of treating a condition treatable by oral administration of a therapeutically active agent in a subject in need thereof, the method comprising orally administering to the subject the composition of any one of claims 1 to 24.

33. The method of claim 32, comprising enhancing absorption of said therapeutically active agent for a controlled period of time, such that a ratio of AUC to Cmax is 60 minutes or lower and/or such that a Tmax is 60 minutes or lower.

34. The method of claim 33, wherein said ratio of AUC to Cmax is 30 minutes or lower.

35. The method of any one of claims 32 to 34, comprising enhancing absorption of said therapeutically active agent for no more than 60 minutes after said oral administration.

36. The method of claim 35, wherein said treatment comprises enhancing absorption of said therapeutically active agent for no more than 30 minutes after said oral administration.

37. The method of any one of claims 32-36, comprising enhancing absorption of said therapeutically active agent for a controlled period of time, such that a Tmax upon said oral administration is no more than 30 minutes.

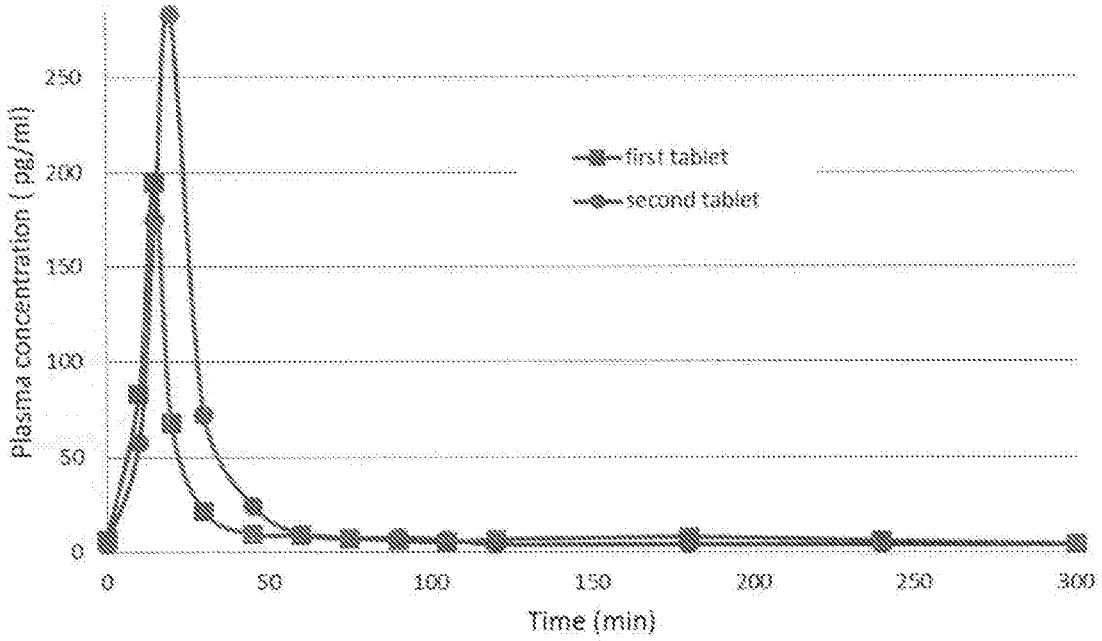

Plasma concentration (pg/ml)
250
200
150
100
50
0
first tablet
second tablet
0
50
100
150
200
250
300
Time (min)

FIG. 1A

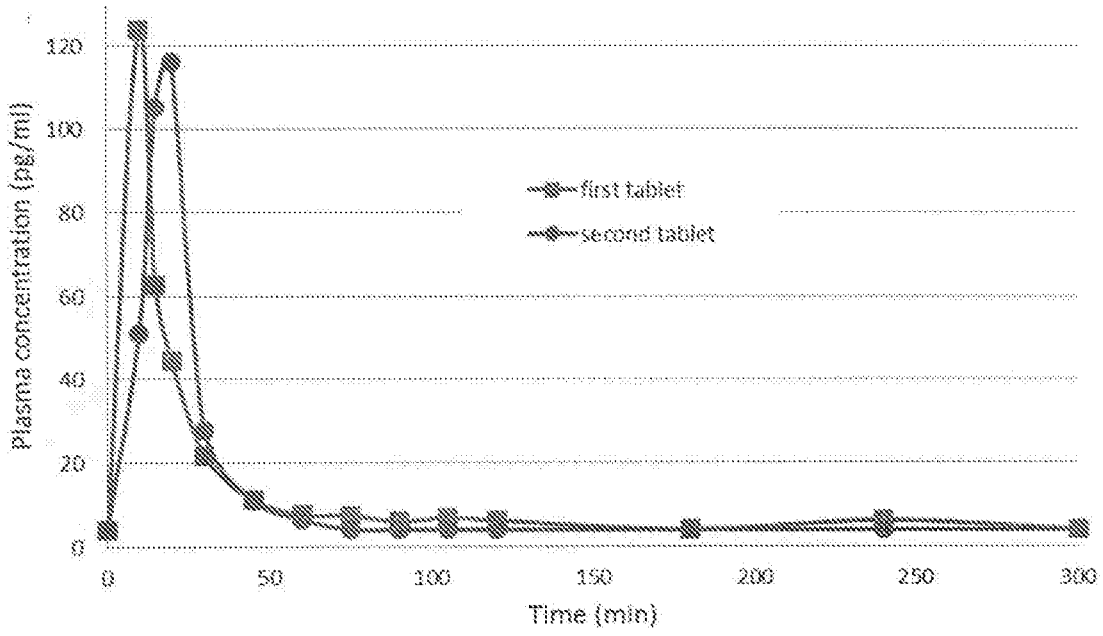

Plasma concentration (pg/ml)
120
100
80
60
40
20
0
first tablet
second tablet
0
50
100
150
200
250
300
Time (min)

FIG. 1B

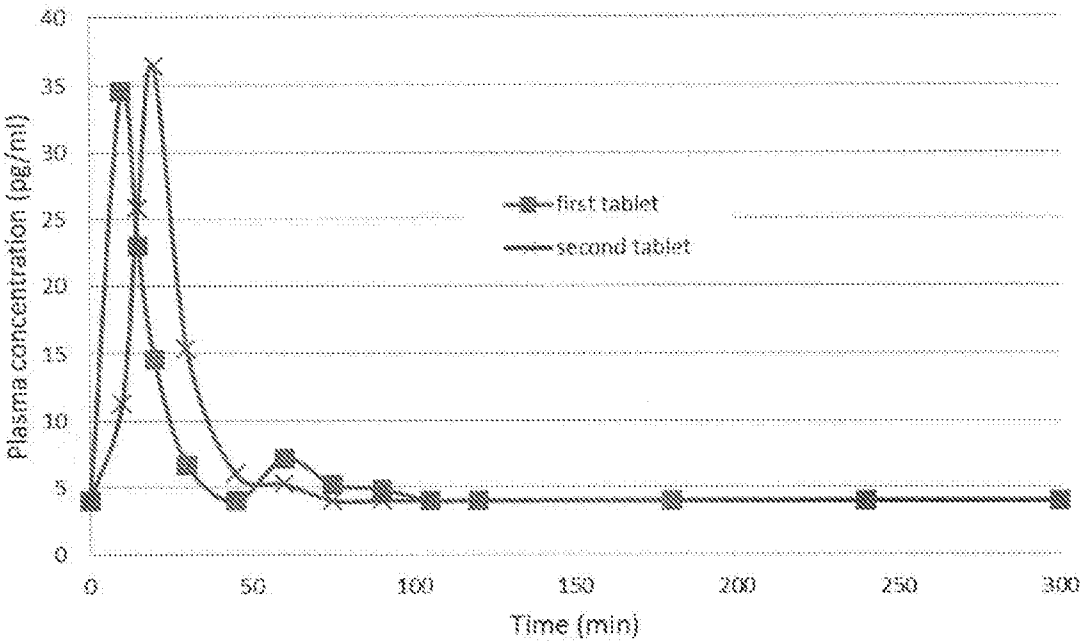

40
35
30
25
20
15
10
5
0
Plasma concentration (pg/ml)
first tablet
second tablet
0
50
100
150
200
250
300
Time (min)

FIG. 1C

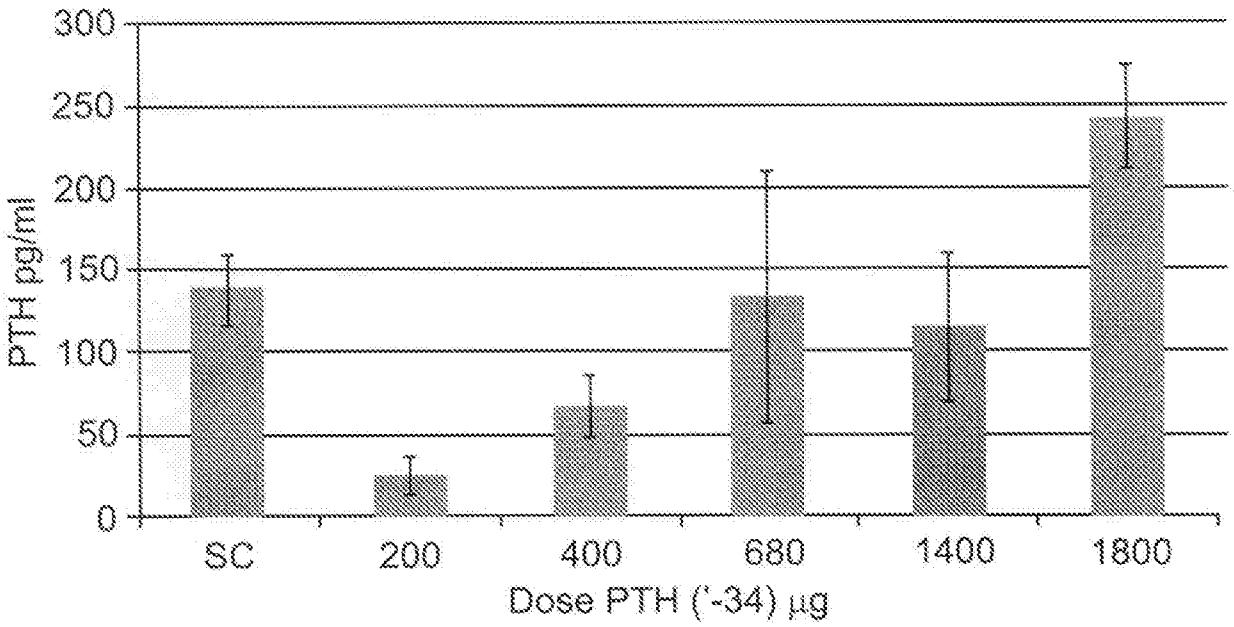

300
250
200
150
100
50
0
PTH pg/ml
SC
200
400
680
1400
1800
Dose PTH (1-34) µg

FIG. 2

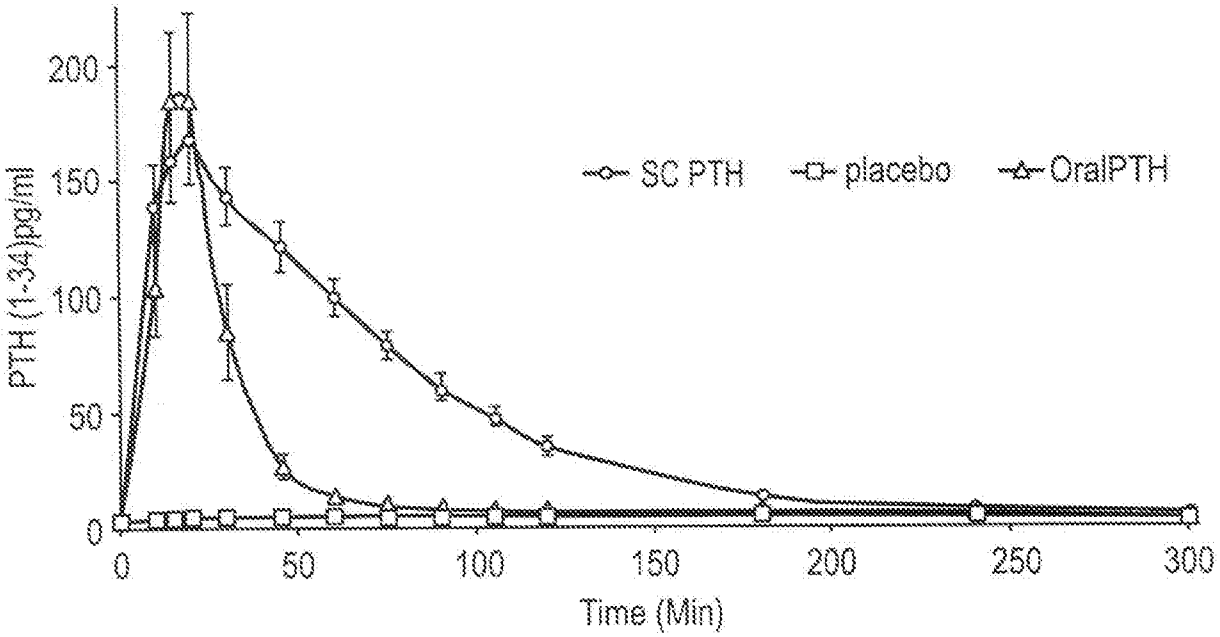

200
150
100
50
0
PTH (1-34)pg/ml
SC PTH
placebo
OralPTH
0
50
100
150
200
250
300
Time (Min)

FIG. 3

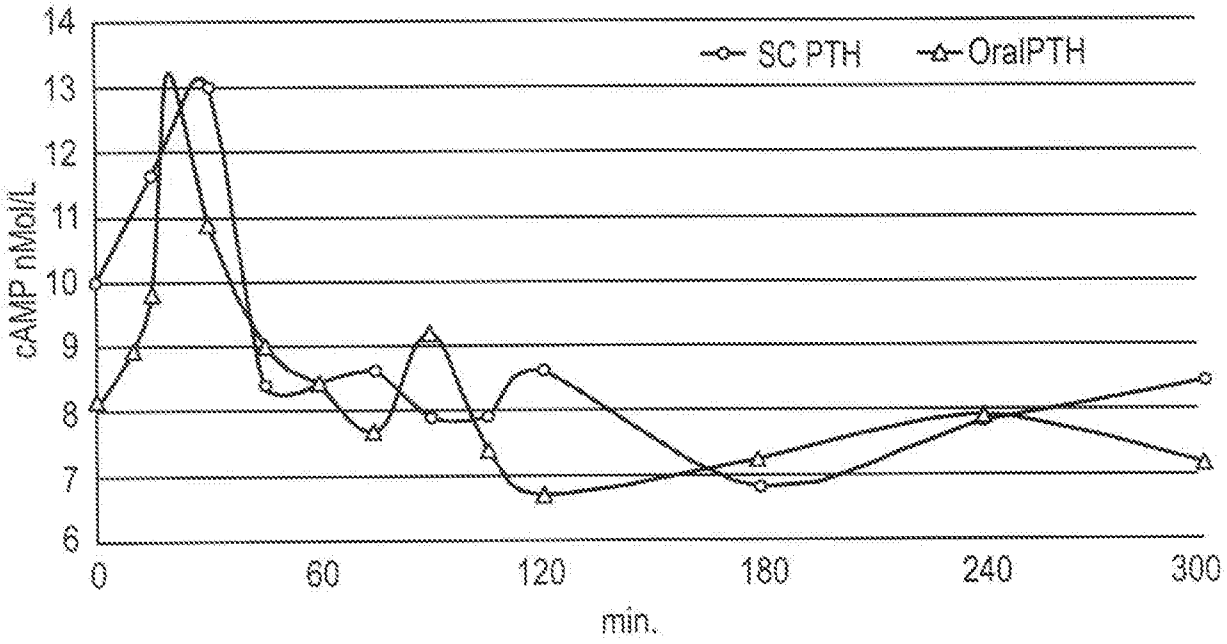

14
13
12
11
10
9
8
7
6
cAMP nMol/L
SC PTH
OralPTH
0
60
120
180
240
300
min.

FIG. 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL2016/050153

A. CLASSIFICATION OF SUBJECT MATTER

IPC (2016.01) A61K 38/55, A61K 38/29, A61K 38/22, A61K 9/28

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC (2016.01) A61K 38/55, A61K 38/29, A61K 38/22, A61K 9/28

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

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

Databases consulted: THOMSON INNOVATION, Esp@cenet, Google Patents, MEDLINE, Google Scholar
Search terms used: SNAC, sodium N-[8-(2-hydroxybenzoyl) amino]caprylate, trypsin inhibitor, parathyroid hormone

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03045331 A2 EMISPHERE TECH INC?[US]; ABBAS RICHAT?[US]; ARBIT EHUD?[US]; GOLDBERG MICHAEL?[US]; WONG VIVIAN?[US]; SARUBBI DONALD J?[US] + 05 Jun 2003 (2003/06/05) p.38 table 5, p.40 table 6, p.45 table 8, p.46 table 9, para 00221	1-5
Y	p.38 table 5, p.40 table 6, p.45 table 8, p.46 table 9, para 00221	1-37
X	WO 2012080471 A1 NOVO NORDISK AS?[DK]; SAUERBERG PER?[DK]; BJERREGAARD SIMON?[DK]; NIELSEN FLEMMING SEIER?[DK] 21 Jun 2012 (2012/06/21) p. 26 table 1, p.29 table 7	1-5
Y	p. 26 table 1, p.29 table 7	1-37
Y	WO 2010020978 A1 ORAMED PHARMACEUTICALS LTD?[IL] 25 Feb 2010 (2010/02/25) abstract, cl. 1-7, para 0067, para 0089	6-37

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents:

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

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

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Date of the actual completion of the international search	Date of mailing of the international search report
19 May 2016	22 May 2016
Name and mailing address of the ISA: Israel Patent Office Technology Park, Bldg.5, Malcha, Jerusalem, 9695101, Israel Facsimile No. 972-2-5651616	Authorized officer SHAPIRA Elena Telephone No. 972-2-5657823

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL2016/050153

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摘要

本文提供了包含治疗活性剂和 SNAC (8-N-(2-羟基苯甲酰基)氨基辛酸钠)的药物组合物。该组合物被配制用于口服给药，并且使得 SNAC 在增强治疗活性剂的吸收中是活性的时间不超过 60 分钟，和/或使得口服给药组合物后治疗活性剂的吸收的特征在于为 60 分钟或更低的 AUC 与 Cmax 的比率和/或为 60 分钟或更低的 Tmax。本文进一步公开了使用本文所述组合物用于治疗可通过在有需要的受试者中口服给药治疗活性剂进行治疗的病症的用途和方法。