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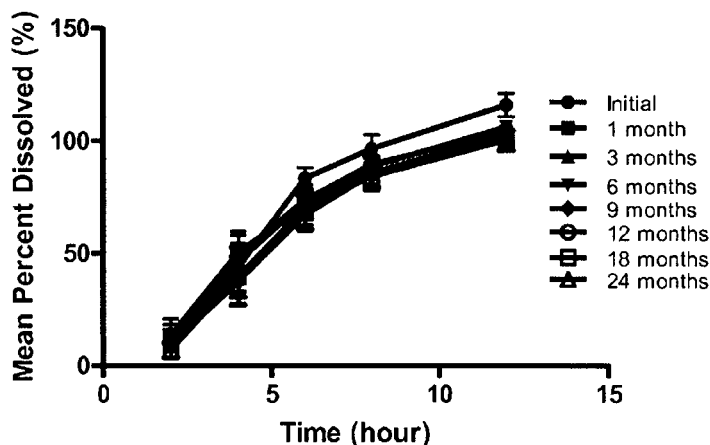
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(54) Title: STABILIZED MODIFIED RELEASE VITAMIN D FORMULATION AND METHOD OF ADMINISTERING SAME

Figure 1A

30 μ g - 25°C/60%RH

(57) Abstract: A stabilized formulation for controlled release of a vitamin D compound is disclosed. The formulation comprises one or both of 25-hydroxyvitamin D2 and 25-hydroxyvitamin D3 and a cellulosic compound. The stabilized formulations exhibit a stable dissolution profile following exposure to storage conditions and demonstrate improved pharmacokinetic parameters compared to unstabilized formulations.

STABILIZED MODIFIED RELEASE VITAMIN D FORMULATION AND METHOD OF ADMINISTERING SAME

CROSS-REFERENCE TO RELATED APPLICATION

[0001] The benefit under 35 U.S.C. §119(e) of U.S. Provisional Patent Application Serial No. 61/801,896 filed March 15, 2013, is hereby claimed and the disclosure thereof is incorporated herein by reference.

BACKGROUND

Field of the Disclosure

[0002] The disclosure relates generally to controlled release pharmaceutical compositions. More particularly, the invention relates to controlled-release formulations for delivery of a vitamin D compound for intestinal absorption, such as a 25-hydroxyvitamin D compound, which are shelf-stable over time.

Brief Description of Related Technology

[0003] The Vitamin D metabolites known as 25-hydroxyvitamin D₂ and 25-hydroxyvitamin D₃ (collectively referred to as “25-hydroxyvitamin D”) are fat-soluble steroid prohormones that contribute to the maintenance of normal levels of calcium and phosphorus in the bloodstream. The prohormone 25-hydroxyvitamin D₂ is produced from Vitamin D₂ (ergocalciferol) and 25-hydroxyvitamin D₃ is produced from Vitamin D₃ (cholecalciferol), primarily by one or more enzymes located in the liver. The two prohormones also can be produced outside of the liver from Vitamin D₂ and Vitamin D₃ (collectively referred to as “Vitamin D”) in certain cells, such as enterocytes, which contain enzymes identical or similar to those found in the liver.

[0004] The 25-hydroxyvitamin D prohormones are further metabolized in the kidneys into potent Vitamin D hormones. The prohormone 25-hydroxyvitamin D₂ is metabolized into 1 α ,25-dihydroxyvitamin D₂; likewise, 25-hydroxyvitamin D₃ is metabolized into 1 α ,25-dihydroxyvitamin D₃ (calcitriol). Production of these active hormones from the 25-hydroxyvitamin D prohormones also can occur outside of the kidney in cells which contain the required enzyme(s).

[0005] Controlled release formulations of 25-hydroxyvitamin D₂ and/or 25-hydroxyvitamin D₃ can be administered to treat 25-hydroxyvitamin D insufficiency and deficiency without

supraphysiological surges in intraluminal, intracellular and blood levels of 25-hydroxyvitamin D and their consequences; without causing substantially increased catabolism of the administered 25-hydroxyvitamin D; and, without causing serious side effects associated with Vitamin D supplementation, namely Vitamin D toxicity. The controlled release formulations effectively lower PTH levels without undesirable increases in serum calcium and serum phosphorus and are therefore useful for treating secondary hyperparathyroidism, for example in CKD patients. See International Patent Application Nos. PCT/US2007/061521 and PCT/US2008/061579 and U.S. Patent Application No. 12/109,983, incorporated herein by reference.

[0006] The controlled released compositions provide substantially increased absorption of 25-hydroxyvitamin D via transport on DBP and decreased absorption via transport in chylomicrons. The compositions also provide maintenance of substantially constant blood levels of 25-hydroxyvitamin D during a 24-hour post-dosing period. By providing a gradual, sustained and direct release of 25-hydroxyvitamin D₂/25-hydroxyvitamin D₃ and absorption preferentially to circulating DBP (rather than to chylomicrons), blood, intraluminal and intracellular 25-hydroxyvitamin D concentration spikes, i.e., supraphysiologic levels and related unwanted catabolism can be mitigated or eliminated. Furthermore, by providing a gradual and sustained release, serum levels of 25-hydroxyvitamin D can be increased and maintained more predictably than by administration of immediate release formulations, allowing for a consistent dosage and reducing or eliminating the need for frequent patient monitoring.

[0007] To deliver the benefits of controlled release formulations of 25-hydroxyvitamin D to patients, there is a need for stabilized pharmaceutical compositions that retain the desired dissolution properties of the formulation, for extended periods of time, e.g., after shipping and storage.

SUMMARY

[0008] The present invention comprises a controlled release Vitamin D formulation comprising a vitamin D compound and a cellulosic compound.

[0009] The present invention also comprises a storage-stabilized formulation for controlled release of a vitamin D compound in the gastrointestinal tract of a subject which ingests the formulation. In one aspect, the stabilized formulation comprises one or both of 25-hydroxyvitamin D₂ and 25-hydroxyvitamin D₃ and a stabilizing agent or stabilizing compound,

e.g. a cellulosic compound. The stabilized formulations of the invention with the recited stabilizing agent(s) can have improved or relatively improved "storage stability", or stability following aging, as well as one or more additional characteristics including improved physical, chemical and biological properties when compared to the disclosed formulations that do not contain such agents. The claimed formulations are thus suitable as therapeutics that possess a long shelf life as well as improved bioavailability compared to aged, unstable formulations.

[0010] In one embodiment, the stabilized formulation includes one or both of 25-hydroxyvitamin D₂ and 25-hydroxyvitamin D₃, a lipophilic matrix (e.g. a wax matrix), and a stabilizing agent (e.g., a cellulosic compound). In one aspect, a stabilized formulation includes one or both of 25-hydroxyvitamin D₂ and 25-hydroxyvitamin D₃, a wax matrix, and a cellulosic stabilizing agent. In another aspect, the formulation includes one or both of 25-hydroxyvitamin D₂ and 25-hydroxyvitamin D₃, a wax matrix, and an effective amount of a cellulosic compound to maintain an advantageous degree of stabilization described herein.

[0011] In one type of embodiment, the stabilized formulation comprises a mixture of an active-loaded wax matrix comprising one or both of 25-hydroxyvitamin D₂ and 25-hydroxyvitamin D₃ and a cellulosic stabilizing agent, wherein the formulation releases an amount of 25-hydroxyvitamin D during *in vitro* dissolution after exposure to storage conditions of at least one month at 25 °C and 60% relative humidity that varies at all dissolution testing time points by 30% or less compared to the amount released at the same dissolution time points during *in vitro* dissolution conducted on fresh product.

[0012] In one type of embodiment, the formulation is an improvement formulation for controlled release of a vitamin D compound. In one aspect, the improvement comprises admixing a stabilizing agent into a formulation for controlled release of a vitamin D compound in the gastrointestinal tract of a subject which ingests the formulation. In another aspect, the improvement comprises an effective amount of a cellulosic compound admixed into a formulation for controlled release of a vitamin D compound in the gastrointestinal tract of a subject which ingests the formulation to provide an advantageous degree of stability described herein.

[0013] In one embodiment, the invention comprises a stable sustained release vitamin D formulation comprising 25-hydroxyvitamin D₂ or 25-hydroxyvitamin D₃ or combinations thereof

and sustained release excipients wherein said formulation has a dissolution profile X at T_0 that retains this profile according to the formula $X=T_0\pm 30\%$ over storage conditions selected from room temperature and ambient humidity, or 25 °C and 60% RH, or 40 °C and 75% RH, for example.

[0014] Further aspects and advantages will be apparent to those of ordinary skill in the art from a review of the following detailed description, taken in conjunction with the drawings. While the compositions and methods are susceptible of embodiments in various forms, the description hereafter includes specific embodiments with the understanding that the disclosure is illustrative, and is not intended to limit the invention to the specific embodiments described herein.

[0015] For the compositions and methods described herein, optional features, including but not limited to components, compositional ranges thereof, substituents, conditions, and steps, are contemplated to be selected from the various aspects, embodiments, and examples provided herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] Figure 1 shows the dissolution profile of formulations according to the disclosure after storage for 0 to 24 months at 25 °C and 60% relative humidity. The dissolution time in hours is depicted on the x-axis and the mean percent of 25-hydroxyvitamin D₃ dissolved is shown on the y-axis. Figures 1A, 1B, and 1C show the dissolution profile of formulations comprising 30 µg, 60 µg, and 90 µg of 25-hydroxyvitamin D₃, respectively.

[0017] Figure 2 shows the dissolution profile of formulations according to the disclosure after storage for 0 to 6 months at 40 °C and 75% relative humidity. The dissolution time in hours is depicted on the x-axis and the mean percent of 25-hydroxyvitamin D₃ dissolved is shown on the y-axis. Figures 2A, 2B, and 2C show the dissolution profile of formulations comprising 30 µg, 60 µg, and 90 µg of 25-hydroxyvitamin D₃, respectively.

[0018] Figure 3 shows the dissolution profile of formulations after storage for 0 to 12 months at 25 °C and 60% relative humidity. The dissolution time in hours is depicted on the x-axis and the mean % Label Claim of 25-hydroxyvitamin D₃ released is shown on the y-axis. Figure 3A shows the dissolution profile of a comparative formulation that does not contain a cellulosic

compound. Figure 3B shows the dissolution profile of a stabilized formulation according to the disclosure.

[0019] Figure 4 shows the resulting mean baseline-adjusted calcifediol concentrations by treatment group (PK population) for the patients described in Example 4 treated with a formulation according to the disclosure.

[0020] Figure 5 shows the resulting summary baseline-adjusted PK parameters for calcifediol concentrations by treatment group (PK population) for the patients described in Example 4 treated with a formulation according to the disclosure.

[0021] Figure 6 shows the resulting mean baseline-adjusted serum 1,25-dihydroxyvitamin D levels during the 6-week treatment (PK population) for the patients described in Example 4 treated with a formulation according to the disclosure.

[0022] Figure 7 shows a summary of the resulting baseline-adjusted repeat-dose PK parameters for serum 1,25-dihydroxyvitamin D by treatment group (PK population) for the patients described in Example 4 treated with a formulation according to the disclosure.

[0023] Figure 8 shows the resulting mean percent of baseline in plasma iPTH levels during the 6-week treatment (PK population) for the patients described in Example 4 treated with a formulation according to the disclosure.

[0024] Figure 9 shows a summary of the resulting baseline-adjusted repeat-dose PK parameters for plasma iPTH by treatment group (PK population) for the patients described in Example 4 treated with a formulation according to the disclosure.

[0025] Figures 10 and 11 show the percent change from baseline at EOT for plasma iPTH relative to baseline-adjusted calcifediol and 1,25-dihydroxyvitamin D exposure (AUC_{0-6wk}) in the PK Population for the patients described in Example 4 treated with a formulation according to the disclosure.

DETAILED DESCRIPTION

[0026] As used herein, the terms “controlled release,” and “modified release” are used interchangeably and refer to the release of the administered vitamin D compound in a way that deviates from immediate release. As used herein, the terms “sustained release” and “extended release” are used interchangeably and refer to the release of the administered vitamin D

compound over a longer period of time than a comparable immediate release formulation, resulting in serum concentrations of the vitamin D compound that remain elevated over baseline for a longer period of time than for a comparable immediate release formulation. The foregoing terms optionally include delayed release characteristics. For example, a delayed release type of controlled release formulation will be characterized by C_{max} at a time greater than C_{max} for an immediate release formulation. As another example, the release of a 25-hydroxyvitamin D compound will preferably be at such a rate that total serum or blood levels of 25-hydroxyvitamin D are maintained or elevated above predosing levels for an extended period of time, e.g. 4 to 24 hours or even longer.

[0027] As used herein, the term “cellulosic compound” can include cellulose $(C_6H_{10}O_5)_n$ or a derivative of cellulose, unless specified otherwise. A “cellulose ether” is a cellulose derivative that has been chemically modified to result in partial or complete etherification of the hydroxyl groups in the cellulose molecule. Examples of cellulose derivatives which can be used as stabilizing agents include, but are not limited to, cellulosic acid, carboxy methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxyl propyl cellulose, hydroxyl propyl methylcellulose, methyl cellulose, polyanionic cellulose, and combinations thereof, for example. Different grades of each cellulosic compound or stabilizing agent, corresponding to variations in, e.g., molecular weight, viscosity, solubility, and hydration, are also encompassed by the terms.

[0028] Any vitamin D compound suitable for prophylactic and/or therapeutic use, and combinations thereof, are contemplated for inclusion in the formulation described herein. Vitamin D, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, and other metabolites and analogs of Vitamin D are also useful as active compounds in pharmaceutical compositions. Specific examples include, but are not limited to, Vitamin D₃ (cholecalciferol), Vitamin D₂ (ergocalciferol), 25-hydroxyvitamin D₃, 25-hydroxyvitamin D₂, 25-hydroxyvitamin D₄, 25-hydroxyvitamin D₅, 25-hydroxyvitamin D₇, 1 α ,25-dihydroxyvitamin D₃, 1 α ,25-dihydroxyvitamin D₂, 1 α ,25-dihydroxyvitamin D₄, and vitamin D analogs (including all hydroxy and dihydroxy forms), including 1,25-dihydroxy-19-nor-vitamin D₂, and 1 α -hydroxyvitamin D₃. In one type of embodiment, the vitamin D compound includes one or more hydroxy forms, such as a combination of 25-hydroxyvitamin D₃ and 25-hydroxyvitamin D₂.

[0029] A type of vitamin D compound particularly contemplated for use in the formulation disclosed herein can include 25-hydroxyvitamin D₂, 25-hydroxyvitamin D₃, or a combination thereof. 25-hydroxyvitamin D₃ is particularly contemplated. As used herein, the term 25-hydroxyvitamin D refers to one or more of 25-hydroxyvitamin D₃, 25-hydroxyvitamin D₂, 25-hydroxyvitamin D₄, 25-hydroxyvitamin D₅, or 25-hydroxyvitamin D₇, and it is contemplated that in any reference thereto a preferred embodiment is one or more of 25-hydroxyvitamin D₃ and 25-hydroxyvitamin D₂, preferably 25-hydroxyvitamin D₃. Thus, in any and all formulations described herein, it is specifically contemplated that the active can include one or both of 25-hydroxyvitamin D₂ and 25-hydroxyvitamin D₃, particularly 25-hydroxyvitamin D₃. In the disclosure herein, the vitamin D compound (or combination thereof) is also referred to as the “active” part of the formulation (or “active” agents), as distinguished from the controlled release matrix, the stabilizing agent, and other excipients. In the pharmacokinetic testing reported herein with samples that used 25-hydroxyvitamin D₃ as the active, references to 25-hydroxyvitamin D should be interpreted to mean 25-hydroxyvitamin D₃, and all pharmacokinetic (PK) results associated with (e.g., $t_{\max}$, $C_{\max}$, AUC) should be understood to be based on 25-hydroxyvitamin D₃.

[0030] As used herein, a “stabilized” formulation refers to a formulation exhibiting a stable *in vitro* dissolution profile (according to any of the parameters described further herein) and controlled release (e.g., sustained release) of a vitamin D compound *in vivo*, for a time following initial manufacture, e.g. following actual shelf storage or accelerated stability storage conditions. The release of the active ingredient can be measured using a suitable *in vitro* dissolution method, such as one of the methods already known in the art. In principle, any of the dissolution studies described in the United States Pharmacopeia, USP 29-NF 24, Dissolution <711> physical tests and determinations, United States Pharmacopeial Convention, Inc., Rockville, MD, 2006, pp. 2673–2682.; European Pharmacopoeia 2.9.3 Dissolution Test for Solid Dosage Forms, or the Japanese Pharmacopoeia 6.10 Dissolution Test, can be used to determine if a formulation is stable. For purposes of the present invention, the *in vitro* dissolution method is United States Pharmacopeia, USP 29-NF 24, Dissolution <711> physical tests and determinations, United States Pharmacopeial Convention, Inc., Rockville, MD, 2006, pp. 2673–2682, using Apparatus 2 (paddle method), as described in the Examples below.

[0031] As used herein, $t_{\max}$ (or Tmax) is defined as the time for the plasma concentration of the active compound to reach its maximum in a dose interval following administration of a formulation according to the invention. When administering a single 25-hydroxyvitamin D compound, for example 25-hydroxyvitamin D₃, $t_{\max}$ is defined as the time for the plasma concentration of serum 25-hydroxyvitamin D₃ to reach its maximum in a dose interval following administration of the formulation, unless specified otherwise.

[0032] Consistent with the NKF K/DOQI Guidelines, as used herein Vitamin D sufficiency is defined as serum 25-hydroxyvitamin D levels ≥ 30 ng/mL, Vitamin D insufficiency is defined as serum 25-hydroxyvitamin D of 16-30 ng/mL, mild Vitamin D deficiency is defined as serum 25-hydroxyvitamin D of 5-15 ng/mL, and severe Vitamin D deficiency is defined as serum 25-hydroxyvitamin D below 5 ng/mL.

[0033] In jurisdictions that forbid the patenting of methods that are practiced on the human body, the meaning of “administering” of a composition to a human subject shall be restricted to prescribing a controlled substance that a human subject will self-administer by any technique (e.g., orally, inhalation, topical application, injection, insertion, etc.). The broadest reasonable interpretation that is consistent with laws or regulations defining patentable subject matter is intended. In jurisdictions that do not forbid the patenting of methods that are practiced on the human body, the “administering” of compositions includes both methods practiced on the human body and also the foregoing activities.

[0034] It is specifically understood that any numerical value recited herein includes all values from the lower value to the upper value, i.e., all possible combinations of numerical values between the lowest value and the highest value enumerated are to be considered to be expressly stated in this application. For example, if a concentration range or a beneficial effect range is stated as 1% to 50%, it is intended that values such as 2% to 40%, 10% to 30%, or 1% to 3%, etc., are expressly enumerated in this specification. As another example, a stated concentration of about 20% is intended to include values from 19.5% up to 20.5%. These are only examples of what is specifically intended.

[0035] Disclosed herein are formulations for controlled release of a Vitamin D compound in the gastrointestinal tract of a subject which ingests the formulation. The formulation will include a vitamin D compound as described herein, a matrix component that releasably binds the vitamin

D compound and controllably releases the vitamin D compound (e.g., a lipophilic matrix), and a stabilizer (e.g. a cellulosic compound).

[0036] A stabilized formulation according to the disclosure herein, following storage for a period of time, releases an amount of 25-hydroxyvitamin D in *in vitro* dissolution that does not substantially differ from the dissolution of the same formulation just after manufacturing and prior to storage. For example, in one embodiment, a formulation releases an amount of 25-hydroxyvitamin D during *in vitro* dissolution after exposure to storage conditions of two months at 25 °C and 60% relative humidity that varies at any given dissolution time point after four hours by 30% or less compared to the amount released at the same dissolution time point during *in vitro* dissolution conducted prior to exposing the formulation to the storage conditions (i.e., freshly-produced product).

[0037] The table below provides examples of advantageous degrees of storage stability contemplated for embodiments of the invention following storage at 25 °C and 60% RH, and alternatively at 40°C and 75% RH for various times following initial manufacturing, and at various times in during dissolution testing. The degrees of storage stability are expressed in terms of the maximum deviation from nominal active potency, i.e. maximum % change from LC. Alternative embodiments of maximum deviation are also provided.

Time (h)	1 month	3 mos.	6 mos.	9 mos.	12 mos.	18 mos.	24 mos.
storage at 25 °C and 60% RH							
2	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%
4	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%
6	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%
8	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or	30%, or 25%, or 20%, or 15%, or	30%, or 25%, or 20%, or 15%, or	30%, or 25%, or 20%, or 15%, or	30%, or 25%, or 20%, or 15%, or	30%, or 25%, or 20%, or 15%, or

		10%	10%	10%	10%	10%	10%
12	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%
storage at 40 °C and 75% RH							
2	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%
4	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%
6	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%
8	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%
12	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%	30%, or 25%, or 20%, or 15%, or 10%

[0038] In one type of embodiment, the formulation will have advantageous degrees of stability described in the table immediately above at multiple time points throughout the dissolution testing, e.g. at least at both 2 and 4 hour time points, optionally also at the 6 hour time point, further optionally also at the 8 hour time point, and further optionally also at the 12 hour time point, such that the dissolution profile after storage follows the dissolution profile of fresh product. Alternatively, the formulation will have advantageous degrees of stability described in the table immediately above at least at the 2, 6, and 12 hour time points. Alternatively, the formulation will have advantageous degrees of stability described in the table immediately above at least at the 4, 8, and 12 hour time points. Alternatively, the formulation will have advantageous degrees of stability described in the table immediately above at least at the 2, 4, and 6, hour time points. Alternatively, the formulation will have advantageous degrees of stability described in the table immediately above at least at the 4, 6, 8, and 12 hour time points, or at all times of 4 hours and thereafter.

[0039] In any and all of the embodiments described in the table immediately above, it is contemplated that the deviation can be positive (more release) or negative (less release) with respect to the fresh product. In one type of embodiment, it is contemplated that the deviation will be in the negative (less release) direction at multiple time points. Still further, in one type of embodiment it is contemplated that the deviation in dissolution release would have been negative (less release) at multiple time points but for the presence of the stabilizing agent in the formulation.

[0040] In any of the embodiments contemplated herein, the dissolution release profile of the formulation can have the characteristics of any one of the examples provided herein below. For example, the formulation can be characterized by a dissolution release profile providing a release of vitamin D compound of less than 30% at 2 hours, greater than 45% at 6 hours, and greater than 80% at 12 hours, and further optionally less than 60% at 6 hours.

[0041] In another type of embodiment, the formulation can be characterized by an in vitro dissolution profile providing release of vitamin D compound of less than 30% at 100 to 140 minutes, greater than 45% at 5 to 7 hours, and greater than 80% at 11 to 13 hours. In another type of embodiment, the formulation can be characterized by an in vitro dissolution profile providing release of vitamin D compound of less than 30% at 2 hours, greater than 45% at 6 hours, and greater than 80% at 12 hours. In these types of embodiments, optionally the release of vitamin D compound at 5 to 7 hours is less than 60%, or at 6 hours is less than 60%.

[0042] In another type of embodiment, the formulation can be characterized by an in vitro dissolution profile providing release of vitamin D compound of about 20% to about 40% at 2 hours, at least 35% at 6 hours, and at least 70% at 12 hours. In another type of embodiment, the formulation can be characterized by an in vitro dissolution profile providing release of vitamin D compound of about 25% to about 35% at 2 hours, at least 40% at 6 hours, and at least 75% at 12 hours. In these types of embodiments, optionally the release of vitamin D compound is 75% or less at 6 hours, or 65% or less at 6 hours, or 60% or less at 6 hours, for example.

[0043] In any of the embodiments described herein, the stabilized formulation can be characterized by a t_{max} following administration of the dosage form to a human patient, of at least 4 hours, or at least 8 hours, or at least 12 hours, or at least 18 hours, or at least 20 hours, or at

least 24 hours, or at least 28 hours, for example in a range of 4 to 96 hours, or in a range of 18 to 30 hours, or in a range of 13 to 28 hours, or is 28 hours, for example.

[0044] In any of the embodiments contemplated herein a formulation comprising 25-hydroxyvitamin D can be characterized by providing a baseline-adjusted $C_{\max}$ per microgram of 25-hydroxyvitamin D in a range of about 0.0133 ng/mL to about 0.04 ng/mL when administered to an adult human.

[0045] In any of the methods contemplated herein, the method can include administering a stabilized sustained release dosage form comprising a 25-hydroxyvitamin D compound to a human patient, comprising administering an effective amount of the formulation to the patient to provide a baseline-adjusted $C_{\max}$ of at least about 0.2 ng/mL and optionally less than 110 ng/mL, and further optionally 24 ng/mL or less, for example in a range of about 0.2 to about 24 ng/mL.

[0046] In any of the methods contemplated herein, the method can include administering a stabilized sustained release dosage form comprising a 25-hydroxyvitamin D compound to a human patient, comprising administering an effective amount of the formulation to the patient to provide a baseline-adjusted $AUC_{0-\infty}$ of at least 52 ng*h/mL, and optionally less than 34,500 ng*h/mL, and further optionally about 12,000 ng*h/mL or less, for example in a range of about 52 ng*h/mL to about 12,000 ng*h/mL.

[0047] In any of the embodiments described herein, it is contemplated that the stabilized formulation, following storage, can be bioequivalent to the freshly-made product. Thus, for example, the stabilized formulation, following storage, can provide an area under the curve for the active (or serum total 25-hydroxyvitamin D), AUC (e.g., $AUC_{0-\infty}$ or AUC_{0-t}) within a 90% confidence interval, or within 80% to 125% of the mean, or within 80% to 120% of the mean of the fresh product. In addition or in the alternative, the stabilized formulation, following storage, can provide a maximum serum concentration of the active (or serum total 25-hydroxyvitamin D), $C_{\max}$ (e.g., $C_{\max}$ absolute, or $C_{\max}$ compared to baseline) within a 90% confidence interval, or within 80% to 125% of the mean, or within 80% to 120% of the mean, of the fresh product.

[0048] In one embodiment, a stabilized formulation comprises one or both of 25-hydroxyvitamin D₂ and 25-hydroxyvitamin D₃, a wax matrix, and a cellulosic compound. In one aspect, a stabilized formulation comprises one or both of 25-hydroxyvitamin D₂ and 25-hydroxyvitamin D₃, a wax matrix, and a cellulosic stabilizing agent. In another aspect, the

formulation comprises one or both of 25-hydroxyvitamin D₂ and 25-hydroxyvitamin D₃, a wax matrix, and an effective amount of a cellulosic compound to provide an advantageous degree of stability as described herein, e.g. with respect to the table immediately above or consistent with any of the Examples described below. For example, the amount can be effective to provide a difference of 30% or less between the amount of active released during *in vitro* dissolution after exposure to storage conditions of at least one month at 25 °C and 60% relative humidity at a dissolution time point and the amount released at the same dissolution time point during *in vitro* dissolution conducted prior to exposing the formulation to the storage conditions, while a comparative formulation lacking the stabilizing agent would result in a greater difference in dissolution release following the same storage conditions.

[0049] In one aspect, the formulation is an improved formulation for controlled release of a vitamin D compound in the gastrointestinal tract of a subject which ingests the formulation. In one embodiment, the improvement comprises admixing a cellulosic stabilizing agent into a formulation for controlled release of a vitamin D compound in the gastrointestinal tract of a subject which ingests the formulation. In another embodiment, the improvement comprises an effective amount of a cellulosic compound admixed into a formulation for controlled release of a vitamin D compound in the gastrointestinal tract of a subject which ingests the formulation to provide an advantageous degree of stability as described herein, e.g. with respect to the table immediately above or consistent with any of the Examples described below. For example, the amount can be effective to provide a difference of 30% or less between the amount of active released during *in vitro* dissolution after exposure to storage conditions of at least one month at 25 °C and 60% relative humidity at a dissolution time point and the amount released at the same dissolution time point during *in vitro* dissolution conducted prior to exposing the formulation to the storage conditions, while a comparative formulation lacking the stabilizing agent would result in a greater difference in dissolution release following the same storage conditions.

[0050] The stabilizing agents can include cellulose compounds. Examples of cellulose compounds and stabilizing agents for use in the stabilized formulations of the disclosure can include, but are not limited to, cellulosic acid, carboxy methyl cellulose, ethyl cellulose, hydroxyl ethyl cellulose, hydroxyl propyl cellulose, hydroxyl propyl methyl cellulose, methylcellulose, polyanionic cellulose, and combinations thereof. Also contemplated are one or more of poloxamers (e.g., polaxamer 407), poly (ethylene oxide) polymers (e.g., Dow's

POLYOX polymers), povidones, and fumed silicas (e.g., AEROSIL 200, Evonik Industries AG, Essen, Germany). The stabilizer, e.g. a cellulosic compound, preferably is present in an amount of at least about 5 % of the formulation, based on the total weight of the formulation excluding any additional coatings or shells (wt%). For example, the cellulosic compound can be present in an amount of at least 5 wt% of the formulation, or at least 10 wt% of the formulation, or at least 15 wt% of the formulation, or greater than 5 wt% of the formulation, or greater than 10 wt% of the formulation, or greater than 15 wt% of the formulation. Suitable ranges include 5 wt% to 30 wt%, 10 wt% to 20 wt%, 10 wt% to 15 wt%, 5 wt% to 15 wt%, and 7.5 wt% to 12.5 wt%. Examples include about 5 wt%, about 6 wt%, about 7 wt%, about 8 wt%, about 9 wt%, about 10 wt%, about 11 wt%, about 12 wt%, about 13 wt%, about 14 wt%, and about 15 wt%. It will be understood that the stabilizing agent referred to herein is an agent that stabilizes the dissolution release profile (and thus also the *in vivo* release profile) against substantial change over time during storage conditions, e.g. typical shelf storage conditions. Other agents which are known in the art as preservatives for preventing degradation of the active component itself are not intended to be encompassed within the terms “stabilizing agent” and “stabilizer” although such preservatives are also contemplated for use in the formulations of the present invention.

[0051] In one class of embodiment, the cellulosic compound is a cellulose ether. Examples of cellulose ethers include, but are not limited to, methylcellulose, hydroxyl propyl methylcellulose, hydroxyl ethyl methylcellulose, hydroxyl ethyl cellulose, hydroxyl propyl cellulose, and combinations thereof.

[0052] Hydroxyl propyl methylcellulose (HPMC) is particularly contemplated. The HPMC can be characterized by one or more of the following features, which are specifically contemplated individually and in combinations. The % methoxyl component in the HPMC can be in a range of 19 to 24. The % hydroxypropyl component can be in a range of 7 to 12. The apparent viscosity (2% solution in water at 20°C) can be at least 50,000 cP, or at least 80,000 cP, or in a range of about 80 to 120,000 cP, or 3000 to 120,000 cP, or 11,000 to 120,000 cP, or 80,000 to 120,000 cP. Particularly, the apparent viscosity (2% solution in water at 20°C) can be in a range of 80,000 to 120,000 cP. The pH (1% solution in water) can be in a range of 5.5 to 8.0. For example, a suitable hydroxyl propyl methylcellulose having all of the foregoing properties, including an apparent viscosity (2% solution in water at 20°C) in a range of 80,000 to 120,000 cP, is METHOCEL K100M CR (Dow Wolff Cellulosics, Midland, Michigan).

[0053] In one type of embodiment, the cellulosic compound will be insoluble in the matrix formulation at the melt point of the primary components of the matrix, e.g., at 65 °C or in a range of 60 °C to 75 °C.

[0054] In one type of embodiment, the cellulosic compound will be hydrophilic.

[0055] The pharmaceutical formulations according to the disclosure comprising one of more of 25-hydroxyvitamin D₂ and 25-hydroxyvitamin D₃ and a cellulosic compound have unexpectedly improved stability compared to formulations lacking a cellulosic compound. In one embodiment, a stabilized formulation according to the disclosure comprises a mixture of an active-loaded lipophilic matrix comprising one or both of 25-hydroxyvitamin D₂ and 25-hydroxyvitamin D₃ and a cellulosic stabilizing agent, wherein the formulation releases an amount of 25-hydroxyvitamin D during *in vitro* dissolution after exposure to storage conditions of at least one month at 25 °C and 60% relative humidity that varies at any given dissolution time point by 30% or less compared to the amount released at the same dissolution time point during *in vitro* dissolution conducted on freshly-made product.

[0056] Formulations that are not stabilized exhibit changes in the amount of active ingredient released after the composition is stored for a period of time, as shown in the Examples below. An unstabilized formulation releases an amount of 25-hydroxyvitamin D following exposure to storage conditions that can vary at a given dissolution time point, for example by more than 30% compared to the amount released at the same dissolution time point during *in vitro* dissolution conducted on freshly-made product. The changes may be an increase or decrease in the dissolution rate at a given time point, and such changes produce a dissolution profile whose curve is distinct from the shape of the initial dissolution profile. An unstabilized formulation also exhibits different *in vivo* effects compared to a stabilized formulation according to the disclosure, following storage as described herein, e.g. following 3 months or more of storage at 25 °C and 60% RH. A stabilized formulation demonstrates different clinical pharmacokinetic parameters, such as improved bioavailability, compared to an unstabilized formulation, following storage as described herein, e.g. following 3 months or more of storage at 25 °C and 60% RH. A stabilized formulation according to the disclosure can have a base formulation which is storage unstable, combined with a stabilizing agent which renders the formulation storage stable as described herein.

[0057] The matrix that releasably binds and controllably releases the active component can be, for example, a lipophilic matrix, including a wax matrix. A wax matrix can provide a formulation which is solid or semi-solid at room temperature and solid, semi-solid, or liquid at body temperature, preferably semi-solid or liquid at body temperature. In one aspect, the wax matrix comprises a controlled release agent, an emulsifier, and an absorption enhancer.

[0058] Examples of controlled release agents suitable for use include, but are not limited to, waxes, including synthetic waxes, microcrystalline wax, paraffin wax, carnauba wax, and beeswax; polyethoxylated castor oil derivatives, hydrogenated vegetable oils, glyceryl mono-, di- or tribehenates; long-chain alcohols, such as stearyl alcohol, cetyl alcohol, and polyethylene glycol; and mixtures of any of the foregoing. Non-digestible waxy substances, such as hard paraffin wax, are preferred.

[0059] The controlled release agent can be present in an amount of at least 5 wt% of the formulation, or greater than about 5 wt% of the formulation. For example, depending on the controlled release agent used, the controlled release agent can comprise at least 5 wt% of the formulation or at least 10 wt% of the formulation, or at least 15 wt% of the formulation, or at least 20 wt% of the formulation, or at least 25 wt% of the formulation, or greater than 5 wt% of the formulation, or greater than 10 wt% of the formulation, or greater than 15 wt% of the formulation, or greater than 20 wt% of the formulation, and or greater than 25 wt% of the formulation. The controlled release agent can be present in an amount 50 wt% or less, 40 wt% or less, 35 wt% or less, or 30 wt% or less. Suitable ranges include 5 wt% to 40 wt%, 10 wt% to 30 wt% and 15 wt% to 25 wt%. Examples include about 15 wt%, about 16 wt%, about 17 wt%, about 18 wt%, about 19 wt%, about 20 wt%, about 21 wt%, about 22 wt%, about 23 wt%, about 24 wt%, and about 25 wt%.

[0060] Examples of emulsifiers suitable for use in the formulation include, but are not limited to, lipophilic agents having an HLB of less than 7, such as mixed fatty acid monoglycerides; mixed fatty acid diglycerides; mixtures of fatty acid mono- and diglycerides; lipophilic polyglycerol esters; glycerol esters including glyceryl monooleate, glyceryl dioleate, glyceryl monostearate, glyceryl distearate, glyceryl monopalmitate, and glyceryl dipalmitate; glyceryl-lacto esters of fatty acids; propylene glycol esters including propylene glycol monopalmitate, propylene glycol monostearate, and propylene glycol monooleate; sorbitan esters including

sorbitan monostearate, sorbitan sesquioleate; fatty acids and their soaps including stearic acid, palmitic acid, and oleic acid; and mixtures thereof glyceryl monooleate, glyceryl dioleate, glyceryl monostearate, glyceryl distearate, glyceryl monopalmitate, and glyceryl dipalmitate; glyceryl-lacto esters of fatty acids; propylene glycol esters including propylene glycol monopalmitate, propylene glycol monostearate, and propylene glycol monooleate; sorbitan esters including sorbitan monostearate, sorbitan sesquioleate; fatty acids and their soaps including stearic acid, palmitic acid, and oleic acid; and mixtures thereof.

[0061] A preferred lipoidic agent is selected from glycerides and derivatives thereof. Preferred glycerides are selected from the group consisting of medium or long chain glycerides, caprylocaproyl macrogolglycerides, and mixtures thereof.

[0062] Preferred medium chain glycerides include, but are not limited to, medium chain monoglycerides, medium chain diglycerides, caprylic/capric triglyceride, glyceryl monolaurate, glyceryl monostearate, caprylic/capric glycerides, glycerylmonocaprylate, glyceryl monodicaprylate, caprylic/capric linoleic triglyceride, and caprylic/capric/succinic triglyceride.

[0063] Monoglycerides having a low melting point are preferred for making the formulation. Preferred monoglycerides include but are not limited to, glyceryl monostearate, glyceryl monopalmitate, glyceryl monooleate, glyceryl monocaprylate, glyceryl monocaprinate, glyceryl monolaurate, etc., preferably glycerol monostearate (GMS). GMS is a natural emulsifying agent. It is oil soluble, but poorly soluble in water. GMS has an HLB value of 3.8. The lipophilic emulsifier can be present in an amount in a range of about 10 wt% to about 40 wt%, or about 20 wt% to about 25 wt%, for example. Other examples include about 20 wt%, about 21 wt%, about 22 wt%, about 23 wt%, about 24 wt%, and about 25 wt%.

[0064] Examples of suitable absorption enhancers include, but are not limited to, caprylocaproyl macrogolglycerides such as polyethylene glycosylated glycerides, also known as polyglycolized glycerides or PEGylated glycerides. PEGylated glycerides which may be employed in the composition include, but are not limited to, mixtures of monoglycerides, diglycerides, and triglycerides and monoesters and diesters of polyethylene glycol, polyethylene glycosylated almond glycerides, polyethylene glycosylated corn glycerides, and polyethylene glycosylated caprylic/capric triglyceride. The absorption enhancer can have an HLB value from 13 to 18, or from 13 to 15.

[0065] One preferred absorption enhancer is known under the trade name GELUCIRE (Gattefossé Corporation, Paramus, New Jersey, USA). GELUCIRE is a well known excipient which is a family of fatty acid esters of glycerol and PEG esters, also known as polyglycolized glycerides. GELUCIRE is used in various applications including preparing sustained release pharmaceutical compositions. GELUCIRE compounds are inert, semi-solid waxy materials which are amphiphilic and are available with varying physical characteristics such as melting point, HLB, and solubilities in various solvents. They are surface active in nature and disperse or solubilize in aqueous media forming micelles, microscopic globules or vesicles. They are identified by their melting point/HLB value. The melting point is expressed in degrees Celsius. One or a mixture of different grades of GELUCIRE excipient may be chosen to achieve the desired characteristics of melting point and/or HLB value. A preferred GELUCIRE composition is GELUCIRE 44/14, a mixture of lauroyl macrogolglycerides and lauroyl polyoxylglycerides that has a melting point of 44 °C and a HLB of 14. The absorption enhancer can be present in an amount of about 5 wt% to about 20 wt%, or about 8 wt% to about 15 wt%, for example. Other examples include about 8 wt%, about 9 wt%, about 10 wt%, about 11, wt% about 12 wt%, about 13 wt%, about 14 wt%, and about 15 wt%.

[0066] The low melting points of the wax matrix provide a means of incorporating the pharmaceutically active ingredients, e.g. the vitamin D compound such as 25-D₂, 25-D₃, or both, at temperatures from about 0 °C to about 50 °C above the melting point of the wax matrix and then filling the melt (solution and/or dispersion) in suitable capsules. The capsules can be of any variety that is compatible with the temperature of the melt fill, including soft or hard gelatin capsules, and animal or vegetable gelatin capsules. The melt solidifies inside the capsules upon cooling to room temperature.

[0067] In one aspect, a stabilized formulation may further comprise an oily vehicle for the 25-hydroxyvitamin D₂ and/or 25-hydroxyvitamin D₃. Any pharmaceutically-acceptable oil can be used. Examples include animal (e.g., fish), vegetable (e.g., soybean), and mineral oils. The oil preferably will readily dissolve the 25-hydroxyvitamin D compound used. Preferred oily vehicles include non-digestible oils, such as mineral oils, particularly liquid paraffins, and squalene. The oily vehicle can be present at a concentration in a range about 10 wt% to about 50 wt% of the formulation, or about 15 wt% to about 45 wt%, or about 20 wt% to about 40 wt%, or about 30 wt% to about 40 wt%, for example. In one type of embodiment, a suitable liquid

paraffin can be characterized by one or more of the following parameters: specific gravity about 0.88 to 0.89; kinematic viscosity (40 °C) about 64 cSt to about 70 cSt; molecular weight 424; % paraffinic hydrocarbons about 59; and pour point -24 °C. The ratio between the wax matrix and the oily vehicle can be optimized in order to achieve the desired rate of release of the vitamin D compound. Thus, if a heavier oil component is used, relatively less of the wax matrix can be used, and if a lighter oil component is used, then relatively more wax matrix can be used.

[0068] The stabilized controlled release compositions in accordance with the invention preferably are designed to contain concentrations of 25-hydroxyvitamin D₂ and/or 25-hydroxyvitamin D₃ of 1 to 1000 µg per unit dose, for example, and are prepared in such a manner as to effect controlled or substantially constant release of the 25-hydroxyvitamin D₂/25-hydroxyvitamin D₃, optionally into the ileum of the gastrointestinal tract, of humans or animals over an extended period of time. Example dosages include 1 µg to 1000 µg per unit dose, 1 µg to 600 µg, 1 µg to 400 µg, 1 µg to 200 µg, 1 µg to 100 µg, 5 µg to 90 µg, 30 µg to 80 µg, 20 µg to 60 µg, 30 µg to 60 µg, 35 µg to 50 µg, 5 µg to 50 µg, and 10 µg to 25 µg, for example 20 µg, 25 µg, 30 µg, 40 µg, 50 µg, 60 µg, 70 µg, 80 µg, 90 µg, and 100 µg.

[0069] In one preferred class of embodiments, the controlled release formulation releases at least 70%, more preferably at least 80% of the vitamin D compound within the first 24 hours after dosing.

[0070] Advantageously, 25-hydroxyvitamin D₂, 25-hydroxyvitamin D₃ or combinations thereof together with other therapeutic agents can be administered, e.g. orally, in accordance with the above described embodiments in dosage amounts of from 1 to 100 µg per day, for example. In one type of embodiment, the dose will be selected to provide an average rise in serum 25-hydroxyvitamin D₃ of about 1 to 3 ng/ml in a dose interval.

[0071] In embodiments, the formulations described herein can be administered to raise and preferably also maintain blood 1,25-dihydroxyvitamin D levels at 25 pg/mL, 30 pg/mL, or higher, e.g. 25-65 pg/mL for an extended period, for example at least one month, at least three months, at least six months, or longer.

[0072] In one aspect, the formulations described herein can be administered to patients to lower or maintain lowered serum parathyroid hormone levels, preferably an amount that lowers PTH levels by at least 30%, or alternatively the amount needed to reduce serum levels of PTH to

the target range for the CKD stage (e.g., for Stage 3 is 35-70 pg/mL (equivalent to 3.85-7.7 pmol/L), for Stage 4 is 70-110 pg/mL (equivalent to 7.7-12.1 pmol/L), and for Stage 5 is 150-300 pg/mL (equivalent to 16.5-33.0 pmol/L) (defined in K/DOQI Guideline No. 1)).

[0073] In another aspect, the formulations according to the disclosure herein can be administered to a patient suffering from hyperparathyroidism secondary to chronic kidney disease (e.g., Stage 3 or 4, or Stage 3, 4 or 5) to lower the serum PTH level.

[0074] The dosages described herein are contemplated for any of the therapeutic methods described herein. It will be appreciated that the actual preferred amount of a vitamin D compound in a specific case will vary according the particular compositions formulated, the mode of application, and the particular situs being treated. Dosages can be determined using conventional considerations, e.g., by customary comparison of the differential activity of the hormone and of a known agent, e.g. by means of an appropriate conventional pharmacological protocol.

[0075] The specific doses for each particular patient can depend on a wide variety of factors, for example, on the age, body weight, general state of health, sex, on the diet, on the timing and mode of administration, on the rate of excretion, and on medicaments used in combination and the severity of the particular disorder to which the therapy is applied.

[0076] Patients in need of vitamin D supplementation include healthy subjects and subjects at risk for vitamin D insufficiency or deficiency, for example, subjects with Stage 1, 2, 3, 4 or 5 CKD; infants, children and adults that do not drink vitamin D fortified milk (e.g. lactose intolerant subjects, subjects with milk allergy, vegetarians who do not consume milk, and breast fed infants); subjects with rickets; subjects with dark skin (e.g., in the U.S., 42% of African American women between 15 and 49 years of age were vitamin D deficient compared to 4% of white women); the elderly (who have a reduced ability to synthesize vitamin D and also are more likely to stay indoors); institutionalized adults (who are likely to stay indoors, including subjects with Alzheimer's disease or mentally ill); subjects who cover all exposed skin (such as members of certain religions or cultures); subjects who always use sunscreen (e.g., the application of sunscreen with a Sun Protection Factor (SPF) value of 8 reduces production of vitamin D by 95%, and higher SPF values may further reduce vitamin D); subjects with fat malabsorption syndromes (including but not limited to cystic fibrosis, cholestatic liver disease, other liver

disease, gallbladder disease, pancreatic enzyme deficiency, Crohn's disease, inflammatory bowel disease, sprue or celiac disease, or surgical removal of part or all of the stomach and/or intestines); subjects with inflammatory bowel disease; subjects with Crohn's disease; subjects who have had small bowel resections; subjects with gum disease; subjects taking medications that increase the catabolism of vitamin D, including phenytoin, fosphenytoin, phenobarbital, carbamazepine, and rifampin; subjects taking medications that reduce absorption of vitamin D, including cholestyramine, colestipol, orlistat, mineral oil, and fat substitutes; subjects taking medications that inhibit activation of vitamin D, including ketoconazole; subjects taking medications that decrease calcium absorption, including corticosteroids; subjects with obesity (vitamin D deposited in body fat stores is less bioavailable); subjects with osteoporosis; patients who have low bone mineral density and osteoporosis; and/or postmenopausal women. According to the Institute of Medicine's report on the Dietary Reference Intakes for vitamin D, food consumption data suggest that median intakes of vitamin D for both younger and older women are below current recommendations; data suggest that more than 50% of younger and older women are not consuming recommended amounts of vitamin D.

[0077] Optionally excluded from the methods of the invention described herein are therapeutic treatment of subjects suffering from renal osteodystrophy (including osteomalacia and osteitis fibrosa cystica).

[0078] In other aspects, the compositions and methods of the invention are useful for prophylactic or therapeutic treatment of vitamin D-responsive diseases, i.e., diseases where vitamin D, 25-hydroxyvitamin D or active vitamin D (e.g., 1,25-dihydroxyvitamin D) prevents onset or progression of disease, or reduces signs or symptoms of disease. Such vitamin D-responsive diseases include cancer (e.g., breast, lung, skin, melanoma, colon, colorectal, rectal, prostate and bone cancer). 1,25-dihydroxyvitamin D has been observed to induce cell differentiation and/or inhibit cell proliferation *in vitro* for a number of cells. Vitamin D-responsive diseases also include autoimmune diseases, for example, type I diabetes, multiple sclerosis, rheumatoid arthritis, polymyositis, dermatomyositis, scleroderma, fibrosis, Grave's disease, Hashimoto's disease, acute or chronic transplant rejection, acute or chronic graft versus host disease, inflammatory bowel disease, Crohn's disease, systemic lupus erythematosus, Sjogren's Syndrome, eczema and psoriasis, dermatitis, including atopic dermatitis, contact dermatitis, allergic dermatitis and/or chronic dermatitis. Vitamin D-responsive diseases also

include other inflammatory diseases, for example, asthma, chronic obstructive pulmonary disease, polycystic kidney disease, polycystic ovary syndrome, pancreatitis, nephritis, hepatitis, and/or infection. Vitamin D-responsive diseases have also been reported to include hypertension and cardiovascular diseases. Thus, the invention contemplates prophylactic or therapeutic treatment of subjects at risk of or suffering from cardiovascular diseases, for example, subjects with atherosclerosis, arteriosclerosis, coronary artery disease, cerebrovascular disease, peripheral vascular disease, myocardial infarction, myocardial ischemia, cerebral ischemia, stroke, congestive heart failure, cardiomyopathy, obesity or other weight disorders, lipid disorders (e.g. hyperlipidemia, dyslipidemia including associated diabetic dyslipidemia and mixed dyslipidemia hypoalphalipoproteinemia, hypertriglyceridemia, hypercholesterolemia, and low HDL (high density lipoprotein)), metabolic disorders (e.g. Metabolic Syndrome, Type II diabetes mellitus, Type I diabetes mellitus, hyperinsulinemia, impaired glucose tolerance, insulin resistance, diabetic complication including neuropathy, nephropathy, retinopathy, diabetic foot ulcer and cataracts), and/or thrombosis.

[0079] Diseases which can benefit from a modulation in the levels of vitamin D compounds, include, but are not limited to: (i) in the parathyroid-- hypoparathyroidism, pseudohypoparathyroidism, secondary hyperparathyroidism; (ii) in the pancreas--diabetes; (iii) in the thyroid--medullary carcinoma; (iv) in the skin--psoriasis; wound healing; (v) in the lung--sarcoidosis and tuberculosis; (vi) in the kidney--chronic kidney disease, hypophosphatemic VDDR, vitamin D dependent rickets; (vii) in the bone--anticonvulsant treatment, fibrogenesis imperfecta ossium, osteitis fibrosa cystica, osteomalacia, osteoporosis, osteopenia, osteosclerosis, renal osteodystrophy, rickets; (viii) in the intestine--glucocorticoid antagonism, idiopathic hypercalcemia, malabsorption syndrome, steatorrhea, tropical sprue; and (ix) autoimmune disorders.

[0080] In embodiments of the invention, the disease that benefits from a modulation in the levels of vitamin D compounds are selected from cancer, dermatological disorders (for example, psoriasis), parathyroid disorders (for example, hyperparathyroidism and secondary hyperparathyroidism), bone disorders (for example, osteoporosis) and autoimmune disorders.

[0081] The formulation can be prepared by procedures well within the capabilities of the ordinary skilled artisan. For example, the components of the matrix (e.g. wax and oily vehicle)

can be melted, if necessary, to provide a flowable liquid thereby making it easier to obtain a homogeneous mixture. The active (e.g., 25-hydroxyvitamin D₂ and/or 25-hydroxyvitamin D₃) is added to the liquid carrier, for example dissolved in an alcohol such as anhydrous ethanol, and the ingredients are mixed to provide a homogeneous mixture. In one type of embodiment, the stabilizer can be added after all matrix components (e.g., waxes and oils) are blended and prior to combination with the active. The mixture can be cooled and stored prior to later division into unit dosage forms, such as filled gelatin capsules.

[0082] In one type of method, a portion of the oily vehicle, controlled release agent, and emulsifier are heated to a relatively high temperature (e.g., 65 °C) and mixed prior to adding an absorption enhancer, followed by additional mixing until homogenous, then cooling to an intermediate elevated temperature (e.g., 50 °C to 55 °C). In a separate vessel, an antioxidant preservative and the remainder of the oily vehicle are mixed and heated to an intermediate elevated temperature (e.g., 50 °C), then combined and mixed with the wax mixture until a homogenous solution is obtained. Next, the stabilizer is added, with mixing. Next, a solution of the vitamin D compound(s) in alcohol is combined with the homogenous waxy solution, mixed until a homogenous solution is obtained, preferably filled into capsules, and then cooled to room temperature. In another preferred method, a portion of the oily vehicle, controlled release agent, and emulsifier are heated at a temperature of 55 °C to 60 °C and mixed prior to adding an absorption enhancer, followed by additional mixing until homogenous. In a separate vessel, an antioxidant preservative, the remainder of the oily vehicle, and the stabilizer are mixed and heated to a temperature of 55 °C to 60 °C, then combined and mixed with the wax mixture until a homogenous solution is obtained. Next, a solution of vitamin D compound in alcohol is combined with the homogenous waxy solution, mixed until a homogenous solution is obtained, preferably filled into capsules, and then cooled to room temperature.

[0083] The formulation preferably is placed in capsules prior to administration to the patient in need of treatment. Such capsules may be hard or soft, and soft capsules are particularly contemplated. The formulation may be filled into gelatin capsules using standard capsule filling machinery, such as by melting the formulation and injection-filling it into soft capsule shells. Example soft capsule shells include VEGICAPS and OPTISHELL technologies (Catalent, Somerset, NJ, USA). In the alternative, the formulation can be made into a unit dosage form by

any other suitable processes, for example to yield tablets, sachets, dragees, suppositories, or the like.

[0084] In one type of embodiment, the formulation is prepared for and administered by oral delivery. In another type of embodiment, the formulation is prepared for and administered as a suppository, e.g. a rectal suppository.

[0085] The formulation and methods of use and making are contemplated to include embodiments including any combination of one or more of the additional optional elements, features, and steps further described below, unless stated otherwise.

[0086] Thus, in one type of embodiment, the formulation further includes a preservative, such as an antioxidant. Butylated hydroxytoluene (BHT) is preferred.

[0087] In another type of embodiment, the vitamin D compound is administered in combination with one or more other therapeutic agents.

[0088] If the vitamin D compound is administered in combination with one or more other therapeutic agents, the proportions of each of the compounds in the combination being administered will be dependent on the particular disease state being addressed. For example, one may choose to administer 25-hydroxyvitamin D₂ and/or 25-hydroxyvitamin D₃ (e.g., orally) with one or more calcium salts (intended as a calcium supplement or dietary phosphate binder), bisphosphonates, calcimimetics, nicotinic acid, iron, phosphate binders, cholecalciferol, ergocalciferol, active Vitamin D sterols, glycemic and hypertension control agents, various antineoplastic agents and inhibitors of CYP24 and other cytochrome P450 enzymes that can degrade vitamin D agents. In addition, one may choose to intravenously administer 25-hydroxyvitamin D₂ and/or 25-hydroxyvitamin D₃ with cholecalciferol, ergocalciferol, active Vitamin D sterols, glycemic and hypertension control agents, various antineoplastic agents and inhibitors of CYP24 and other cytochrome P450 enzymes that can degrade vitamin D agents. In practice, higher doses of the compounds of the present invention are used where therapeutic treatment of a disease state is the desired end, while the lower doses are generally used for prophylactic purposes, it being understood that the specific dosage administered in any given case will be adjusted in accordance with the specific compounds being administered, the disease to be treated, the condition of the subject and the other relevant medical facts that may modify the activity of the drug or the response of the subject, as is well known by those skilled in the art.

[0089] As described above, the formulation is preferably filled into gelatin capsules, but it may also be administered in neat form, or with one or more external coating layers, such as an enteric coating. It is also contemplated that the formulation can be pressed into tablets, and in such cases one or more tablet pressing excipients may be included.

[0090] In the compositions and methods described herein, preferred steps, preferred components, preferred compositional ranges thereof, and preferred combinations of the foregoing, can be selected from the various specific examples provided herein. For example, a preferred formulation includes 25-hydroxyvitamin D (e.g., about 30 µg, about 60 µg, or about 90 µg 25-hydroxyvitamin D₃), about 2 wt% (e.g., 2.32 wt%) anhydrous ethanol, about 10 wt% (e.g., 9.75 wt%) GELUCIRE 44/14, about 20 wt% (e.g., 20.00 wt.%) hard paraffin, about 23 wt% (e.g., 22.55 wt%) GMS, about 35 wt% (e.g., 35.36 wt%) liquid paraffin or mineral oil, about 10 wt% HPMC, and optionally a small amount of preservative (e.g., 0.02 wt% BHT). A variation on this formulation will include about 15% (e.g., 15.29 wt%) HPMC and about 30 wt% (e.g., 29.88 wt%) liquid paraffin or mineral oil.

EXAMPLES

[0091] The following Examples illustrate specific formulations and methods for their preparation. The Examples are provided for illustration and are not intended to limit the scope of the invention.

[0092] *In vitro* dissolution testing in the Examples was performed using USP Apparatus 2 (paddle method) as described in USP 29- NF 24, general chapter <711> Dissolution, using the Dissolution Medium described below. In general, the method proceeds according to the following steps. Place the stated volume of the Dissolution Medium ($\pm 1\%$) in the vessel of the specified apparatus, assemble the apparatus, equilibrate the Dissolution Medium to $37 \pm 0.5^\circ$, and remove the thermometer. Place the dosage units in the apparatus, taking care to exclude air bubbles from the surface of the dosage units, and immediately operate the apparatus at the specified rate. At each of the times stated, withdraw specimens from a zone midway between the surface of the Dissolution Medium and the top of the rotating blade, not less than 1 cm from the vessel wall. Replace the aliquots withdrawn for analysis with equal volumes of fresh Dissolution Medium at 37° or. Keep the vessel covered for the duration of the test, and verify the

temperature of the mixture under test at suitable times. Perform the analysis using a suitable assay method, ultra performance liquid chromatography (UPLC) in this case .

[0093] Six capsules of each formulation were tested per time point. The Dissolution Medium was 0.05 M pH 6.8 phosphate buffer/1% sodium dodecyl sulfate dissolution medium at 37 ± 0.5 °C, and the apparatus was operated at 100 rotations per minute. Samples were taken at 2, 4, 6, 8, and 12 hours and the 25-hydroxyvitamin D content of each sample was determined using UPLC.

Example 1 – *In vitro* Dissolution of Unstabilized Sustained Release Formulations of 25-hydroxyvitamin D

[0094] The dissolution of a formulation made from a mixture of 90 µg of 25-hydroxyvitamin D₃, 19.98 wt% hard paraffin, 37.85 wt% GMS, 9.76 wt% GELUCIRE 44/14, 2.36 wt% anhydrous ethanol, 29.88 wt% liquid paraffin, and 0.02 wt% BHT (Comparative Formulation 1) was tested. The formulation did not comprise a cellulosic compound. The mean amount of 25-hydroxyvitamin D₃ released, calculated as a mean percentage of the nominal drug loading per dosage form (mean % of label claim, % LC) at T=0 and after controlled storage of the formulation at 5 °C and ambient humidity for up to 12 months are summarized in the table below. It was determined that the samples were stored for a period of about 3 months at a temperature in a range of 15 °C to 30 °C and ambient humidity, prior to testing. Thus, the sample which should have represented time zero is labeled as T=0_p (pseudo time zero), and it should be understood that the nominal 1 month, 3 month, 6 month, 9 month, and 12 month aged samples also experienced the approximately 3-month aging period just described. To provide a more accurate baseline, a fresh batch of the same type of samples was prepared and tested without any aging; this data is labeled as T=0_f to indicate fresh samples. The coefficient of variation (%CV) is also reported. The percent change from the initial amount of 25-hydroxyvitamin D₃ released by T=0_p and T=0_f lots is provided in brackets and double brackets, respectively.

Dissolution Following Storage at 5 °C / Ambient Humidity							
Time (hours)	T=0 _p pseudo	T=0 _f fresh	1 Month (%CV) [% change from T=0 _p] [[% change from T=0 _f]]	3 Months (% CV) [% change from T=0 _p] [[% change from T=0 _f]]	6 months (% CV) [% change from T=0 _p] [[% change from T=0 _f]]	9 months (% CV) [% change from T=0 _p] [[% change from T=0 _f]]	12 months (% CV) [% change from T=0 _p] [[% change from T=0 _f]]
2	6.1 (29.6)	22.1 (17.2)	8.9 (13.4)	15.7 (27.4)	9.1 (23)	15.2 (47.2)	12.7 (16.8)

			[45.9] [[59.7]]	[157.4] [[29.0]]	[49.2] [[58.8]]	[149.2] [[31.2]]	[108.2] [[42.5]]
4	14.5 (15.7)	52.0 (4.6)	20.7 (19.1) [42.8] [[60.2]]	22.3 (15.6) [53.8] [[57.1]]	22.9 (7.1) [57.9] [[56.0]]	25.2 (19.2) [73.8] [[51.5]]	24.7 (13.5) [70.3] [[52.5]]
6	27.6 (21.2)	77.9 (4.6)	35.7 (9.6) [29.3] [[54.2]]	33.5 (2.6) [21.4] [[57.0]]	34.1 (7.1) [23.6] [[56.2]]	36.2 (20.5) [31.2] [[53.5]]	34.8 (14.6) [26.1] [[55.3]]
8	45.7 (23.6)	96.8 (2.9)	53.0 (9.9) [16.0] [[45.2]]	47.4 (3.7) [3.7] [[51.0]]	46.8 (6) [2.4] [[51.7]]	47.8 (18.6) [4.6] [[50.6]]	46.4 (8.9) [1.5] [[52.1]]
12	89.7 (15.6)	112.3 (1.6)	100.0 (4.8) [11.5] [[11.0]]	78.9 (8.1) [12.0] [[29.7]]	76.9 (5.7) [14.3] [[31.5]]	74.1 (17.3) [17.4] [[34.0]]	78.8 (5.3) [12.2] [[29.8]]

[0095] The dissolution of Comparative Formulation 1 after storage at 25 °C and 60% relative humidity for 0 to 12 months was tested. The results are summarized in the table below.

Dissolution Following Storage at 25 °C / 60% Relative Humidity							
Dissolution Time (hours)	T=0 _p pseudo	T=0 _f fresh	1 Month (%CV) [% change from T=0 _p] [[% change from T=0 _f]]	3 Months (% CV) [% change from T=0 _p] [[% change from T=0 _f]]	6 months (% CV) [% change from T=0 _p] [[% change from T=0 _f]]	9 months (% CV) [% change from T=0 _p] [[% change from T=0 _f]]	12 months (% CV) [% change from T=0 _p] [[% change from T=0 _f]]
2	6.1 (29.6)	22.1 (17.2)	7.6 (7.7) [24.6] [[65.6]]	10.8 (15.7) [77.0] [[51.1]]	8.5 (19.2) [39.3] [[61.5]]	10.8 (15.8) [77.0] [[51.1]]	13.5 (24.7) [121.3] [[38.9]]
4	14.5 (15.7)	52.0 (4.6)	18.7 (18.6) [29.0] [[64.0]]	22.8 (23.7) [57.2] [[56.2]]	17.9 (11.9) [23.4] [[65.6]]	21.4 (5.5) [47.6] [[58.8]]	24.5 (17.4) [69.0] [[52.9]]
6	27.6 (21.2)	77.9 (4.6)	27.1 (22.7) [1.8] [[65.2]]	30.7 (29.6) [11.2] [[60.6]]	23.8 (11.6) [13.8] [[69.4]]	27.0 (7.3) [2.2] [[65.3]]	30.0 (15.7) [8.7] [[61.5]]
8	45.7 (23.6)	96.8 (2.9)	37.1 (18.1) [18/8] [[61.7]]	40.6 (29.9) [11.2] [[58.1]]	28.5 (13.2) [37.6] [[70.6]]	32.3 (6.4) [29.3] [[66.6]]	35.6 (14.7) [22.1] [[63.2]]
12	89.7 (15.6)	112.3 (1.6)	61.6 (16.6) [31.3] [[45.1]]	53.0 (32.2) [40.9] [[52.8]]	38.5 (12.2) [57.1] [[65.7]]	38.9 (6) [56.6] [[65.4]]	44.2 (12.2) [50.7] [[60.6]]

[0096] The dissolution of Comparative Formulation 1 after storage at 40 °C and 75% relative humidity for 0, 1, 3, and 6 months was tested. The results are summarized in the table below.

Dissolution Following Storage at 40 °C / 75% Relative Humidity					
Dissolution Time (hours)	T=0 _p pseudo	T=0 _f fresh	1 Month (%CV) [% change from T=0 _p] [[% change from T=0 _f]]	3 Months (%CV) [% change from T=0 _p] [[% change from T=0 _f]]	6 Months (%CV) [% change from T=0 _p] [[% change from T=0 _f]]
2	6.1 (29.6)	22.1 (17.2)	11.7 (50) [91.8] [[47.1]]	16.9 (36.3) [177.0] [[23.5]]	1.8 (75) [70.5] [[91.9]]
4	14.5 (15.7)	52.0 (4.6)	52.0 (45.1) [258.6] [[0]]	59.8 (31.3) [312.4] [[15.0]]	36.2 (21.8) [149.7] [[30.4]]
6	27.6 (21.2)	77.9 (4.6)	87.0 (21.5) [215.2] [[11.7]]	97.8 (24) [254.3] [[25.5]]	76.7 (12.3) [177.9] [[1.5]]
8	45.7 (23.6)	96.8 (2.9)	107.3 (8.1) [134.8] [[10.8]]	110.9 (13) [142.7] [[14.6]]	101.2 (6.1) [121.4] [[4.5]]
12	89.7 (15.6)	112.3 (1.6)	118.7 (1.7) [32.3] [[5.7]]	115.1 (3.7) [28.3] [[2.5]]	112.6 (2.1) [25.5] [[0.3]]

Without intending to be bound by any particular theory, the increase in the extent of dissolution following storage at 40 °C compared to the pseudo T=0 values is believed to be due to a combination of the aging effect described above on the pseudo T=0 samples tested, and a temperature-dependent phase change in the formulation when stored at 40 °C.

[0097] Aged product according to Comparative Formulation 1 was heat cured and then subject to dissolution testing. Curing consists of applying a heat treatment and has been shown to stabilize pharmaceutical formulations (see, e.g., U.S. Patent No. 6,645,527). Comparative Formulation 1 (aged samples) was heated at 40 °C for 72 hours for curing, and then was stored at room temperature for 8 weeks. Release of 25-hydroxyvitamin D₃ from the cured formulation was tested after storage for 0, 2, 4, and 8 weeks at room temperature. The results are summarized in the table below.

Dissolution Following Curing at 40 °C for 72 Hours				
Dissolution Time	T=0	2 weeks	4 weeks	8 weeks

(hours)		% LC [% change]	% LC [% change]	% LC [% change]
2	17.4	12.4 [28.7]	11.4 [34.5]	8.2 [52.9]
4	53.3	46.4 [12.9]	40.1 [24.8]	26.6 [50.1]
6	86.2	76.2 [11.6]	69.0 [20.0]	44.8 [48.0]
8	103.8	102.0 [1.7]	95.8 [7.7]	66.6 [35.8]
12	115.7	110.5 [4.5]	119.8 [3.5]	103.3 [10.7]

Example 2 – *In Vitro* Dissolution of Stabilized Controlled Release Formulations of 25-hydroxyvitamin D

[0098] The dissolution of a sustained release formulation comprising 90 µg of 25-hydroxyvitamin D₃, 19.88 wt% hard paraffin, 15.29 wt% hydroxypropyl methylcellulose, 22.55 wt% GMS, 9.76 wt% GELUCIRE 44/14, 2.36 wt % anhydrous ethanol, 29.88 wt% liquid paraffin, and 0.02 wt% BHT (Example Formulation A) was tested after 0 to 11 weeks of storage at room temperature. The results are summarized in the table below.

Dissolution Following Storage at Room Temperature / Ambient Humidity			
Dissolution Time (hours)	T=0	3 weeks % LC [% change]	11 weeks % LC [% change]
2	15.45	14.20 [8.1%]	12.08 [21.8%]
4	36.3	38.80 [6.9%]	37.13 [2.3%]
6	56.9	62.70 [10.2%]	59.51 [4.6%]
8	71.1	71.90 [1.1%]	69.76 [1.9%]
12	89.4	91.20 [2.0%]	89.90 [0.6%]

[0099] The dissolution of a sustained release formulation comprising 90 µg of 25-hydroxyvitamin D₃, 19.88 wt% hard paraffin, 10.00 wt% hydroxyl propyl methylcellulose, 22.55 wt% GMS, 9.76 wt% GELUCIRE 44/14, 2.36 wt % anhydrous ethanol, 35.17 wt% liquid paraffin, and 0.02 wt% BHT (Example Formulation B) was tested after 0 to 26 weeks of storage at room temperature. The results are summarized in the table below.

Dissolution Following Storage at Room Temperature / Ambient Humidity				
Dissolution Time (hours)	T=0	6 weeks % LC [% change]	13 weeks % LC [% change]	26 weeks % LC [% change]
2	30.15	25.40 [15.8%]	25.20 [16.4%]	21.10 [30.0%]
4	58.55	51.90 [11.4%]	51.80 [11.5%]	45.20 [22.8%]
6	72.1	74.40 [3.2%]	73.00 [1.2%]	67.63 [6.2%]
8	80.55	84.30 [4.7%]	84.50 [4.9%]	77.30 [4.0%]
12	91.8	94.10 [2.5%]	94.40 [2.8%]	91.16 [0.7%]

Example Formulation B demonstrated a substantially stable dissolution profile following storage for at least 26 weeks at room temperature.

[00100] The stability of stabilized formulations comprising 30 µg (Example Formulation C), 60 µg (Example Formulation D), or 90 µg (Example Formulation E) of 25-hydroxyvitamin D₃ was tested using storage conditions of 25 °C and 60% relative humidity and 40 °C and 75% relative humidity. The compositions of Example Formulations C to E are summarized in the table below:

Component	Amount
25-hydroxyvitamin D ₃	30 µg, 60 µg, or 90 µg
Paraffin Wax	20.00 wt%
Mineral Oil	35.36 wt%
Hydroxy propyl Methylcellulose K100M CR (METHOCEL)	10.00 wt%

Glycerol monostearate	22.55 wt%
Lauroyl macrogolglycerides and polyoxylglycerides (GELUCIRE 44/14)	9.75 wt%
Anhydrous Alcohol	2.32 wt%
BHT	0.02 wt%
Soft Capsule Shell (VEGICAPS)	

The formulations exhibited substantially stable dissolution profiles following storage at 25 °C and 60% relative humidity for at least 24 months (Figure 1). The dissolution results (%LC and %CV) are summarized in the table below.

Dissolution Following Storage at 25 °C/ 60% Relative Humidity								
Time (hours)	T=0 %LC (% CV)	1 month %LC (% CV)	3 mos. %LC (% CV)	6 mos. %LC (% CV)	9 mos. %LC (% CV)	12 mos. %LC (% CV)	18 mos. %LC (% CV)	24 mos. %LC (% CV)
30 µg 25-hydroxyvitamin D ₃ (Example Formulation C)								
2	10.1 (16.1)	12.9 (25.2)	14.0 (48.5)	9.6 (38.3)	10.5 (18.2)	13.5 (35.8)	10.6 (26.5)	7.0 (47.8)
4	43.6 (12.7)	48.8 (10.9)	45.9 (29.9)	36.8 (25)	37.2 (11.1)	50.2 (14.8)	39.3 (22.9)	39.6 (32.3)
6	83.1 (5.7)	73.4 (9.2)	72.4 (7.5)	71.4 (6.8)	66.7 (10.6)	70.6 (11.5)	70.1 (7.2)	69.3 (12.6)
8	96.4 (6.5)	89.6 (4.4)	88.4 (4.7)	88.4 (5.7)	85.2 (4.9)	85.4 (9)	84 (5.1)	85.7 (8.2)
12	115.8 (4.5)	104.2 (1.9)	105.6 (1.4)	106.1 (1.6)	101.5 (1.5)	100.8 (3.9)	100.2 (4.5)	103 (2.6)
60 µg 25-hydroxyvitamin D ₃ (Example Formulation D)								
2	17.5 (20)	16.3 (27.4)	16.1 (25.3)	17.7 (34.7)	11.2 (20.2)	14.3 (29.1)	16.1 (25.8)	12.4 (52.3)
4	53.6 (19.6)	55.1 (18.8)	53.8 (12.8)	55.3 (17.9)	43.7 (14)	51 (22.5)	52.9 (16.7)	41 (36.6)
6	83.9 (7.5)	78.7 (8.3)	79.9 (6.6)	78.4 (4.7)	72.2 (7.1)	75 (13)	72 (9.9)	64.7 (29.6)
8	99.2 (3.9)	94.3 (5.2)	97.2 (4.8)	92.5 (3.3)	87 (5.5)	88.9 (6.3)	84.9 (12.3)*	81.3 (21.7)
12	104.8 (3.3)	108.7 (1.8)	111.9 (1.1)	104.5 (0.5)	103.1 (0.8)	104.7 (1.4)	99.8 (4.6)*	101.7 (8)
90 µg 25-hydroxyvitamin D ₃ (Example Formulation E)								
2	14.9 (19.9)	14.9 (8.6)	13.3 (41.2)	13.5 (23.4)	14.3 (30.4)	15 (35.1)	9.5 (37.1)	8.5 (53.2)

4	49.9 (16.4)	46.9 (10.2)	52.4 (18.5)	49.7 (16.4)	45.9 (25.6)	51.8 (14)	36.8 (34.5)	34.4 (24.9)
6	89.4 (7.2)	71.4 (4.1)	81.1 (5.6)	74.2 (11.1)	71.6 (17.6)	77 (4.9)	64.4 (10.3)	64.5 (15.1)
8	101.7 (2.5)	84.9 (2.8)	96.1 (2.3)	90.8 (6.4)	89 (9.4)	91.6 (3.3)	77.4 (15.7)	83.6 (11.2)
12	103 (2.1)	99.3 (2.4)	110 (1.3)	104.4 (1.1)	100.5 (2.4)	104.6 (0.3)	96.8 (5)	102.8 (3.4)

* 4 replicates instead of 6

[00101] The percent change between the amount of 25-hydroxyvitamin D₃ released following aging compared to the initial amount released is summarized in the table below.

Time (h)	1 month % change	3 mos. % change	6 mos. % change	9 mos. % change	12 mos. % change	18 mos. % change	24 mos. % change
30 µg 25-hydroxyvitamin D ₃ (Example Formulation C)							
2	27.7%	38.6%	5.0%	4.0%	33.7%	5.0%	30.7%
4	11.9%	5.3%	15.6%	14.7%	15.1%	9.9%	9.2%
6	11.7%	12.9%	14.1%	19.7%	15.0%	15.6%	16.6%
8	7.1%	8.3%	8.3%	11.6%	11.4%	12.9%	11.1%
12	10.0%	8.8%	8.4%	12.3%	13.0%	13.5%	11.1%
60 µg 25-hydroxyvitamin D ₃ (Example Formulation D)							
2	6.9%	8.0%	1.1%	36.0%	18.3%	8.0%	29.1%
4	2.8%	0.4%	3.2%	18.5%	4.9%	1.3%	23.5%
6	6.2%	4.8%	6.6%	13.9%	10.6%	14.2%	22.9%
8	4.9%	2.0%	6.8%	12.3%	10.4%	14.4%	18.0%
12	3.7%	6.8%	0.3%	1.6%	0.1%	4.8%	3.0%
90 µg 25-hydroxyvitamin D ₃ (Example Formulation E)							
2	0.0%	10.7%	9.4%	4.0%	0.7%	36.2%	43.0%
4	6.0%	5.0%	0.4%	8.0%	3.8%	26.3%	31.1%
6	20.1%	9.3%	17.0%	19.9%	13.9%	28.0%	27.9%
8	16.5%	5.5%	10.7%	12.5%	9.9%	23.9%	17.8%
12	3.6%	6.8%	1.4%	2.4%	1.6%	6.0%	0.2%

[00102] Example Formulations C to E also exhibited substantially stable dissolution profiles following storage at 40 °C and 75% RH for at least 6 months (Figure 2). The dissolution results are summarized in the table below.

Dissolution Following Storage at 40 °C/ 75% Relative Humidity				
Time (hours)	Initial % LC	1 month % LC	3 months % LC	6 months % LC

	(%CV)	(%CV)	(%CV)	(%CV)
30 µg 25-hydroxyvitamin D ₃ (Example Formulation C)				
2	10.1 (16.1)	11.3 (54.3)	13.5 (53.8)	11.1 (14.8)
4	43.6 (12.7)	46 (27.1)	44.4 (23.9)	40.9 (13.9)
6	83.1 (5.7)	72.7 (9.7)	62.8 (20.4)	68.7 (7.3)
8	96.4 (6.5)	88.7 (5)	76.5 (12.5)	82.5 (4.1)
12	115.8 (4.5)	103.1 (0.9)	93.4 (7.6)	96.4 (2.8)
60 µg 25-hydroxyvitamin D ₃ (Example Formulation D)				
2	17.5 (20)	12.9 (40.7)	15.5 (37)	13.9 (40)
4	53.6 (19.6)	50.7 (18.5)	54.4 (12)	49.8 (16.3)
6	83.9 (7.5)	75.8 (9.7)	78.3 (10.6)	74.7 (8.1)
8	99.2 (3.9)	91.2 (7.9)	91.6 (9.1)	88.5 (6.5)
12	104.8 (3.3)	100.7 (5.1)	104.1 (6.5)	101.5 (2.3)
90 µg 25-hydroxyvitamin D ₃ (Example Formulation E)				
2	14.9 (19.9)	18.5 (32.5)	10.2 (44.6)	8.3 (34.7)
4	49.9 (16.4)	50.7 (12.8)	47 (14.6)	44.8 (10.6)
6	89.4 (7.2)	74.7 (8)	72.9 (5.2)	73 (3.4)
8	101.7 (2.5)	90.5 (5)	86.6 (4.8)	87.9 (3)
12	103 (2.1)	100.1 (1.4)	102.5 (1.6)	101.0 (1.9)

[00103] The percent change between the amount of 25-hydroxyvitamin D₃ released following exposure to storage conditions compared to the initial amount released is summarized in the table below.

Time (hours)	1 month % change	3 months % change	6 months % change
30 µg 25-hydroxyvitamin D ₃ (Example Formulation C)			
2	11.9%	33.7%	9.9%
4	5.5%	1.8%	6.2%
6	12.5%	24.4%	17.3%
8	8.0%	20.6%	14.4%

12	11.0%	19.3%	16.8%
60 µg 25-hydroxyvitamin D₃ (Example Formulation D)			
2	26.3%	11.4%	20.6%
4	5.4%	1.5%	7.1%
6	9.7%	6.7%	11.0%
8	8.1%	7.7%	10.8%
12	3.9%	0.7%	3.1%
90 µg 25-hydroxyvitamin D₃ (Example Formulation E)			
2	24.2%	31.5%	44.3%
4	1.6%	5.8%	10.2%
6	16.4%	18.5%	18.3%
8	11.0%	14.8%	13.6%
12	2.8%	0.5%	1.9%

[00104] The stability of Comparative Formulation 1, which does not contain a cellulosic compound, and Example Formulation E comprising hydroxyl propyl methylcellulose was evaluated following storage for 12 months at 25 °C and 60% relative humidity (Figure 3). The dissolution results are summarized in the table below.

Dissolution Following Storage at 25 °C/ 60% Relative Humidity				
Dissolution Time (hours)	Comparative Formulation 1		Example Formulation E	
	Initial % LC	12 months % LC	Initial % LC	12 months % LC
2	22.1	13.5	14.9	15.0
4	52.2	24.5	49.9	51.8
6	77.9	30.0	89.4	77.0
8	96.8	35.6	101.7	91.6

12	112.3	44.2	103.0	104.6
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[00105] The percent change between the amount of 25-hydroxyvitamin D₃ released following exposure to storage conditions compared to the initial amount released is summarized in the table below.

Dissolution Time (hours)	Comparative Formulation 1 % change from initial	Example Formulation E % change from initial
2	38.9%	0.7%
4	53.1%	3.8%
6	61.5%	13.9%
8	63.2%	9.9%
12	60.6%	1.6%

Example 3: *In vivo* Results for Unstabilized and Stabilized Controlled Release Formulations

[00106] *In vivo* studies were conducted to evaluate the clinical pharmacokinetics of unstabilized and stabilized controlled release formulations of 25-hydroxyvitamin D₃ in human subjects. In Study A, 28 subjects with stage 3 or stage 4 CKD, secondary hyperparathyroidism (stage 3: 70-1000 pg/mL iPTH; stage 4: 110-1000 pg/mL iPTH), and vitamin D insufficiency (serum total baseline 25-hydroxyvitamin D of 15 ng/mL to 29 ng/mL) received a single oral dose of a controlled release capsule comprising 450 µg or 900 µg of 25-hydroxyvitamin D₃, 20.00 wt% hard paraffin, 37.85 wt% GMS, 9.75 wt% GELUCIRE 44/14, 2.32 wt % anhydrous ethanol, 30.06 wt% mineral oil, and 0.02 wt% BHT (Comparative Formulation 3) or a single intravenous dose of 448 µg 25-hydroxyvitamin D₃ in an ethanol solution. None of the formulations comprised a cellulosic compound.

[00107] The serum concentration of 25-hydroxyvitamin D₃ increased gradually following the administration of an oral dose. The increase in 25-hydroxyvitamin D₃ was dose proportional and reached an approximate mean maximum observed serum concentration (C_{max}) of 32 ng/mL

following the administration of the 900 µg capsule. The time at which C_{max} occurred (T_{max}) was approximately 13 hours post-dose. In contrast, concentrations of 25-hydroxyvitamin D₃ increased rapidly following the administration of the i.v. dose. Peak serum levels were achieved immediately following administration of the i.v. dose (T_{max} = 0.5 hours) and reached an approximate mean C_{max} of 134 ng/mL. The bioavailability of the oral doses was approximately 6 to 11%. The terminal half-life (t_{1/2}) of 25-hydroxyvitamin D₃ following the administration of the oral dose was approximately 12 to 22 days. No adverse effects on serum calcium or phosphorous, or urine calcium were observed in any treatment group.

[00108] The mean serum total 1,25-dihydroxyvitamin D rose rapidly following the administration of the i.v. injection, increasing from pre-treatment baseline by approximately 13 pg/mL by 6 hours post-dose. In contrast, mean serum total 1,25-dihydroxyvitamin D increased dose proportionally and gradually by approximately 7 pg/mL by 48 hours post-dose following the administration of the 900 µg capsule.

[00109] Serum iPTH showed no meaningful change over the first 96 hours after the i.v. dose was administered. In contrast, serum PTH declined gradually following dosing, reaching a maximum suppression of approximately 20% from pretreatment baseline for subjects who received the 900 µg capsule. The observed pharmacokinetic parameters for all the treatment groups are summarized in the table below.

Parameter	450 µg po (N=9)			900 µg po (N=9)			448 µg iv (N=9)		
	n	Mean	(SD)	n	Mean	(SD)	n	Mean	(SD)
		Median			Median			Median	
		Range			Range			Range	
PK/PD Population									
Observed 25-hydroxyvitamin D ₃									
AUC _{0-42 days} (ng*h/mL)	9	13353.12 (10606.47) 12196.45 888.39, 32885.95		9	21563.95 (9165.53) 17940.11 9292.88, 38631.91		9	43463.51 (12589.57) 47115.66 23340.59, 63006.78	
AUC _{0-inf} (ng*h/mL)	9	13353.12 (10606.47) 12196.45 888.39, 32885.95		9	21563.95 (9165.53) 17940.11 9292.88, 38631.91		9	43463.51 (12589.57) 47115.66 23340.59, 63006.78	
AUC _{0-inf} (ng*h/mL)	9	81511.71 (103037.08) 54967.57 4927.95, 333366.90		9	122901.73 (114168.13) 79902.04 25729.84, 378935.59		9	137955.58 (66746.71) 123580.87 39282.49, 243322.76	
C _{max} (ng/mL)	9	25.18 (10.134) 20.52 15.35, 42.24		9	31.54 (15.765) 30.12 12.21, 67.01		9	133.99 (19.311) 133.68 91.71, 160.91	
C _{last} (ng/mL)	9	18.11 (7.846) 15.84 10.30, 29.80		9	19.08 (7.611) 21.37 7.30, 27.93		9	35.07 (12.330) 36.91 12.68, 53.39	
t _{max} (h)	9	13.11 (9.597) 10.00 6.00, 36.00		9	13.56 (9.989) 10.00 2.00, 30.00		9	0.49 (0.638) 0.25 0.083, 2.00	
λ _z (h ⁻¹)	9	0.0015 (0.0028) 0.0003 0.0001, 0.0087		9	0.0003 (0.0002) 0.0004 0.0001, 0.0005		9	0.0005 (0.0002) 0.0004 0.0002, 0.0008	
R ²	9	0.89 (0.130) 0.96 0.662, 1.000		9	0.90 (0.169) 0.99 0.523, 0.998		9	0.91 (0.090) 0.93 0.730, 1.000	
t _{1/2} (h)	9	2477.72 (2581.24) 2483.61 79.24, 8615.11		9	3228.63 (2734.74) 1937.32 1300.13, 9646.71		9	1775.86 (779.13) 1694.69 871.46, 3297.78	

V_d (L/ng)	9	49.42 (18.30) 50.93 23.20, 72.76	9	45.06 (19.38) 40.080 20.77, 87.51	9	20.35 (7.42) 19.550 13.04, 32.68
CL (L/ng*h)	9	0.0499 (0.0155) 0.0182 0.0030, 0.2029	9	0.0155 (0.0119) 0.0125 0.0026, 0.0389	9	0.0095 (0.0065) 0.0081 0.0041, 0.0255
F	NA	0.306 (NA) NA NA	NA	0.247 (NA) NA NA	NA	1.000 (NA) NA NA

[00110] The baseline-adjusted pharmacokinetic parameters for all the treatment groups are summarized in the table below.

Parameter	n	450 µg po (N=9)		n	900 µg po (N=9)		n	448 µg iv (N=9)	
		Mean	(SD)		Mean	(SD)		Mean	(SD)
		Median	Range		Median	Range		Median	Range
$AUC_{0-42 \text{ days}}$ (ng*h/mL)	9	1394.89 (1911.41) 605.42 48.87, 4956.68		8	4525.43 (3123.29) 4801.54 148.07, 8843.74		9	19609.07 (5319.01) 18764.48 11066.02, 28611.05	
AUC_{0-30d} (ng*h/mL)	9	1257.30 (2047.74) 48.87 -325.43, 4956.68		8	4274.27 (3488.40) 4801.54 -877.99, 8843.74		9	19609.07 (5319.01) 18764.48 11066.02, 28611.05	
AUC_{0-inf} (ng*h/mL)	6	3318.90 (4606.89) 547.25		8	6791.49 (5224.54) 6872.86		9	34543.75 (22103.97) 26962.25	

		50.78, 9878.03		285.04, 14979.17		16868.97, 89126.53
C_{max} (ng/mL)	9	6.90 (4.266)	8	14.17 (9.884)	9	110.33 (14.536)
		5.70		12.30		111.08
		2.93, 14.87		2.55, 35.59		76.63, 127.40
C_{min} (ng/mL)	9	2.36 (2.257)	8	2.64 (1.784)	9	11.40 (5.648)
		2.05		3.01		9.01
		0.16, 5.49		0.42, 5.40		5.84, 22.86
t_{max} (h)	9	13.11 (9.597)	8	15.00 (9.621)	9	0.49 (0.638)
		10.00		10.00		0.25
		6.00, 36.00		8.00, 30.00		0.083, 2.00
λ_z (h ⁻¹)	6	0.018 (0.359)	7	0.0020 (0.0013)	9	0.0011 (0.0005)
		0.0042		0.0016		0.0010
		0.0008, 0.0910		0.0008, 0.0037		0.0004, 0.0021
R^2	6	0.92 (0.101)	6	0.99 (0.020)	9	0.92 (0.086)
		0.96		0.99		0.95
		0.743, 0.999		0.948, 1.000		0.720, 0.999
$t_{1/2}$ (h)	6	307.86 (336.42)	6	522.96 (320.80)	9	745.86 (437.65)
		165.72		530.00		663.43
		7.61, 914.23		189.84, 879.31		337.37, 1834.71
V_d (L/ng)	6	340.42 (269.11)	6	82.92 (29.70)	9	32.94 (11.00)
		249.77		77.11		29.70
		80.51, 771.79		39.96, 127.06		24.28, 58.95
CL (L/ng*h)	6	4.588 (7.525)	6	0.141 (0.080)	9	0.036 (0.014)
		2.119		0.1200		0.037
		0.101, 19.692		0.0668, 0.2860		0.011, 0.059
F	NA	0.064 (NA)	NA	0.109 (NA)	NA	1.000 (NA)
		NA		NA		NA
		NA		NA		NA

[00111] In Study B, 20 healthy subjects with mean baseline serum 25-hydroxyvitamin D of about 24 ng/mL (range 11 ng/mL to 45 ng/mL) received a single oral dose of a stabilized controlled release capsule comprising 900 µg of 25-hydroxyvitamin D₃, 20.00 wt% hard paraffin, 10.00 wt% HPMC, 22.55 wt% GMS, 9.75 wt% GELUCIRE 44/14, 2.32 wt % anhydrous ethanol, 35.36 wt% mineral oil, and 0.02 wt% BHT (Example Formulation F) or a single intravenous dose of 448 µg 25-hydroxyvitamin D₃ in an ethanol solution.

[00112] The gradual increase in 25-hydroxyvitamin D₃ levels was demonstrated by the prolonged T_{max} following administration of the stabilized oral formulation compared to the i.v. dose. The pharmacokinetic profile following administration of the stabilized oral formulation

demonstrated a gradual increase in 25-hydroxyvitamin D₃ concentrations, with a mean T_{max} of 28 hours, while avoiding rapid increases in blood levels in the majority of subjects.

Administration of the i.v. dose resulted in a rapid increase in 25-hydroxyvitamin D₃ concentrations in all subjects. The avoidance of the rapid increase in 25-hydroxyvitamin D₃ levels was highlighted by the marked difference in the observed C_{max} between the treatment groups. The C_{max} following the oral dose was 58 ng/mL, compared to a C_{max} of 153 ng/mL following the i.v. dose.

[00113] The exposure to 25-hydroxyvitamin D₃ following administration of the controlled release capsule was approximately two-fold lower than following the i.v. dose despite the oral dose being approximately two-fold higher, resulting in a bioavailability of approximately 25%. The t_{1/2}, clearance (CL) and volume of distribution (Vd) appeared to be similar between treatment groups. The values for t_{1/2} and CL were consistent with the reported prolonged elimination of 25-hydroxyvitamin D₃. In addition, the Vd values suggested that 25-hydroxyvitamin D₃ was maintained in systemic circulation, likely highly bound to the DBP. The observed pharmacokinetic parameters for all the treatment groups are summarized in the table below.

Parameter	900 µg CTAP101 Capsules (N=10)	448 µg CTAP101 Injection (N=10)
AUC₀₋₄ (ng·h/mL)		
Mean (SD)	21545.20 (7054.02)	25274.44 (7206.93)
Median	19904.00	25810.85
Minimum, Maximum	10176.40, 35885.02	8434.02, 35382.55
AUC_{0-inf} (ng·h/mL)		
Mean (SD)	77945.13 (55896.15)	55234.52 (27268.64)
Median	58974.22	51247.29
Minimum, Maximum	19504.43, 194796.33	22979.18, 119865.38
C_{max} (ng/mL)		
Mean (SD)	57.657 (39.3810)	153.029 (20.8620)
Median	37.925	152.890
Minimum, Maximum	24.43, 146.86	125.94, 185.33
t_{max} (h)		
Mean (SD)	28.100 (27.4000)	0.272 (0.2910)
Median	21.000	0.167
Minimum, Maximum	4.00, 96.00	0.05, 1.00

$t_{1/2}$ (h)		
Mean (SD)	1389.40 (1144.48)	660.23 (415.82)
Median	1042.60	607.65
Minimum, Maximum	557.32, 4173.67	238.46, 1733.68
λ_z (h⁻¹)		
Mean (SD)	0.00072 (0.00036)	0.00136 (0.00071)
Median	0.00067	0.00115
Minimum, Maximum	0.00017, 0.00124	0.00040, 0.00291
CL (L/h)		
Mean (SD)	0.0064 (0.0027)	0.0098 (0.0046)
Median	0.0066	0.0087
Minimum, Maximum	0.0018, 0.0098	0.0037, 0.0195
Vd (L)		
Mean (SD)	9.27 (0.97)	7.50 (1.19)
Median	9.39	7.24
Minimum, Maximum	7.93, 10.49	6.02, 9.77
R²		
Mean (SD)	0.80 (0.24)	0.92 (0.075)
Median	0.88	0.94
Minimum, Maximum	0.25, 0.99	0.74, 1.0
F^a		
Mean	0.42 (0.14)	N/A
Median	0.39	N/A
Minimum, Maximum	0.20, 0.71	N/A

^aaverage of individual subjects' bioavailabilities

Abbreviations: N/A, not applicable

[00114] The baseline-adjusted pharmacokinetic parameters for all the treatment groups are summarized in the table below.

Parameter	900 µg CTAPI01 Capsules (N=10)	448 µg CTAPI01 Injection (N=10)
AUC₀₋₁₂ (ng·h/mL)		
Mean (SD)	6891.81 (6678.97)	13583.95 (3908.42)
Median	4360.23	14853.46
Minimum, Maximum	1017.88, 20340.68	5302.50, 17194.59
AUC₀₋₂₄ (ng·h/mL)		
Mean (SD)	9418.00 (9410.58)	17735.09 (5249.38)
Median	5420.04	18229.25
Minimum, Maximum	1179.07, 28031.64	9820.16, 25534.45
C_{max} (ng/mL)		
Mean (SD)	35.867 (39.3886)	133.653 (20.7925)
Median	14.910	133.785
Minimum, Maximum	6.50, 120.52	103.88, 166.34
t_{max} (h)		
Mean (SD)	28.100 (27.4001)	0.272 (0.2914)
Median	21.000	0.167
Minimum, Maximum	4.00, 96.00	0.05, 1.00
t_{1/2} (h)		
Mean (SD)	270.61 (215.00)	264.08 (82.23)
Median	194.00	269.57
Minimum, Maximum	107.90, 832.70	132.46, 382.99
λ_e (h⁻¹)		
Mean (SD)	0.00362 (0.00182)	0.00292 (0.00112)
Median	0.00363	0.00257
Minimum, Maximum	0.00083, 0.00624	0.00181, 0.00523
CL (L/h)		
Mean (SD)	0.027 (0.0063)	0.028 (0.0093)
Median	0.028	0.025
Minimum, Maximum	0.012, 0.033	0.018, 0.046
Vd (L)		
Mean (SD)	8.78 (3.08)	9.74 (2.02)
Median	8.08	9.47
Minimum, Maximum	5.06, 14.17	6.54, 13.27
R²		
Mean (SD)	0.83 (0.22)	0.92 (0.072)
Median	0.88	0.94
Minimum, Maximum	0.25, 1.0	0.74, 1.0
F²		
Mean (SD)	0.25 (0.24)	N/A

Median	0.16	N/A
Minimum, Maximum	0.057, 0.75	N/A

*average of individual subjects' bioavailabilities
Abbreviations: N/A, not applicable

[00115] The study demonstrated that the stabilized controlled release formulation modified the rate of absorption of 25-hydroxyvitamin D₃, yielding a more gradual increase in serum 25-hydroxyvitamin D₃ levels while maintaining the distribution and elimination characteristics. The stabilized formulation demonstrated improved pharmacokinetic parameters, such as increased T_{max}, AUC, and bioavailability, compared to the same dose of the unstabilized formulation in Study A.

[00116] In Study C, 78 subjects with stage 3 CKD (eGFR 25-70 mL/min/1.73m²), SHPT (>70 pg/mL plasma iPTH) and vitamin D insufficiency (serum total baseline 25-hydroxyvitamin D of 10 ng/mL to 29 ng/mL) received daily oral doses of stabilized controlled release formulations comprising 30 µg, 60 µg, or 90 µg of 25-hydroxyvitamin D₃, 20.00 wt% hard paraffin, 10.00 wt% HPMC, 22.55 wt% GMS, 9.75 wt% GELUCIRE 44/14, 2.32 wt % anhydrous ethanol, 35.36 wt% mineral oil, and 0.02 wt% BHT (Example Formulations C, D, and E from Example 2) or placebo for 6 weeks.

[00117] The mean baseline serum 25-hydroxyvitamin D₃ concentrations were comparable across treatment groups and ranged from approximately 16 to 20 ng/mL. Following treatment with 25-hydroxyvitamin D₃, mean levels of serum 25-hydroxyvitamin D₃ increased gradually and in a dose-proportional manner following repeated daily administration of 25-hydroxyvitamin D₃ and began to approach steady-state by 6 weeks (Figure 4). The mean baseline adjusted C_{max} values were approximately 28, 60 and 86 ng/mL for the groups administered 30 µg, 60 µg and 90 µg of 25-hydroxyvitamin D₃, respectively. Mean exposures to 25-hydroxyvitamin D₃, assessed as background adjusted AUC_{0-6 Weeks}, were dose proportional across dose groups. Following the last dose, mean serum 25-hydroxyvitamin D₃ levels declined slowly, but by the end of the study remained above baseline for all groups. Mean t_{1/2} was determined to be approximately between 25 to 50 days. The baseline-adjusted pharmacokinetic parameters for 25-hydroxyvitamin D₃ are summarized in the table below.

	Placebo	30 µg	60 µg	90 µg
Baseline (ng/mL)				
Mean (SD)	16.4 (8.2)	16.2 (7.3)	19.8 (8.7)	18.4 (9.8)

	Placebo	30 µg	60 µg	90 µg
Median	12.9	17.2	21.2	16.7
Minimum, Maximum	4.4, 30.4	5.0, 25.8	5.8, 32.5	6.7, 38.9
C_{max} (ng/mL)				
Mean (SD)	4.1 (3.5)	27.8 (8.2)	60.3 (19.0)	85.7 (26.9)
Median	3.1	28.1	60.8	76.0
Minimum, Maximum	0.6, 13.8	10.8, 43.4	30.3, 89.5	55.4, 146.4
AUC_{0-6 weeks} (ng·d/mL)				
Mean (SD)	45.9 (60.0)	709.2 (246.3)	1531.4 (374.8)	2134.3 (584.3)
Median	32.1	6843.0	1573.0	1963.8
Minimum, Maximum	-60.1, 222.3	307.8, 1249.0	712.7, 2221.8	1377.5, 3207.3
t_{max} (d)				
Mean (SD)	NA	37.8 (10.4)	41.1 (5.2)	42.6 (5.3)
Median	NA	42.50	43.0	43.0
Minimum, Maximum	NA	8.0, 44.0	29.0, 45.0	35.0, 57.0
t_{1/2} (d)				
Mean (SD)	NA	25.8 (16.3)	33.1 (9.3)	50.1 (51.0)
Median	NA	24.1	31.6	37.7
Minimum, Maximum	NA	5.2, 52.6	17.4, 52.3	23.2, 224.0

[00118] Mean baseline serum 1,25-dihydroxyvitamin D concentrations were comparable across treatment groups and increased gradually, similar to the effect on serum 25-hydroxyvitamin D₃ concentrations. Mean ± SD baseline-adjusted C_{max} values were higher in the 60 µg and 90 µg groups (18.4 ± 6.24 and 19.9 ± 14.30 ng/mL, respectively) compared to the placebo and 30 µg groups (5.7 ± 6.35 and 6.4 ± 7.66 ng/mL, respectively). Mean exposures to 1,25-dihydroxyvitamin D, assessed as baseline-adjusted AUC_{0-6 weeks}, were dose-proportional across the 25-hydroxyvitamin D₃ dose groups. The baseline-adjusted pharmacokinetic parameters for 1,25-dihydroxyvitamin D are summarized in the table below.

	Placebo N=23	30 µg N=12	60 µg N=16	90 µg N=14
Baseline (pg/mL)				
Mean (SD)	20.8 (10.11)	18.3 (7.53)	20.6 (7.62)	20.6 (7.29)
Median	17.0	17.0	18.0	21.0
Minimum, Maximum	7.0, 41.4	5.1, 30.7	8.2, 33.6	9.3, 34.5
C_{max} (pg/mL)				
Mean (SD)	7.6 (5.71)	6.4 (7.66)	18.4 (6.24)	19.9 (14.30)
Median	4.9	5.0	18.4	18.9
Minimum, Maximum	1.9, 22.6	-6.3, 21.0	7.3, 29.9	-11.6, 48.3
AUC_{0-6 weeks} (g·d/mL)				

	Placebo N=23	30 µg N=12	60 µg N=16	90 µg N=14
Mean (SD)	11.5 (112.97)	100.6 (185.38)	249.9 (198.83)	371.1 (290.81)
Median	16.2	23.0	298.7	352.2
Minimum, Maximum	-267.1, 219.8	-145.4, 452.3	-191.7, 563.6	-5.8, 1235.8
t_{max} (d)				
Mean (SD)	24.4 (15.55)	16.8 (16.09)	26.4 (11.52)	25.5 (13.88)
Median	23.0	12.0	23.0	23.00
Minimum, Maximum	2.0, 45.0	1.0, 44.0	8.0, 44.0	1.0, 44.0

[00119] The stabilized controlled release formulations of 25-hydroxyvitamin D₃ increased serum total 25-hydroxyvitamin D levels to ≥ 30 ng/mL in significantly greater number of subjects in all active groups compared to placebo. Similarly, the stabilized formulations significantly decreased mean plasma iPTH from baseline in all dose groups compared to placebo.

[00120] Daily administration of 25-hydroxyvitamin D₃ in a stabilized controlled release formulation increased mean serum total 25-hydroxyvitamin D in proportion to the dose administered. The lowest administered dose (30 µg) increased serum total 25-hydroxyvitamin D at end of treatment by 15.6 ± 1.7 (SE) ng/mL from pre-treatment baseline (21.7 ± 1.8 ng/mL) and the highest dose (90 µg) increased serum total 25-hydroxyvitamin D by 61.1 ± 6.1 ng/mL from 21.8 ± 1.2 ng/mL. In contrast, a decrease at end of treatment of 1.2 ± 0.7 ng/mL was observed in the combined placebo groups. Differences between the treatment and placebo groups were significant for all three dose levels studied ($p < 0.0001$). The mean serum 25-hydroxyvitamin D level in the 30 µg dose group at the end of treatment was 37.3 ± 1.8 ng/mL, (slightly higher than K/DOQI-specified minimum adequate level of 30 ng/mL), indicating that 30 µg was the minimum effective dose.

[00121] The percentage of treated subjects achieving serum total 25-hydroxyvitamin D levels of ≥ 30 ng/mL at end of treatment was 92.3%, 100.0% and 100.0% in the 30 µg, 60 µg and 90 µg dose groups compared with 0% in the placebo group. These differences in response rates between active and placebo treatment were all significant ($p < 0.001$).

[00122] Mean plasma iPTH decreased at end of treatment in proportion to the administered dose of 25-hydroxyvitamin D₃. The lowest administered dose (30 µg) decreased iPTH by 20.2 ± 5.8 (SE) % from pre-treatment baseline, and the highest dose (90 µg) decreased iPTH by $35.9 \pm$

4.2%. An increase of $17.2 \pm 7.8\%$ was observed at end of treatment in the combined placebo groups. Differences between groups receiving 25-hydroxyvitamin D₃ and placebo were significant for all three dose levels studied ($p < 0.005$) and they compared favorably with differences observed with longer treatment in placebo-controlled studies with the more potent and calcemic oral vitamin D hormone replacement therapies (e.g., doxercalciferol, paricalcitol and calcitriol).

[00123] Percentages of subjects receiving 25-hydroxyvitamin D₃ who achieved confirmed reductions (i.e., two consecutive measurements) in iPTH of at least 20% or 30% from pre-treatment baseline at EOT increased with dose through 60 µg. Similar response rates were observed in the 60 and 90 µg treatment groups, indicating that no further benefit in iPTH lowering was observed in this study for the 90 µg dose. Response rates for a confirmed 20% reduction in iPTH were 38.5%, 70.6% and 76.5% for the 30 µg, 60 µg and 90 µg dose groups respectively compared with 9.7% in the combined placebo group. Differences in the observed response rates for a 20% reduction were significant only for the 60 µg and 90 µg dose groups ($p < 0.005$) and for a 30% reduction were significant in all three dose groups ($p < 0.05$). The data supported the conclusion that 30 µg per day of 25-hydroxyvitamin D₃ in a stabilized controlled release formulation is the minimum effective dose.

[00124] The stabilized formulations of 25-hydroxyvitamin D₃ had no clinically significant effect on corrected albumin-corrected serum calcium, serum phosphorus and urinary calcium excretion. There were no adverse effects on serum calcium or serum phosphorus or urine calcium during the 6-week treatment period.

[00125] Pharmacokinetic analyses revealed that the stabilized formulations of 25-hydroxyvitamin D₃ increased 25-hydroxyvitamin D₃ exposure over 6 weeks (AUC and C_{max}) in a dose proportional manner across the three dose groups with no difference in t_{1/2}. Following 6 weeks of administration, the three treatment groups had not quite reached steady state. However, steady state modeling demonstrated that steady state would have been achieved by 7-9 weeks in all dose groups.

[00126] Data from this study clearly demonstrated that stabilized controlled release formulations of 25-hydroxyvitamin D₃ were effective in elevating serum total 25-hydroxyvitamin D to the minimum adequate level of 30 ng/mL and lowering plasma iPTH. The

study also showed that stabilized formulations of 25-hydroxyvitamin D₃ had no clinically meaningful impact on serum calcium or phosphorous at the doses investigated.

[00127] *Example 4: Pharmacokinetic and Pharmacodynamic Profile of Modified-Release Calcifediol in CKD Subjects with Secondary Hyperparathyroidism and Vitamin D Insufficiency*

[00128] A multi-center, randomized, double blind, placebo-controlled, repeat dose, safety, efficacy and PK/PD study of stabilized, sustained release 25-hydroxyvitamin D₃ (calcifediol, 25D₃) capsules was conducted in 2 cohorts of subjects. Male and female subjects aged 18 to 85 years with stage 3 CKD (eGFR of 25-70 mL/min/1.73m²), vitamin D insufficiency (serum 25-hydroxyvitamin D ≥ 10 and ≤ 29 ng/mL), SHPT (plasma iPTH > 70 pg/mL) and not requiring regular hemodialysis, were recruited for this study. Eligible subjects in the first cohort were randomized into 3 treatment groups in a 1:1:1 ratio: 2 groups received the capsules at daily oral doses of 60 or 90 μ g, respectively, and 1 group received a matching placebo capsule. Subjects in cohort 2 were randomized into 2 treatment groups in a 1:1 ratio: 1 group received 30 μ g capsules daily and the other received placebo. Subjects in each cohort completed 6 weeks of treatment and entered a 6 week follow-up period, during which PK and PD samples were collected weekly. Serum calcium (Ca), phosphorus (P), 25D₃, total 1,25-dihydroxyvitamin D (1,25D) and plasma iPTH were monitored weekly during 6 weeks of treatment and 6 weeks of follow-up. ANCOVA models examined the association of 25D₃ exposure with change from baseline for 1,25D and iPTH. Covariates included were baseline eGFR, body weight and height, gender, age, race, diabetic status, and baseline concentration of 1,25D or iPTH.

[00129] Figure 4 shows the resulting mean baseline-adjusted calcifediol concentrations by treatment group (PK population). Mean levels of serum calcifediol increased gradually and in a dose-proportional manner and began to approach steady-state by 6 weeks. After 6 weeks of follow-up, levels decreased but remained above baseline in all active-treated groups.

[00130] Figure 5 shows the resulting summary baseline-adjusted PK parameters for calcifediol concentrations by treatment group (PK population).

[00131] Figure 6 shows the resulting mean baseline-adjusted serum 1,25-dihydroxyvitamin D levels during the 6-week treatment (PK population). Mean baseline-adjusted serum total 1,25

dihydroxyvitamin D levels increased over time in those subjects administered the active capsules, compared to those subjects administered placebo.

[00132] Figure 7 shows a summary of the resulting baseline-adjusted repeat-dose PK parameters for serum 1,25-dihydroxyvitamin D by treatment group (PK population).

[00133] Figure 8 shows the resulting mean percent of baseline in plasma iPTH levels during the 6-week treatment (PK population). The active capsules significantly decreased mean plasma iPTH from baseline by 21%, 33% and 39% in all dose groups (30, 60 and 90 μ g, respectively) compared to a 17% increase in the combined placebo group.

[00134] Figure 9 shows a summary of the resulting baseline-adjusted repeat-dose PK parameters for plasma iPTH by treatment group (PK population).

[00135] Figures 10 and 11 show the percent change from baseline at EOT for plasma iPTH relative to baseline-adjusted calcifediol and 1,25-dihydroxyvitamin D exposure (AUC_{0-6wk}) in the PK Population. Percent reductions in plasma iPTH from baseline to EOT increased as serum calcifediol and total 1,25 dihydroxyvitamin D exposures during treatment (expressed as baseline-adjusted AUC_{0-6wk}) increased.

[00136] The stabilized, sustained release 25-hydroxyvitamin D₃ capsules normalized 25D levels in the majority of subjects and significantly reduced iPTH in all dose groups (30, 60 and 90 μ g). The stabilized, sustained release 25-hydroxyvitamin D₃ capsules increased serum 25D₃ and serum 1,25D levels gradually with dose-dependent increases in exposure. Both 25D₃ and total 1,25D exposure were significantly and inversely associated with change from baseline for plasma iPTH. Only eGFR was a significant covariate in both models. These findings demonstrate that the stabilized, sustained release 25-hydroxyvitamin D₃ capsules reliably normalized 25D levels, increased serum 1,25D levels and suppressed elevated plasma iPTH without clinically meaningful effects on serum Ca and P at the doses investigated.

[00137] The foregoing description is given for clearness of understanding only, and no unnecessary limitations should be understood therefrom, as modifications within the scope of the invention may be apparent to those having ordinary skill in the art.

[00138] Throughout this specification and the claims which follow, unless the context requires otherwise, the word “comprise” and variations such as “comprises” and “comprising” will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

[00139] Throughout the specification, where compositions are described as including components or materials, it is contemplated that the compositions can also consist essentially of, or consist of, any combination of the recited components or materials, unless described otherwise. Likewise, where methods are described as including particular steps, it is contemplated that the methods can also consist essentially of, or consist of, any combination of the recited steps, unless described otherwise. The invention illustratively disclosed herein suitably may be practiced in the absence of any element or step which is not specifically disclosed herein.

[00140] The practice of a method disclosed herein, and individual steps thereof, can be performed manually and/or with the aid of electronic equipment. Although processes have been described with reference to particular embodiments, a person of ordinary skill in the art will readily appreciate that other ways of performing the acts associated with the methods may be used. For example, the order of various of the steps may be changed without departing from the scope or spirit of the method, unless described otherwise. In addition, some of the individual steps can be combined, omitted, or further subdivided into additional steps.

[00141] All patents, publications and references cited herein are hereby fully incorporated by reference. In case of conflict between the present disclosure and incorporated patents, publications and references, the present disclosure should control.

[00142] Embodiments contemplated in view of the foregoing description include those described in the following numbered paragraphs.

[00143] 1. A controlled release formulation of a vitamin D compound comprising one or both of 25-hydroxyvitamin D₂ and 25-hydroxyvitamin D₃, the formulation comprising a matrix that releasably binds and controllably releases the vitamin D compound, the matrix comprising a cellulose derivative.

[00144] 2. A stabilized formulation for controlled release of a vitamin D compound in the gastrointestinal tract of a subject which ingests the formulation, the formulation comprising a mixture of:

one or both of 25-hydroxyvitamin D₂ and 25-hydroxyvitamin D₃;

and an effective amount of a stabilizing agent, which is optionally a cellulosic compound, to maintain a difference of less than 30% between the amount of vitamin D compound released at any given time point after four hours during *in vitro* dissolution after two months exposure to storage conditions of 25 °C and 60% relative humidity and the amount released at the same dissolution time point during *in vitro* dissolution conducted prior to exposing the formulation to the storage conditions.

[00145] 3. A stabilized formulation for controlled release of a vitamin D compound, said formulation comprising a mixture of:

one or both of 25-hydroxyvitamin D₂ and 25-hydroxyvitamin D₃;

a wax matrix; and

a stabilizing agent, which is optionally a cellulosic compound.

[00146] 4. A stabilized formulation for controlled release of a vitamin D compound in the gastrointestinal tract of a subject which ingests the formulation, said formulation comprising a mixture of:

one or both of 25-hydroxyvitamin D₂ and 25-hydroxyvitamin D₃;

a wax matrix; and

a stabilizing agent, which is optionally a cellulosic stabilizing agent.

[00147] 5. A stabilized formulation for controlled release of a vitamin D, said formulation comprising a mixture of:

one or both of 25-hydroxyvitamin D₂ and 25-hydroxyvitamin D₃;

a wax matrix; and

an effective amount of a stabilizing agent, optionally a cellulosic compound, to maintain a difference of less than 30% between the amount of vitamin D compound released at any given time point after four hours during *in vitro* dissolution testing after exposure for two months to

storage conditions of 25 °C and 60% relative humidity and the amount released at the same dissolution time point during *in vitro* dissolution conducted prior to exposing the formulation to the storage conditions.

[00148] 6. A stabilized formulation for controlled release of a vitamin D compound in the gastrointestinal tract of a subject which ingests the formulation, said formulation comprising a mixture of:

an active-loaded wax matrix comprising one or both of 25-hydroxyvitamin D₂ and 25-hydroxyvitamin D₃; and

a cellulosic stabilizing agent;

wherein the formulation releases an amount of 25-hydroxyvitamin D during *in vitro* dissolution after two months exposure to storage of 25 °C and 60% relative humidity that varies at any given dissolution time point compared to the amount released at the same dissolution time point during *in vitro* dissolution conducted prior to exposing the formulation to the storage conditions by 30% or less in the absence of the cellulosic stabilizing agent.

[00149] 7. In a formulation for controlled release of a vitamin D compound in the gastrointestinal tract of a subject which ingests the formulation, the improvement comprising admixing a cellulosic stabilizing agent into the formulation.

[00150] 8. In a formulation for controlled release of a vitamin D compound in the gastrointestinal tract of a subject which ingests the formulation, the improvement comprising an effective amount of a cellulosic compound admixed in the formulation to maintain a change of less than 30% in the amount of 25-hydroxyvitamin D released during *in vitro* dissolution after exposure to storage conditions of at least one month at 25 °C and 60% relative humidity at any given dissolution time point after four hours compared to the amount released at the same dissolution time point during *in vitro* dissolution conducted prior to exposing the formulation to the storage conditions.

[00151] 9. The formulation according to any of the preceding paragraphs, wherein the cellulosic compound or cellulosic stabilizing agent comprises a cellulose ether.

[00152] 10. The formulation according to paragraph 9, wherein the cellulose ether is selected from the group consisting of methylcellulose, hydroxyl propyl methylcellulose, hydroxyl ethyl methylcellulose, hydroxyl ethyl cellulose, and hydroxyl propyl cellulose.

[00153] 11. The formulation according to paragraph 9, wherein the cellulosic compound or cellulosic stabilizing agent is hydroxyl propyl methylcellulose.

[00154] 12. The formulation according to any of the preceding paragraphs, wherein the formulation releases an amount of 25-hydroxyvitamin D during *in vitro* dissolution after exposure to storage conditions for 2 months at 25 °C and 60% relative humidity that varies at any given dissolution time point after four hours compared to the amount released at the same dissolution time point during *in vitro* dissolution conducted prior to exposing the formulation to the storage conditions, by 30% or less.

[00155] 13. The formulation according to any of the preceding paragraphs, wherein the formulation releases an amount of 25-hydroxyvitamin D during *in vitro* dissolution after exposure to storage conditions for one month at 40 °C and 75% relative humidity that varies at any given dissolution time point after four hours compared to the amount released at the same dissolution time point during *in vitro* dissolution conducted prior to exposing the formulation to the storage conditions, by 30% or less.

[00156] 14. The formulation according to any one of the preceding paragraphs, wherein the matrix comprises a wax matrix comprising a controlled release agent, an emulsifier, and an absorption enhancer.

[00157] 15. The formulation according to paragraph 14, wherein the controlled release agent comprises paraffin.

[00158] 16. The formulation according to paragraph 14 or 15, wherein the emulsifier has a HLB value less than 7.

[00159] 17. The formulation according to paragraph 16, wherein the emulsifier comprises glycerol monostearate.

[00160] 18. The formulation according to any one of paragraphs 14 to 17, wherein the absorption enhancer has a HLB value in a range of about 13 to about 18.

- [00161] 19. The formulation according to paragraph 18, wherein the absorption enhancer is a mixture of lauroyl macrogolglycerides and lauroyl polyoxylglycerides.
- [00162] 20. The formulation according to any of the preceding paragraphs, wherein the vitamin D compound comprises 25-hydroxyvitamin D₃.
- [00163] 21. The formulation according to any of the preceding paragraphs, further comprising an oily vehicle.
- [00164] 22. The formulation according to paragraph 21, wherein the oily vehicle comprises mineral oil.
- [00165] 23. The formulation according to paragraph 22, wherein the formulation comprises about 20 wt% paraffin, about 20 wt% to about 25 wt% glycerol monostearate, about 10 wt% a mixture of lauroyl macrogolglycerides and lauroyl polyoxylglycerides, about 30 wt% to about 35 wt% mineral oil, and about 10 wt% to about 15 wt% hydroxyl propyl methylcellulose.
- [00166] 24. A formulation according to any one of the preceding paragraphs, wherein the formulation comprises glycerol monostearate.
- [00167] 25. A formulation according to any one of the preceding paragraphs, wherein the formulation comprises one or more polyglycolized glycerides.
- [00168] 26. A sustained release dosage form in the form of a capsule, tablet, sachet, dragee, or suppository comprising a formulation according to any one of the preceding paragraphs.
- [00169] 27. The dosage form according to paragraph 26, comprising a capsule or tablet.
- [00170] 28. The dosage form according to paragraph 27, comprising a capsule.
- [00171] 29. The dosage form according to paragraph 26, comprising an oral capsule, tablet, sachet, dragee.
- [00172] 30. A stabilized dosage form according to any one of the preceding paragraphs characterized by a dissolution profile providing a release of vitamin D compound of
- less than 30% at 2 hours;
 - greater than 45% at 6 hours; and
 - greater than 80% at 12 hours.

[00173] 31. The stabilized dosage form according to paragraph 26, wherein the release of vitamin D compound at 6 hours is less than 60%.

[00174] 32. A stabilized sustained release oral dosage form comprising a vitamin D compound characterized by an in vitro dissolution profile providing release of vitamin D compound of

less than 30% at 100 to 140 minutes;

greater than 45% at 5 to 7 hours; and

greater than 80% at 11 to 13 hours.

[00175] 33. The dosage form of paragraph 32, wherein the release of vitamin D compound is

less than 30% at 2 hours;

greater than 45% at 6 hours; and

greater than 80% at 12 hours.

[00176] 34. The dosage form according to paragraph 32 or 33, wherein the release of vitamin D compound at 5 to 7 hours is less than 60%.

[00177] 35. The dosage form according to paragraph 34, wherein the release of vitamin D compound at 6 hours is less than 60%.

[00178] 36. A stabilized sustained release oral dosage form comprising a vitamin D compound characterized by an in vitro dissolution profile providing release of vitamin D compound of

about 20% to about 40% at 2 hours;

at least 35% at 6 hours; and

at least 70% at 12 hours.

[00179] 37. The dosage form of paragraph 36, wherein the release of vitamin D compound is about 25% to about 35% at 2 hours;

at least 40% at 6 hours; and

at least 75% at 12 hours.

- [00180] 38. The dosage form of paragraph 36 or 37, wherein the release of vitamin D compound is 75% or less at 6 hours.
- [00181] 39. The dosage form of paragraph 38, wherein the release of vitamin D compound is 65% or less at 6 hours.
- [00182] 40. The dosage form of paragraph 39, wherein the release of vitamin D compound is 60% or less at 6 hours.
- [00183] 41. A stabilized sustained release dosage form comprising a vitamin D compound characterized by a $t_{\max}$ following administration of the dosage form to a human patient, of at least 4 hours.
- [00184] 42. The dosage form of paragraph 41, wherein the $t_{\max}$ is at least 8 hours.
- [00185] 43. The dosage form of paragraph 42, wherein the $t_{\max}$ is at least 12 hours.
- [00186] 44. The dosage form of paragraph 43, wherein the $t_{\max}$ is at least 18 hours.
- [00187] 45. The dosage form of paragraph 44, wherein the $t_{\max}$ is at least 20 hours.
- [00188] 46. The dosage form of paragraph 45, wherein the $t_{\max}$ is at least 24 hours.
- [00189] 47. The dosage form of paragraph 46, wherein the $t_{\max}$ is at least 28 hours.
- [00190] 48. The dosage form of paragraph 41, wherein the $t_{\max}$ is in a range of 4 to 96 hours.
- [00191] 49. The dosage form of paragraph 48, wherein the $t_{\max}$ is in a range of 18 to 30 hours.
- [00192] 50. The dosage form of paragraph 49, wherein the $t_{\max}$ is in a range of 13 to 28 hours.
- [00193] 51. The dosage form of paragraph 50, wherein the $t_{\max}$ is about 28 hours.
- [00194] 52. A stabilized sustained release dosage form comprising a 25-hydroxyvitamin D compound, the dosage form characterized by providing a baseline-adjusted $C_{\max}$ per microgram of 25-hydroxyvitamin D in a range of about 0.0133 ng/mL to about 0.04 ng/mL when administered to an adult human.
- [00195] 53. A method of administering a stabilized sustained release dosage form comprising a 25-hydroxyvitamin D compound to a human patient, comprising administering an effective amount of the dosage form to the patient to provide a baseline-adjusted $C_{\max}$ of at least about 0.2 ng/mL and less than 110 ng/mL.

[00196] 54. The method of paragraph 53, comprising administering an effective amount of the dosage form to provide a baseline-adjusted C_{max} in a range of about 0.2 to about 24 ng/mL.

[00197] 55. A method of administering a stabilized sustained release dosage form comprising a 25-hydroxyvitamin D compound to a human patient, comprising administering an effective amount of the dosage form to the patient to provide a baseline-adjusted AUC_{0-inf} of at least 52 ng*h/mL and less than 34500 ng*h/mL.

[00198] 56. The method of paragraph 55, comprising administering an effective amount of the dosage form to the patient to provide a baseline-adjusted AUC_{0-inf} in a range of about 52 ng*h/mL to about 12,000 ng*h/mL.

[00199] 57. A method of vitamin D supplementation comprising administering to a subject in need thereof a formulation or dosage form according to any one of the preceding paragraphs.

[00200] 58. A method of treatment or prophylaxis of a vitamin-D responsive disease in a subject comprising administering to the subject a formulation or dosage form according to any one of the preceding paragraphs.

[00201] 59. The method of paragraph 58, wherein the disease is selected from cancer (e.g., breast, lung, skin, melanoma, colon, colorectal, rectal, prostate and bone cancer), autoimmune diseases, for example, type I diabetes, multiple sclerosis, rheumatoid arthritis, polymyositis, dermatomyositis, scleroderma, fibrosis, Grave's disease, Hashimoto's disease, acute or chronic transplant rejection, acute or chronic graft versus host disease, inflammatory bowel disease, Crohn's disease, systemic lupus erythematosus, Sjogren's Syndrome, eczema and psoriasis, dermatitis, including atopic dermatitis, contact dermatitis, allergic dermatitis and/or chronic dermatitis, inflammatory diseases, for example, asthma, chronic obstructive pulmonary disease, polycystic kidney disease, polycystic ovary syndrome, pancreatitis, nephritis, hepatitis, and/or infection, hypertension, cardiovascular diseases, for example, subjects with atherosclerosis, arteriosclerosis, coronary artery disease, cerebrovascular disease, peripheral vascular disease, myocardial infarction, myocardial ischemia, cerebral ischemia, stroke, congestive heart failure, cardiomyopathy, obesity or other weight disorders, lipid disorders (e.g. hyperlipidemia, dyslipidemia including associated diabetic dyslipidemia and mixed dyslipidemia hypoalphalipoproteinemia, hypertriglyceridemia, hypercholesterolemia, and low HDL (high density lipoprotein)), metabolic disorders (e.g. Metabolic Syndrome, Type II diabetes mellitus,

Type I diabetes mellitus, hyperinsulinemia, impaired glucose tolerance, insulin resistance, diabetic complication including neuropathy, nephropathy, osteoporosis, retinopathy, diabetic foot ulcer and cataracts), and/or thrombosis.

[00202] 60. The method of paragraph 59, wherein the disease is selected from (i) in the parathyroid-- hypoparathyroidism, Pseudohypo-parathyroidism, secondary hyperparathyroidism; (ii) in the pancreas--diabetes; (iii) in the thyroid--medullary carcinoma; (iv) in the skin--psoriasis; wound healing; (v) in the lung--sarcoidosis and tuberculosis; (vi) in the kidney--chronic kidney disease, hypophosphatemic VDDR, vitamin D dependent rickets; (vii) in the bone--anticonvulsant treatment, fibrogenesis imperfecta ossium, osteitis fibrosa cystica, osteomalacia, osteoporosis, osteopenia, osteosclerosis, renal osteodystrophy, rickets; (viii) in the intestine--glucocorticoid antagonism, idiopathic hypercalcemia, malabsorption syndrome, steatorrhea, tropical sprue; and (ix) autoimmune disorders.

[00203] 61. The method of paragraph 60, wherein the disease is selected from cancer, dermatological disorders (for example psoriasis), parathyroid disorders (for example hyperparathyroidism and secondary hyperparathyroidism), bone disorders (for example osteoporosis) and autoimmune disorders.

[00204] 62. The method of paragraph 61, wherein the disease is secondary hyperparathyroidism.

[00205] 63. The method of paragraph 62, wherein the subject has chronic kidney disease (CKD).

[00206] 64. The method of paragraph 63, wherein the CKD is Stage 3 or 4.

[00207] 65. The method of paragraph 64, wherein the patient is vitamin-D deficient.

[00208] 66. The method of any one of the preceding paragraphs, wherein the patient is human.

[00209] 67. The method of paragraph 66, wherein the human is an adult human.

[00210] 68. A composition as substantially herein described.

WHAT IS CLAIMED:

1. A controlled release formulation of a vitamin D compound comprising one or both of 25-hydroxyvitamin D₂ and 25-hydroxyvitamin D₃, the formulation comprising a matrix that releasably binds and controllably releases the vitamin D compound, the matrix comprising a cellulose derivative.

2. A stabilized formulation for controlled release of a vitamin D compound, said formulation comprising a mixture of:

one or both of 25-hydroxyvitamin D₂ and 25-hydroxyvitamin D₃;

a wax matrix; and

a stabilizing agent, which is optionally a cellulosic compound.

3. The formulation of claim 1 or 2, wherein the formulation is an oral formulation for controlled release of the vitamin D compound in the gastrointestinal tract of a subject which ingests the formulation.

4. The formulation of any one of the preceding claims, said formulation comprising a mixture of:

one or both of 25-hydroxyvitamin D₂ and 25-hydroxyvitamin D₃;

a wax matrix; and

an effective amount of a stabilizing agent, optionally a cellulosic compound, to maintain a difference of less than 30% between the amount of vitamin D compound released at any given time point after four hours during *in vitro* dissolution testing after exposure for two months to storage conditions of 25 °C and 60% relative humidity and the amount released at the same dissolution time point during *in vitro* dissolution conducted prior to exposing the formulation to the storage conditions.

5. The formulation of any one of the preceding claims, said formulation comprising:

an active-loaded wax matrix comprising one or both of 25-hydroxyvitamin D₂ and 25-hydroxyvitamin D₃; and

a cellulosic stabilizing agent;

wherein the formulation releases an amount of 25-hydroxyvitamin D during *in vitro* dissolution after two months exposure to storage of 25 °C and 60% relative humidity that varies at any given dissolution time point compared to the amount released at the same dissolution time point during *in vitro* dissolution conducted prior to exposing the formulation to the storage conditions by 30% or less in the absence of the cellulosic stabilizing agent.

6. The formulation according to any one of the preceding claims, wherein the cellulosic compound or cellulosic stabilizing agent comprises a cellulose ether.

7. The formulation according to claim 6, wherein the cellulose ether is selected from the group consisting of methylcellulose, hydroxyl propyl methylcellulose, hydroxyl ethyl methylcellulose, hydroxyl ethyl cellulose, and hydroxyl propyl cellulose.

8. The formulation according to claim 6, wherein the cellulosic compound or cellulosic stabilizing agent comprises hydroxyl propyl methylcellulose.

9. The formulation according to any one of the preceding claims, wherein the formulation releases an amount of 25-hydroxyvitamin D during *in vitro* dissolution after exposure to storage conditions for one month at 40 °C and 75% relative humidity that varies at any given dissolution time point after four hours compared to the amount released at the same dissolution time point during *in vitro* dissolution conducted prior to exposing the formulation to the storage conditions, by 30% or less.

10. The formulation according to any one of the preceding claims, wherein the matrix comprises a wax matrix comprising a controlled release agent, an emulsifier, and an absorption enhancer.

11. The formulation according to claim 10, wherein the controlled release agent comprises paraffin.

12. The formulation according to claim 10 or 11, wherein the emulsifier has a HLB value less than 7.
13. The formulation according to claim 12, wherein the emulsifier comprises glycerol monostearate.
14. The formulation according to any one of claims 10 to 13, wherein the absorption enhancer has a HLB value in a range of about 13 to about 18.
15. The formulation according to claim 14, wherein the absorption enhancer is a mixture of lauroyl macrogolglycerides and lauroyl polyoxylglycerides.
16. The formulation according to any one of claims 10-15, further comprising an oily vehicle.
17. The formulation according to claim 16, wherein the oily vehicle comprises mineral oil.
18. The formulation according to claim 17, wherein the formulation comprises about 20 wt% paraffin, about 20 wt% to about 25 wt% glycerol monostearate, about 10 wt% a mixture of lauroyl macrogolglycerides and lauroyl polyoxylglycerides, about 30 wt% to about 35 wt% mineral oil, and about 10 wt% to about 15 wt% hydroxyl propyl methylcellulose.
19. A formulation according to any one of claims 10-18 wherein the formulation comprises glycerol monostearate.
20. A formulation according to any one of claims 10-19, wherein the formulation comprises one or more polyglycolized glycerides.
21. A sustained release dosage form in the form of a capsule, tablet, sachet, dragee, or suppository comprising a formulation according to any one of the preceding claims.
22. The dosage form according to claim 21, comprising a capsule or tablet.
23. The dosage form according to claim 22, comprising a capsule.

24. The dosage form according to claim 21, comprising an oral capsule, tablet, sachet, or dragee.

25. A formulation or stabilized dosage form according to any one of the preceding claims characterized by a dissolution profile providing a release of vitamin D compound of

less than 30% at 2 hours;

greater than 45% at 6 hours; and

greater than 80% at 12 hours.

26. The formulation or stabilized dosage form according to claim 25, wherein the release of vitamin D compound at 6 hours is less than 60%.

27. A formulation or stabilized sustained release oral dosage form according to any one of claims 1 to 24, characterized by an *in vitro* dissolution profile providing release of vitamin D compound of

less than 30% at 100 to 140 minutes;

greater than 45% at 5 to 7 hours; and

greater than 80% at 11 to 13 hours.

28. The formulation or dosage form of claim 27, wherein the release of vitamin D compound is

less than 30% at 2 hours;

greater than 45% at 6 hours; and

greater than 80% at 12 hours.

29. The formulation or dosage form according to claim 27 or 28, wherein the release of vitamin D compound at 5 to 7 hours is less than 60%.

30. The formulation or dosage form according to claim 29, wherein the release of vitamin D compound at 6 hours is less than 60%.

31. A formulation or stabilized sustained release oral dosage form according to any one of claims 1 to 24, characterized by an *in vitro* dissolution profile providing release of vitamin D compound of

about 20% to about 40% at 2 hours;

at least 35% at 6 hours; and

at least 70% at 12 hours.

32. The formulation or dosage form of claim 31, wherein the release of vitamin D compound is about 25% to about 35% at 2 hours;

at least 40% at 6 hours; and

at least 75% at 12 hours.

33. The formulation or dosage form of claim 31 or 32, wherein the release of vitamin D compound is 75% or less at 6 hours.

34. The formulation or dosage form of claim 33, wherein the release of vitamin D compound is 65% or less at 6 hours.

35. The formulation or dosage form of claim 34, wherein the release of vitamin D compound is 60% or less at 6 hours.

36. A formulation or stabilized sustained release dosage form according to any one of the preceding claims characterized by a $t_{\max}$ following administration of the dosage form to a human patient, of at least 4 hours.

37. The formulation or dosage form of claim 36, wherein the $t_{\max}$ is at least 8 hours.

38. The formulation or dosage form of claim 37, wherein the $t_{\max}$ is at least 12 hours.

39. The formulation or dosage form of claim 38, wherein the $t_{\max}$ is at least 18 hours.
40. The formulation or dosage form of claim 39, wherein the $t_{\max}$ is at least 20 hours.
41. The formulation or dosage form of claim 40, wherein the $t_{\max}$ is at least 24 hours.
42. The formulation or dosage form of claim 41, wherein the $t_{\max}$ is at least 28 hours.
43. The formulation or dosage form of claim 36, wherein the $t_{\max}$ is in a range of 4 to 96 hours.
44. The formulation or dosage form of claim 43, wherein the $t_{\max}$ is in a range of 18 to 30 hours.
45. The formulation or dosage form of claim 44, wherein the $t_{\max}$ is in a range of 13 to 28 hours.
46. The formulation or dosage form of claim 45, wherein the $t_{\max}$ is about 28 hours.
47. A formulation or stabilized sustained release dosage form comprising a 25-hydroxyvitamin D compound, the dosage form characterized by providing a baseline-adjusted $C_{\max}$ per microgram of 25-hydroxyvitamin D in a range of about 0.0133 ng/mL to about 0.04 ng/mL when administered to an adult human.
48. A method of administering a formulation or stabilized sustained release dosage form according to any one of the preceding claims to a human patient, comprising administering an effective amount of the dosage form to the patient to provide a baseline-adjusted $C_{\max}$ of at least about 0.2 ng/mL and less than 110 ng/mL.
49. The method of claim 48, comprising administering an effective amount of the formulation or dosage form to provide a baseline-adjusted $C_{\max}$ in a range of about 0.2 to about 24 ng/mL.
50. A method of administering a formulation or stabilized sustained release dosage form of any one of claims 1-47 to a human patient, comprising administering an effective

amount of the dosage form to the patient to provide a baseline-adjusted $AUC_{0-\infty}$ of at least 52 ng*h/mL and less than 34500 ng*h/mL.

51. The method of claim 50, comprising administering an effective amount of the formulation or dosage form to the patient to provide a baseline-adjusted $AUC_{0-\infty}$ in a range of about 52 ng*h/mL to about 12,000 ng*h/mL.

52. A method of vitamin D supplementation comprising administering to a subject in need thereof a formulation or dosage form according to any one of claims 1-47.

53. A method of treatment or prophylaxis of a vitamin-D responsive disease in a subject comprising administering to the subject a formulation or dosage form according to any one of claims 1-47.

54. The method of claim 53, wherein the disease is selected from cancer (e.g., breast, lung, skin, melanoma, colon, colorectal, rectal, prostate and bone cancer), autoimmune diseases, for example, type I diabetes, multiple sclerosis, rheumatoid arthritis, polymyositis, dermatomyositis, scleroderma, fibrosis, Grave's disease, Hashimoto's disease, acute or chronic transplant rejection, acute or chronic graft versus host disease, inflammatory bowel disease, Crohn's disease, systemic lupus erythematosus, Sjogren's Syndrome, eczema and psoriasis, dermatitis, including atopic dermatitis, contact dermatitis, allergic dermatitis and/or chronic dermatitis, inflammatory diseases, for example, asthma, chronic obstructive pulmonary disease, polycystic kidney disease, polycystic ovary syndrome, pancreatitis, nephritis, hepatitis, and/or infection, hypertension, cardiovascular diseases, for example, subjects with atherosclerosis, arteriosclerosis, coronary artery disease, cerebrovascular disease, peripheral vascular disease, myocardial infarction, myocardial ischemia, cerebral ischemia, stroke, congestive heart failure, cardiomyopathy, obesity or other weight disorders, lipid disorders (e.g. hyperlipidemia, dyslipidemia including associated diabetic dyslipidemia and mixed dyslipidemia hypoalphalipoproteinemia, hypertriglyceridemia, hypercholesterolemia, and low HDL (high density lipoprotein)), metabolic disorders (e.g. Metabolic Syndrome, Type II diabetes mellitus, Type I diabetes mellitus, hyperinsulinemia, impaired glucose tolerance, insulin resistance, diabetic complication including neuropathy, nephropathy, osteoporosis, retinopathy, diabetic foot ulcer and cataracts), and/or thrombosis.

55. The method of claim 53, wherein the disease is selected from (i) in the parathyroid--hypoparathyroidism, Pseudohypo-parathyroidism, secondary hyperparathyroidism; (ii) in the pancreas--diabetes; (iii) in the thyroid--medullary carcinoma; (iv) in the skin--psoriasis; wound healing; (v) in the lung--sarcoidosis and tuberculosis; (vi) in the kidney--chronic kidney disease, hypophosphatemic VDDR, vitamin D dependent rickets; (vii) in the bone--anticonvulsant treatment, fibrogenesis imperfecta ossium, osteitis fibrosa cystica, osteomalacia, osteoporosis, osteopenia, osteosclerosis, renal osteodystrophy, rickets; (viii) in the intestine--glucocorticoid antagonism, idiopathic hypercalcemia, malabsorption syndrome, steatorrhea, tropical sprue; and (ix) autoimmune disorders.

56. The method of claim 53, wherein the disease is selected from cancer, dermatological disorders (for example psoriasis), parathyroid disorders (for example hyperparathyroidism and secondary hyperparathyroidism), bone disorders (for example osteoporosis) and autoimmune disorders.

57. The method of claim 56, wherein the disease is secondary hyperparathyroidism.

58. The method of claim 57, wherein the subject has chronic kidney disease (CKD).

59. The method of claim 58, wherein the CKD is Stage 3 or 4.

60. The method of claim 59, wherein the patient is vitamin-D deficient.

61. The method of any one of claims 52-60, wherein the patient is human.

62. The method of claim 61, wherein the human is an adult human.

63. A formulation or stabilized sustained release dosage form according to any one of claims 1-47 for use in vitamin D supplementation in a patient.

64. A formulation or stabilized sustained release dosage form according to any one of claims 1-47 for use in treating or preventing a vitamin D-responsive disease in a patient.

65. The use of claim 64, wherein the disease is selected from cancer (e.g., breast, lung, skin, melanoma, colon, colorectal, rectal, prostate and bone cancer), autoimmune diseases,

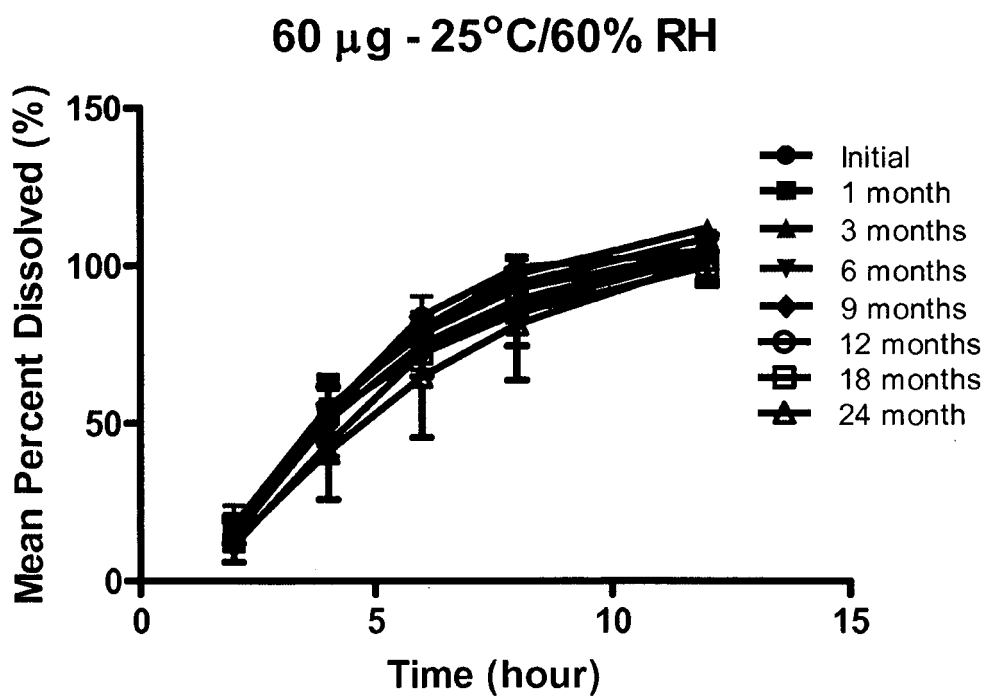
for example, type I diabetes, multiple sclerosis, rheumatoid arthritis, polymyositis, dermatomyositis, scleroderma, fibrosis, Grave's disease, Hashimoto's disease, acute or chronic transplant rejection, acute or chronic graft versus host disease, inflammatory bowel disease, Crohn's disease, systemic lupus erythematosus, Sjogren's Syndrome, eczema and psoriasis, dermatitis, including atopic dermatitis, contact dermatitis, allergic dermatitis and/or chronic dermatitis, inflammatory diseases, for example, asthma, chronic obstructive pulmonary disease, polycystic kidney disease, polycystic ovary syndrome, pancreatitis, nephritis, hepatitis, and/or infection, hypertension, cardiovascular diseases, for example, subjects with atherosclerosis, arteriosclerosis, coronary artery disease, cerebrovascular disease, peripheral vascular disease, myocardial infarction, myocardial ischemia, cerebral ischemia, stroke, congestive heart failure, cardiomyopathy, obesity or other weight disorders, lipid disorders (e.g. hyperlipidemia, dyslipidemia including associated diabetic dyslipidemia and mixed dyslipidemia hypoalphalipoproteinemia, hypertriglyceridemia, hypercholesterolemia, and low HDL (high density lipoprotein)), metabolic disorders (e.g. Metabolic Syndrome, Type II diabetes mellitus, Type I diabetes mellitus, hyperinsulinemia, impaired glucose tolerance, insulin resistance, diabetic complication including neuropathy, nephropathy, osteoporosis, retinopathy, diabetic foot ulcer and cataracts), and/or thrombosis.

66. The use of claim 64, wherein the disease is selected from (i) in the parathyroid--hypoparathyroidism, Pseudohypo-parathyroidism, secondary hyperparathyroidism; (ii) in the pancreas--diabetes; (iii) in the thyroid--medullary carcinoma; (iv) in the skin--psoriasis; wound healing; (v) in the lung--sarcoidosis and tuberculosis; (vi) in the kidney--chronic kidney disease, hypophosphatemic VDDR, vitamin D dependent rickets; (vii) in the bone--anticonvulsant treatment, fibrogenesis imperfecta ossium, osteitis fibrosa cystica, osteomalacia, osteoporosis, osteopenia, osteosclerosis, renal osteodystrophy, rickets; (viii) in the intestine--glucocorticoid antagonism, idopathic hypercalcemia, malabsorption syndrome, steatorrhea, tropical sprue; and (ix) autoimmune disorders.

67. The use of claim 64, wherein the disease is selected from cancer, dermatological disorders (for example psoriasis), parathyroid disorders (for example hyperparathyroidism and secondary hyperparathyroidism), bone disorders (for example osteoporosis) and autoimmune disorders.

- 68. The use of claim 67, wherein the disease is secondary hyperparathyroidism.
- 69. The use of claim 68, wherein the patient has chronic kidney disease (CKD).
- 70. The use of claim 69, wherein the CKD is Stage 3 or 4.
- 71. The use of claim 70, wherein the patient is vitamin-D deficient.
- 72. The use of any of claims 63-71, wherein the patient is human.
- 73. The use of claim 72, wherein the human is an adult human.

Figure 1A



2/10

Figure 1C

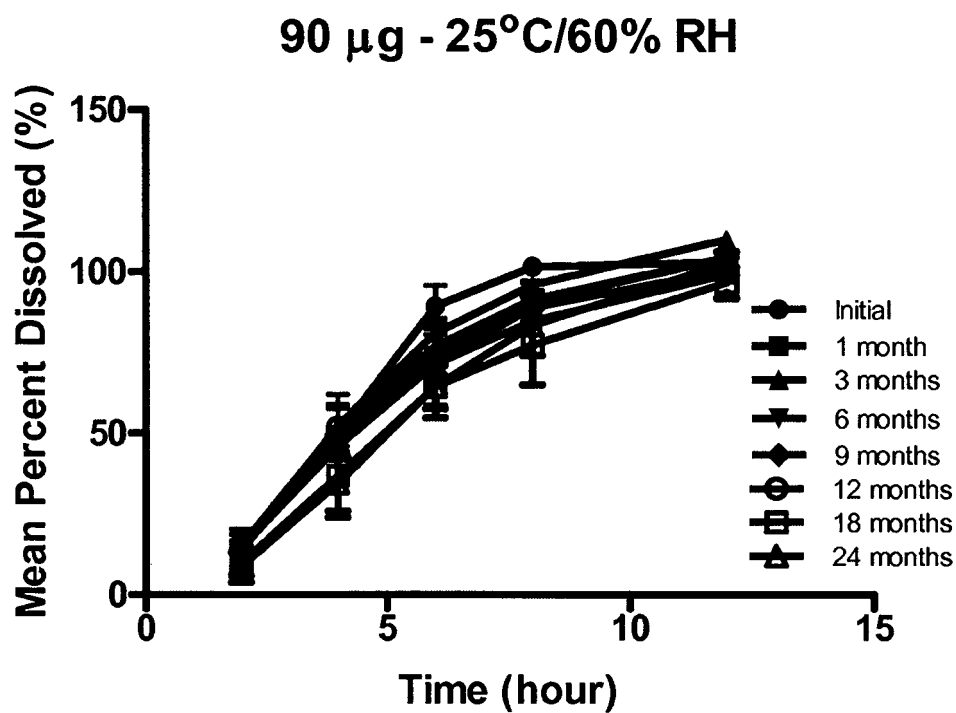
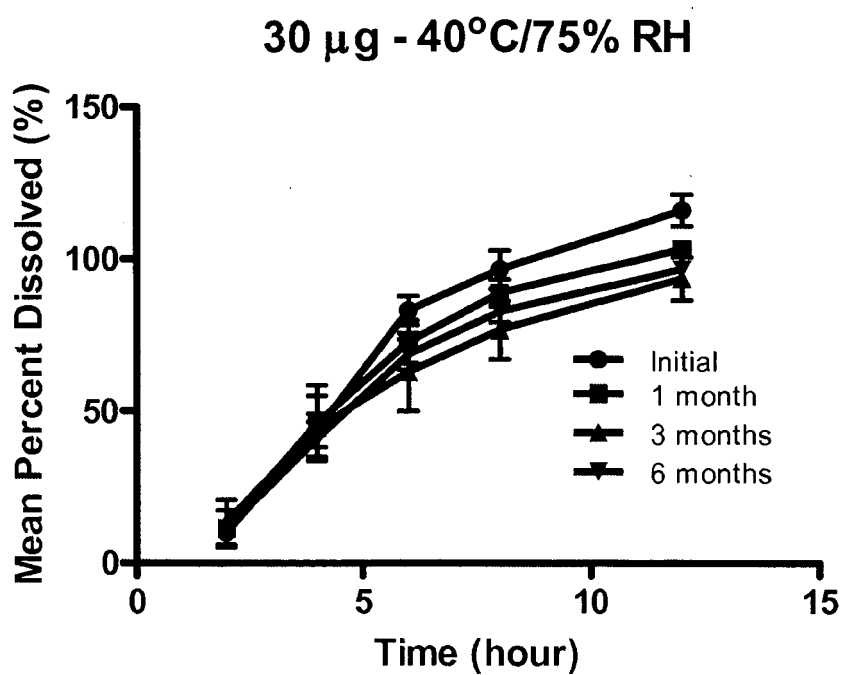


Figure 2A



3/10

Figure 2B

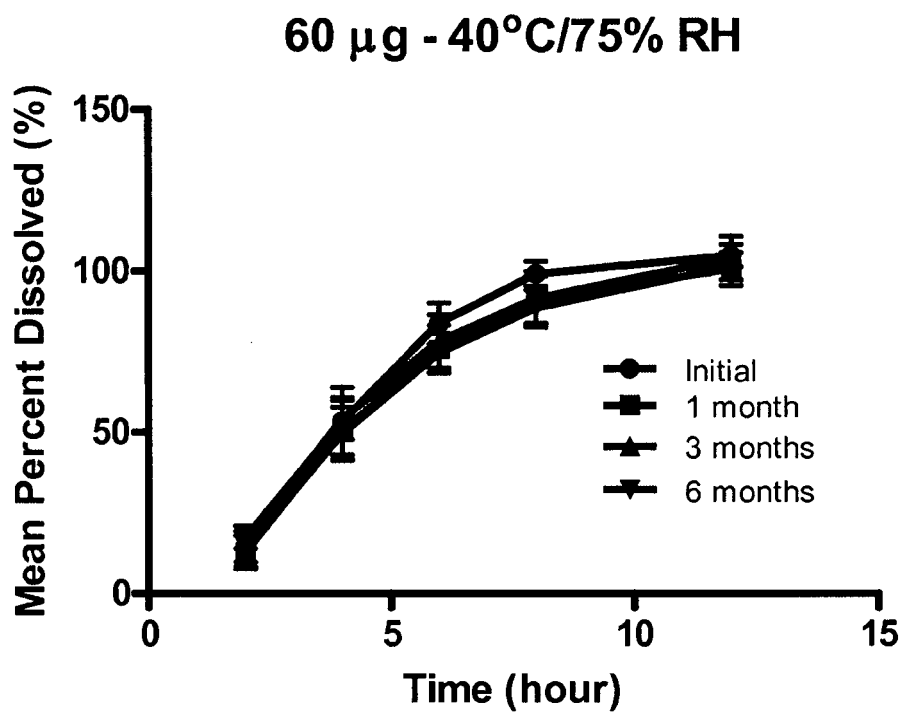
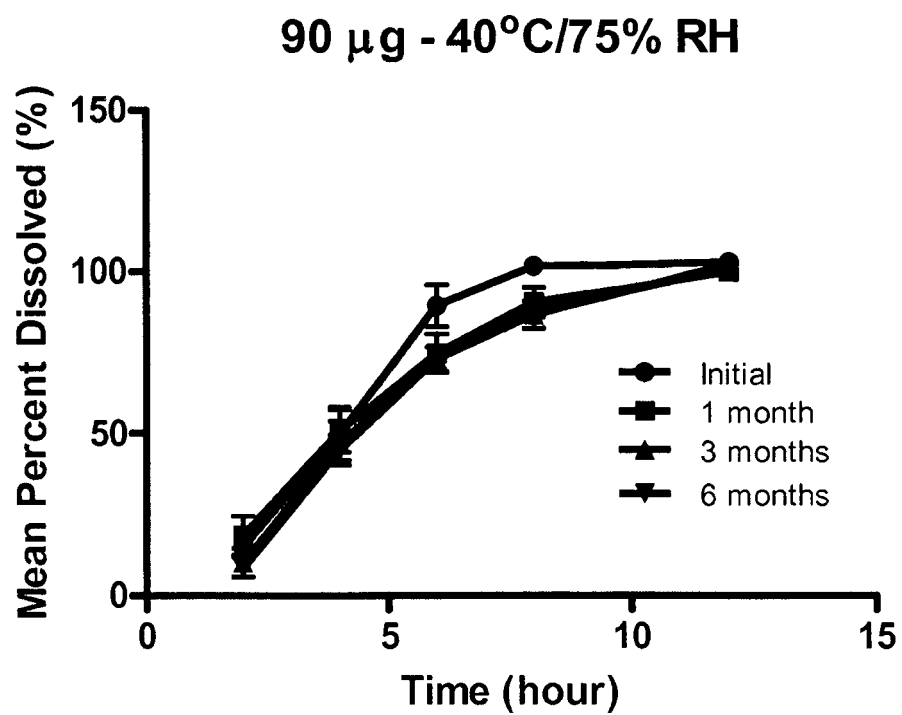


Fig. 2C



4/10

Figure 3

Fig. 3A

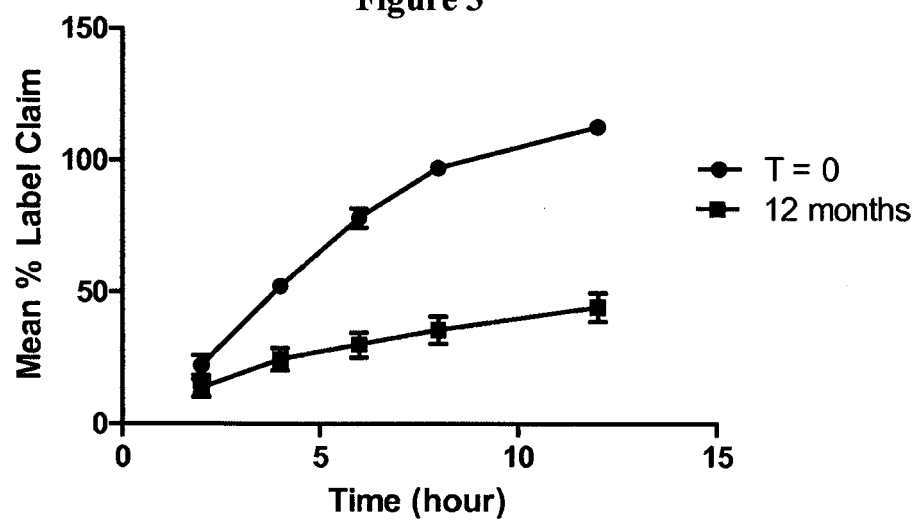
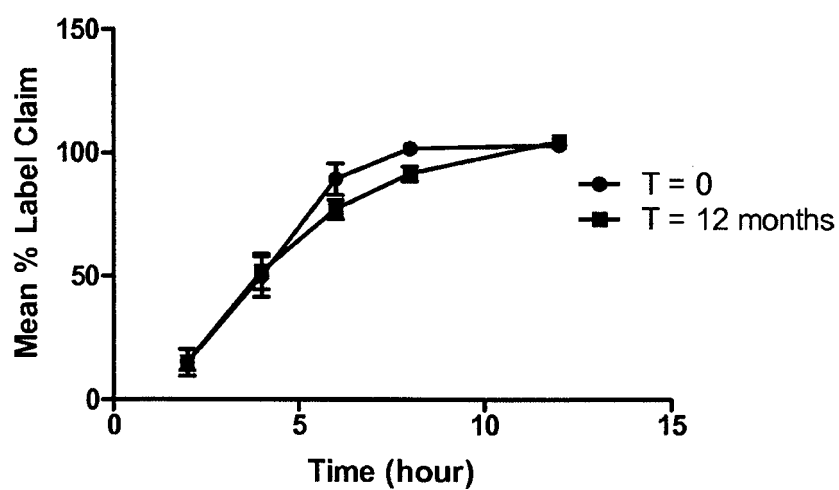
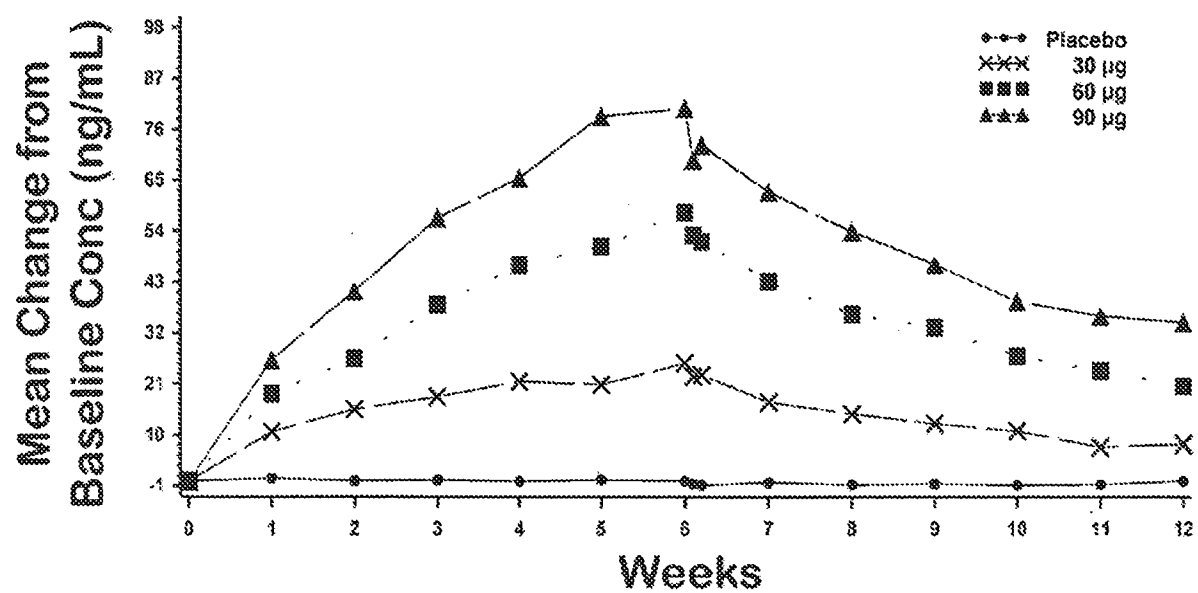


Fig. 3B



5/10

Figure 4



6/10

Figure 5

Characteristics	Placebo N=29	30µg N=12	60µg N=16	90µg N=14
Baseline (ng/mL)				
Mean (SD)	16.23 (8.29)	16.21 (7.34)	19.79 (8.69)	18.37 (9.77)
Median	12.87	17.24	21.21	16.65
Min, Max	4.35, 30.43	5.02, 25.83	5.83, 32.45	6.67, 38.86
C_{max} (ng/mL)¹				
Mean (SD)	3.58 (3.61)	27.75 (8.21)	60.33 (18.97)	85.69 (26.90)
Median	2.97	28.13	60.77	76.04
Min, Max	-0.58, 13.83	10.75, 43.39	30.31, 89.54	55.44, 146.35
AUC_{0-24h} (ng·d/mL)				
Mean (SD)	9.19 (85.66)	689.15 (238.14)	1477.80 (360.22)	2060.95 (586.86)
Median	22.62	657.19	1472.18	1896.27
Min, Max	-171.75, 214.62	303.97, 1208.29	685.75, 2141.08	1316.39, 3206.31
t_{max} (d)¹				
Mean (SD)	34.97 (30.79)	37.75 (10.41)	41.13 (5.24)	42.50 (5.06)
Median	23.00	42.50	43.00	43.00
Min, Max	1.00, 87.00	8.00, 44.00	29.00, 45.00	35.00, 56.00
t_{1/2} (d)¹				
Mean (SD)	- (-)	25.32 (13.98)	32.67 (8.59)	49.62 (51.09)
Median	-	24.06	30.85	36.32
Min, Max	-, -	5.16, 49.35	19.44, 48.11	23.15, 224.03

¹ Data are up to EOS

Abbreviations: Min: minimum; Max, maximum

7/10

Figure 6

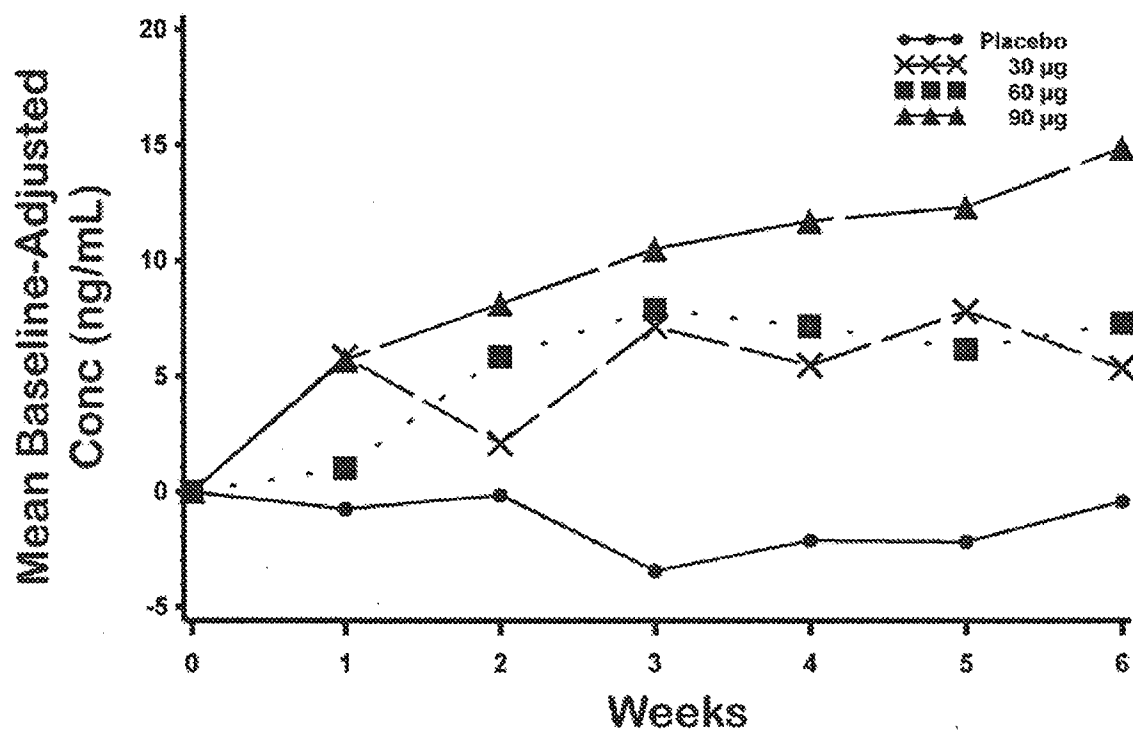


Figure 7

Characteristics	Placebo N=29	30µg N=12	60µg N=16	90µg N=14
Baseline (pg/mL)				
Mean (SD)	23.14 (12.51)	18.47 (7.97)	20.96 (6.56)	21.38 (7.70)
Median	18.57	15.52	18.73	21.02
Min, Max	7.00, 52.07	5.07, 30.67	12.77, 33.63	10.70, 36.63
C_{max} (pg/mL)[†]				
Mean (SD)	9.07 (7.99)	18.05 (20.24)	16.58 (9.30)	23.71 (13.63)
Median	7.30	9.95	17.35	20.92
Min, Max	-1.57, 34.13	3.53, 78.37	-10.33, 29.90	5.50, 48.30
AUC_{0-6wk} (pg•d/mL)				
Mean (SD)	-44.08(262.50)	252.70 (390.07)	198.86 (295.73)	396.03 (291.81)
Median	-12.17	165.83	290.33	393.36
Min, Max	-726.25, 509.95	-112.18, 1295.40	-593.93, 553.00	72.05, 1188.60
t_{max} (d)[†]				
Mean (SD)	21.55 (16.86)	30.67 (8.12)	25.19 (10.81)	26.64 (13.30)
Median	23.00	30.00	22.50	23.00
Min, Max	1.00, 44.00	16.00, 42.00	8.00, 43.00	7.00, 44.00

[†]Data are up to EOS

Abbreviations: Min: minimum; Max, maximum

8/10

Figure 8

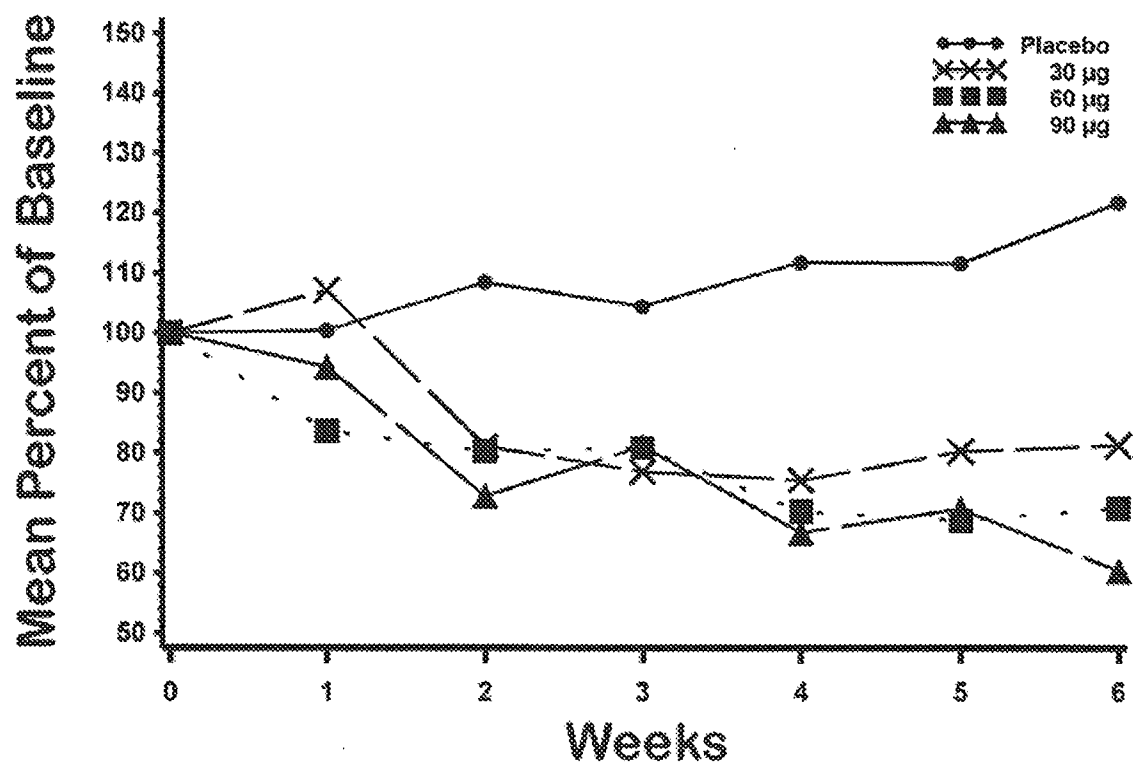


Figure 9

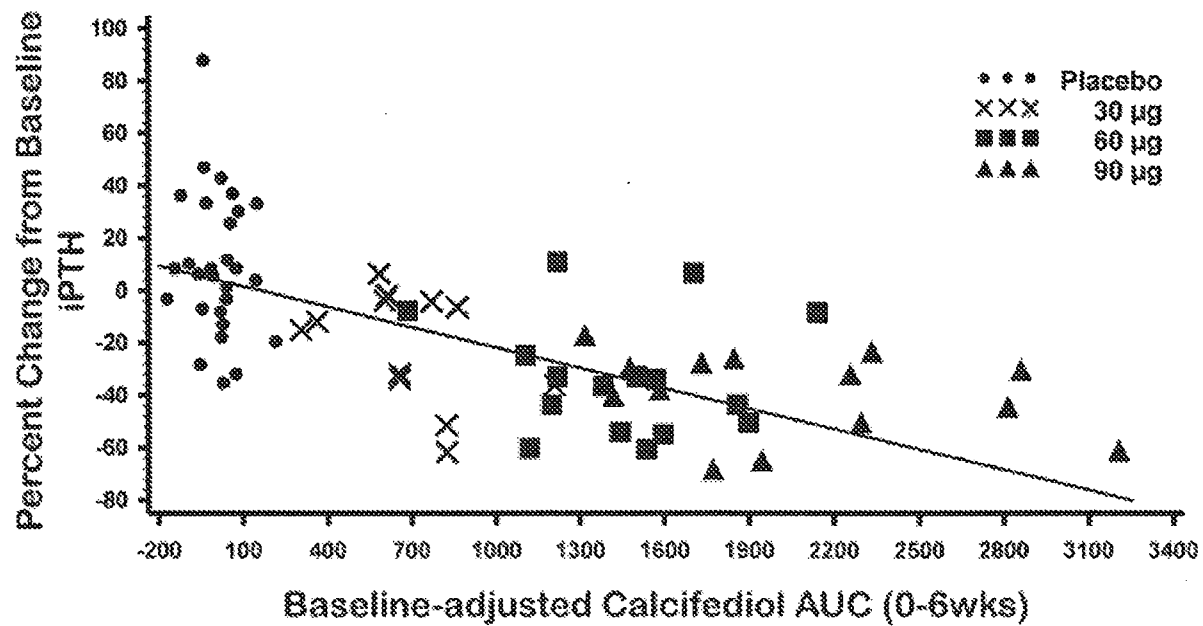
Characteristics	Placebo N=29	30µg N=12	60µg N=16	90µg N=14
Baseline¹ (pg/mL)				
Mean (SD)	144.62 (67.47)	156.28 (57.92)	118.46 (25.89)	155.88 (58.51)
Median	130.63	161.22	113.78	135.08
Min, Max	64.10, 323.27	81.03, 253.97	82.23, 167.85	96.33, 291.25
C_{min} (pg/mL)				
Mean (SD)	-38.80 (33.35)	-67.84 (36.71)	-63.09 (21.57)	-86.04 (37.39)
Median	-32.63	-62.48	-63.33	-80.51
Min, Max	-133.03, -3.90	-140.27, -29.83	-104.77, -24.83	-184.10, -41.27
AUC_{0-5wk} (pg•d/mL)				
Mean (SD)	176.02 (1575.81)	-896.76 (1215.80)	-1322.53 (723.32)	-1560.91 (820.99)
Median	180.95	-1029.50	-1325.92	-1303.40
Min, Max	-3059.00, 4463.65	-2812.60, 1457.05	-2228.40, -177.45	-3743.70, -575.75
t_{min} (d)				
Mean (SD)	21.14 (14.21)	32.08 (8.53)	29.38 (10.39)	32.29 (12.61)
Median	21.00	32.50	32.00	37.00
Min, Max	1.00, 44.00	15.00, 42.00	8.00, 43.00	8.00, 44.00

¹ Baseline is the average of visits 1 (or 2 if washout), 3, and 4.

9/10

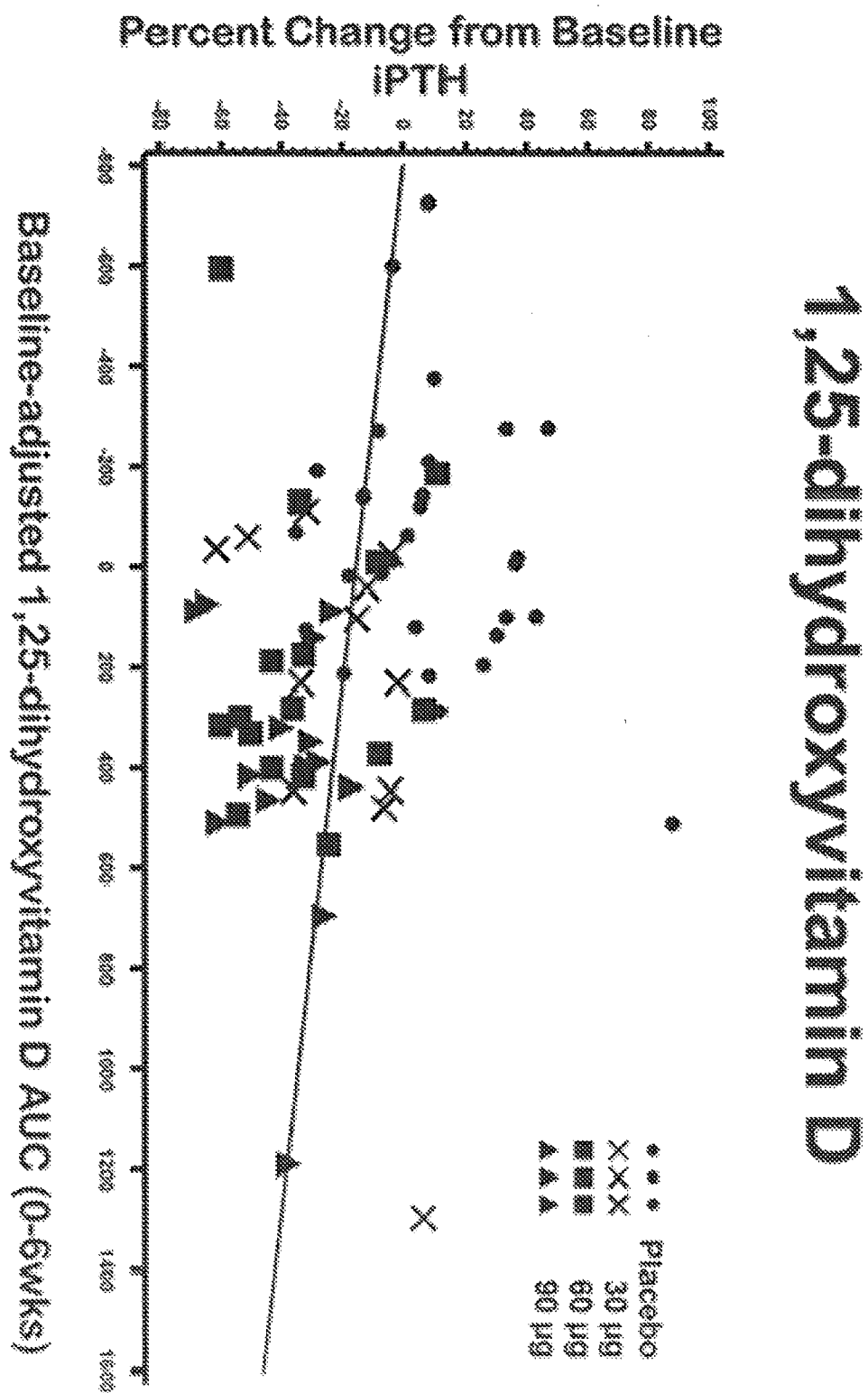
Figure 10

Calcifediol



10/10

Figure 11



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/028132

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K9/20 A61K9/28 A61K9/48 A61K31/00 ADD.		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) A61K		
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) EPO-Internal, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/098617 A2 (NORDIC BONE AS [DK]; HANSEN CHRISTIAN [DK]; NILSSON HENRIK [DK]; ANDER) 18 November 2004 (2004-11-18) the whole document page 18 - page 19; claims 1-53 -----	1-73
X	WO 96/00074 A1 (UNIV BEN GURION [IL]; KOPEIKA NORMAN S [IL]; KOST JOSEPH [IL]; SHANY S) 4 January 1996 (1996-01-04) the whole document claims 1-28; examples 1-4 -----	1-73
X	WO 2012/145491 A2 (FISHER JASON [US]) 26 October 2012 (2012-10-26) the whole document claims 1-47 ----- -/--	1-73
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 6 June 2014		Date of mailing of the international search report 17/06/2014
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Felder, Christian

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2014/028132

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	RAPURI P B ET AL: "Effect of vitamins D2 and D3 supplement use on serum 25OHD concentration in elderly women in summer and winter", CALCIFIED TISSUE INTERNATIONAL, NEW YORK, NY, US, vol. 74, no. 2, 1 February 2004 (2004-02-01), pages 150-156, XP002454820, ISSN: 0171-967X, DOI: 10.1007/S00223-003-0083-8 the whole document -----	1-73

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2014/028132

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004098617 A2	18-11-2004	AU 2004237437 A1	18-11-2004
		AU 2010249227 A1	06-01-2011
		CA 2524603 A1	18-11-2004
		EP 1622629 A2	08-02-2006
		JP 5049589 B2	17-10-2012
		JP 2006525241 A	09-11-2006
		JP 2011121985 A	23-06-2011
		US 2006216358 A1	28-09-2006
		US 2009191282 A1	30-07-2009
		US 2013071496 A1	21-03-2013
		WO 2004098617 A2	18-11-2004

WO 9600074 A1	04-01-1996	AU 2998095 A	19-01-1996
		WO 9600074 A1	04-01-1996

WO 2012145491 A2	26-10-2012	AU 2012245475 A1	28-11-2013
		CA 2833633 A1	26-10-2012
		CN 103781487 A	07-05-2014
		EA 201391553 A1	31-03-2014
		EP 2699250 A2	26-02-2014
		SG 194542 A1	30-12-2013
		US 2014037700 A1	06-02-2014
		WO 2012145491 A2	26-10-2012



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(30) 优先权数据

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61/801, 896 2013. 03. 15 US

A61K 9/48(2006. 01)

A61K 31/00(2006. 01)

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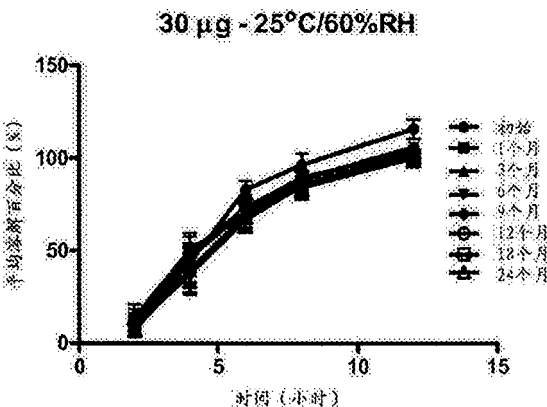
权利要求书5页 说明书45页 附图10页

(54) 发明名称

稳定化修饰释放维生素 D 制剂和施用其的方法

(57) 摘要

公开了一种用于维生素 D 化合物的控制释放的稳定化制剂。这种制剂包含 25- 羟基维生素 D2 和 25- 羟基维生素 D3 中的一者或两者以及纤维素化合物。稳定化制剂在暴露于储存条件之后展现稳定的溶解型态并且与未稳定化制剂相比展示改善的药物动力学参数。



1. 一种维生素 D 化合物的控制释放制剂,其包含 25-羟基维生素 D₂ 和 25-羟基维生素 D₃中的一者或两者,所述制剂包含可释放地结合并且可控地释放所述维生素 D 化合物的基质,所述基质包含纤维素衍生物。

2. 一种用于维生素 D 化合物的控制释放的稳定化制剂,所述制剂包含以下的混合物:
25-羟基维生素 D₂和 25-羟基维生素 D₃中的一者或两者;

蜡基质;以及

稳定剂,任选地是纤维素化合物。

3. 如权利要求 1 或 2 所述的制剂,其中所述制剂是用于在摄取所述制剂的受试者的胃肠道中所述维生素 D 化合物的控制释放的口服制剂。

4. 如前述权利要求中任一项所述的制剂,所述制剂包含以下的混合物:

25-羟基维生素 D₂和 25-羟基维生素 D₃中的一者或两者;

蜡基质;以及

有效量的稳定剂,任选地是纤维素化合物,以维持在持续两个月暴露于 25℃和 60%相对湿度的储存条件之后在体外溶解测试期间在四小时后的任何给定时间点释放的维生素 D 化合物的量与在使所述制剂暴露于所述储存条件之前进行的体外溶解期间的相同溶解时间点释放的量之间小于 30%的差异。

5. 如前述权利要求中任一项所述的制剂,所述制剂包含:

包含 25-羟基维生素 D₂和 25-羟基维生素 D₃中的一者或两者的活性剂加载的蜡基质;
以及

纤维素稳定剂;

其中所述制剂在两个月暴露于 25℃和 60%相对湿度的储存期之后在体外溶解期间释放的 25-羟基维生素 D 的量在任何给定溶解时间点与在使所述制剂暴露于所述储存条件之前进行的体外溶解期间的相同溶解时间点释放的量相比在不存在所述纤维素稳定剂的情况下变化 30%或更小。

6. 如前述权利要求中任一项所述的制剂,其中所述纤维素化合物或纤维素稳定剂包含纤维素醚。

7. 如权利要求 6 所述的制剂,其中所述纤维素醚选自以下组成的群组:甲基纤维素、羟丙基甲基纤维素、羟乙基甲基纤维素、羟乙基纤维素以及羟丙基纤维素。

8. 如权利要求 6 所述的制剂,其中所述纤维素化合物或纤维素稳定剂包含羟丙基甲基纤维素。

9. 如前述权利要求中任一项所述的制剂,其中所述制剂在暴露于 40℃和 75%相对湿度的储存条件持续一个月之后在体外溶解期间释放的 25-羟基维生素 D 的量在四小时后的任何给定溶解时间点与在使所述制剂暴露于所述储存条件之前进行的体外溶解期间的相同溶解时间点释放的量相比变化 30%或更小。

10. 如前述权利要求中任一项所述的制剂,其中所述基质包含有包含控制释放剂、乳化剂以及吸收增强剂的蜡基质。

11. 如权利要求 10 所述的制剂,其中所述控制释放剂包含石蜡。

12. 如权利要求 10 或 11 所述的制剂,其中所述乳化剂具有小于 7 的 HLB 值。

13. 如权利要求 12 所述的制剂,其中所述乳化剂包含单硬脂酸甘油酯。

14. 如权利要求 10 至 13 中任一项所述的制剂,其中所述吸收增强剂具有在约 13 至约 18 的范围内的 HLB 值。

15. 如权利要求 14 所述的制剂,其中所述吸收增强剂是月桂酰聚乙二醇甘油酯与月桂酰聚氧甘油酯的混合物。

16. 如权利要求 10 至 15 中任一项所述的制剂,其进一步包含油性媒剂。

17. 如权利要求 16 所述的制剂,其中所述油性媒剂包含矿物油。

18. 如权利要求 17 所述的制剂,其中所述制剂包含约 20wt% 石蜡、约 20wt% 至约 25wt% 单硬脂酸甘油酯、约 10wt% 月桂酰聚乙二醇甘油酯与月桂酰聚氧甘油酯的混合物、约 30wt% 至约 35wt% 矿物油、以及约 10wt% 至约 15wt% 羟丙基甲基纤维素。

19. 如权利要求 10 至 18 中任一项所述的制剂,其中所述制剂包含单硬脂酸甘油酯。

20. 如权利要求 10 至 19 中任一项所述的制剂,其中所述制剂包含一种或多种聚乙二醇化甘油酯。

21. 一种呈胶囊、片剂、香囊、糖衣丸或栓剂形式的持续释放剂型,其包含如前述权利要求中任一项所述的制剂。

22. 如权利要求 21 所述的剂型,其包含胶囊或片剂。

23. 如权利要求 22 所述的剂型,其包含胶囊。

24. 如权利要求 21 所述的剂型,其包含口服胶囊、片剂、香囊或糖衣丸。

25. 如前述权利要求中任一项所述的制剂或稳定化剂型,其特征为提供维生素 D 化合物的以下释放的溶解型态:

在 2 小时处小于 30%;

在 6 小时处大于 45%;以及

在 12 小时处大于 80%。

26. 如权利要求 25 所述的制剂或稳定化剂型,其中在 6 小时处维生素 D 化合物的所述释放小于 60%。

27. 如权利要求 1 至 24 中任一项所述的制剂或稳定化持续释放口服剂型,其特征为提供维生素 D 化合物的以下释放的体外溶解型态:

在 100 至 140 分钟处小于 30%;

在 5 至 7 小时处大于 45%;以及

在 11 至 13 小时处大于 80%。

28. 如权利要求 27 所述的制剂或剂型,其中维生素 D 化合物的所述释放为在 2 小时处小于 30%;

在 6 小时处大于 45%;以及

在 12 小时处大于 80%。

29. 如权利要求 27 或 28 所述的制剂或剂型,其中在 5 至 7 小时处维生素 D 化合物的所述释放小于 60%。

30. 如权利要求 29 所述的制剂或剂型,其中在 6 小时处维生素 D 化合物的所述释放小于 60%。

31. 如权利要求 1 至 24 中任一项所述的制剂或稳定化持续释放口服剂型,其特征为提供维生素 D 化合物的以下释放的体外溶解型态:

在 2 小时处约 20%至约 40% ;

在 6 小时处至少 35% ;以及

在 12 小时处至少 70%。

32. 如权利要求 31 所述的制剂或剂型,其中维生素 D 化合物的所述释放为在 2 小时处约 25%至约 35% ;

在 6 小时处至少 40% ;以及

在 12 小时处至少 75%。

33. 如权利要求 31 或 32 所述的制剂或剂型,其中维生素 D 化合物的所述释放为在 6 小时处 75%或更小。

34. 如权利要求 33 所述的制剂或剂型,其中维生素 D 化合物的所述释放为在 6 小时处 65%或更小。

35. 如权利要求 34 所述的制剂或剂型,其中维生素 D 化合物的所述释放为在 6 小时处 60%或更小。

36. 如前述权利要求中任一项所述的制剂或稳定化持续释放剂型,其特征为在将所述剂型施用于人类患者之后至少 4 小时的 t_{max} 。

37. 如权利要求 36 所述的制剂或剂型,其中所述 t_{max} 为至少 8 小时。

38. 如权利要求 37 所述的制剂或剂型,其中所述 t_{max} 为至少 12 小时。

39. 如权利要求 38 所述的制剂或剂型,其中所述 t_{max} 为至少 18 小时。

40. 如权利要求 39 所述的制剂或剂型,其中所述 t_{max} 为至少 20 小时。

41. 如权利要求 40 所述的制剂或剂型,其中所述 t_{max} 为至少 24 小时。

42. 如权利要求 41 所述的制剂或剂型,其中所述 t_{max} 为至少 28 小时。

43. 如权利要求 36 所述的制剂或剂型,其中所述 t_{max} 在 4 至 96 小时的范围内。

44. 如权利要求 43 所述的制剂或剂型,其中所述 t_{max} 在 18 至 30 小时的范围内。

45. 如权利要求 44 所述的制剂或剂型,其中所述 t_{max} 在 13 至 28 小时的范围内。

46. 如权利要求 45 所述的制剂或剂型,其中所述 t_{max} 为约 28 小时。

47. 一种包含 25-羟基维生素 D 化合物的制剂或稳定化持续释放剂型,所述剂型的特征为当施用于成年人时提供每微克 25-羟基维生素 D 在约 0.0133ng/mL 至约 0.04ng/mL 的范围内的基线调整 C_{max} 。

48. 一种将如前述权利要求中任一项所述的制剂或稳定化持续释放剂型施用于人类患者的方法,其包括将有效量的所述剂型施用于所述患者以提供至少约 0.2ng/mL 并且小于 110ng/mL 的基线调整 C_{max} 。

49. 如权利要求 48 所述的方法,其包括施用有效量的所述制剂或剂型以提供在约 0.2 至约 24ng/mL 的范围内的基线调整 C_{max} 。

50. 一种将如权利要求 1 至 47 中任一项所述的制剂或稳定化持续释放剂型施用于人类患者的方法,其包括将有效量的所述剂型施用于所述患者以提供至少 52ng · h/mL 并且小于 34500ng · h/mL 的基线调整 AUC_{0-inf} 。

51. 如权利要求 50 所述的方法,其包括将有效量的所述制剂或剂型施用于所述患者以提供在约 52ng · h/mL 至约 12,000ng · h/mL 的范围内的基线调整 AUC_{0-inf} 。

52. 一种维生素 D 补充的方法,其包括向有需要的受试者施用如权利要求 1 至 47 中任

一项所述的制剂或剂型。

53. 一种治疗或预防受试者的维生素 D 反应性疾病的方法,其包括向所述受试者施用如权利要求 1 至 47 中任一项所述的制剂或剂型。

54. 如权利要求 53 所述的方法,其中所述疾病选自癌症(例如,乳癌、肺癌、皮肤癌、黑色素瘤、结肠癌、结肠直肠癌、直肠癌、前列腺癌以及骨癌);自体免疫疾病,例如,I 型糖尿病、多发性硬化、类风湿性关节炎、多肌炎、皮肌炎、硬皮病、纤维化、格雷夫氏病、桥本氏病、急性或慢性移植排斥反应、急性或慢性移植物抗宿主疾病、发炎性肠病、克罗恩氏病、全身性红斑狼疮、修格兰氏综合症、湿疹以及牛皮癣;皮炎,包括异位性皮炎、接触性皮炎、过敏性皮炎和/或慢性皮炎;发炎性疾病,例如,哮喘、慢性阻塞性肺病、多囊性肾病、多囊性卵巢综合症、胰腺炎、肾炎、肝炎和/或感染;高血压;心血管疾病,例如,患有动脉粥样硬化、动脉硬化、冠状动脉疾病、脑血管疾病、外周血管疾病、心肌梗塞、心肌缺血、脑缺血、中风、充血性心脏衰竭、心肌病的受试者;肥胖或其它体重异常;脂质异常(例如,高脂血症;脂代谢异常,包括相关的糖尿病性脂代谢异常和混合性脂代谢异常;低 α 脂蛋白血症;高甘油三酯血症;高胆固醇血症;以及低 HDL(高密度脂蛋白));代谢异常(例如,代谢综合症;II 型糖尿病;I 型糖尿病;高胰岛素血症;葡萄糖耐量减低;胰岛素抵抗;糖尿病并发症,包括神经病、肾病、骨质疏松症、视网膜病、糖尿病足溃疡以及白内障);和/或血栓症。

55. 如权利要求 53 所述的方法,其中所述疾病选自(i)在甲状旁腺中--甲状旁腺功能减退、假性甲状旁腺功能减退、继发性甲状旁腺功能亢进;(ii)在胰腺中--糖尿病;(iii)在甲状腺中--髓样癌;(iv)在皮肤中--牛皮癣、伤口愈合;(v)在肺中--肉状瘤病和结核病;(vi)在肾中--慢性肾病、低磷酸盐血性 VDRR、维生素 D 依赖性佝偻病;(vii)在骨中--抗惊厥剂治疗、骨纤维生成不良、囊性纤维性骨炎、骨软化、骨质疏松症、骨质减少、骨硬化、肾性骨营养不良、佝偻病;(viii)在肠中--糖皮质激素拮抗、特发性高钙血症、吸收不良综合症、脂肪痢、热带口炎性腹泻;以及(ix)自体免疫病症。

56. 如权利要求 53 所述的方法,其中所述疾病选自癌症、皮肤病症(例如,牛皮癣)、甲状旁腺病症(例如,甲状旁腺功能亢进和继发性甲状旁腺功能亢进)、骨病症(例如,骨质疏松症)以及自体免疫病症。

57. 如权利要求 56 所述的方法,其中所述疾病是继发性甲状旁腺功能亢进。

58. 如权利要求 57 所述的方法,其中所述受试者患有慢性肾病(CKD)。

59. 如权利要求 58 所述的方法,其中所述 CKD 是 3 期或 4 期。

60. 如权利要求 59 所述的方法,其中所述患者是维生素 D 缺乏的。

61. 如权利要求 52 至 60 中任一项所述的方法,其中所述患者是人类。

62. 如权利要求 61 所述的方法,其中所述人类是成年人。

63. 如权利要求 1 至 47 中任一项所述的制剂或稳定化持续释放剂型,其用于患者中的维生素 D 补充。

64. 如权利要求 1 至 47 中任一项所述的制剂或稳定化持续释放剂型,其用于治疗或预防患者的维生素 D 反应性疾病。

65. 如权利要求 64 所述的用途,其中所述疾病选自癌症(例如,乳癌、肺癌、皮肤癌、黑色素瘤、结肠癌、结肠直肠癌、直肠癌、前列腺癌以及骨癌);自体免疫疾病,例如,I 型糖尿病、多发性硬化、类风湿性关节炎、多肌炎、皮肌炎、硬皮病、纤维化、格雷夫氏病、桥本氏病、急

性或慢性移植排斥反应、急性或慢性移植抗宿主疾病、发炎性肠病、克罗恩氏病、全身性红斑狼疮、修格兰氏综合症、湿疹以及牛皮癣；皮炎，包括异位性皮炎、接触性皮炎、过敏性皮炎和 / 或慢性皮炎；发炎性疾病，例如，哮喘、慢性阻塞性肺病、多囊性肾病、多囊性卵巢综合症、胰腺炎、肾炎、肝炎和 / 或感染；高血压；心血管疾病，例如，患有动脉粥样硬化、动脉硬化、冠状动脉疾病、脑血管疾病、外周血管疾病、心肌梗塞、心肌缺血、脑缺血、中风、充血性心脏衰竭、心肌病的受试者；肥胖或其它体重异常；脂质异常（例如，高脂血症；脂代谢异常，包括相关的糖尿病性脂代谢异常和混合性脂代谢异常；低 α 脂蛋白血症；高甘油三酯血症；高胆固醇血症；以及低 HDL（高密度脂蛋白））；代谢异常（例如，代谢综合症；II 型糖尿病；I 型糖尿病；高胰岛素血症；葡萄糖耐量减低；胰岛素抵抗；糖尿病并发症，包括神经病、肾病、骨质疏松症、视网膜病、糖尿病足溃疡以及白内障）；和 / 或血栓症。

66. 如权利要求 64 所述的用途，其中所述疾病选自 (i) 在甲状旁腺中 -- 甲状旁腺功能减退、假性甲状旁腺功能减退、继发性甲状旁腺功能亢进；(ii) 在胰腺中 -- 糖尿病；(iii) 在甲状腺中 -- 髓样癌；(iv) 在皮肤中 -- 牛皮癣、伤口愈合；(v) 在肺中 -- 肉状瘤病和结核病；(vi) 在肾中 -- 慢性肾病、低磷酸盐血性 VDDR、维生素 D 依赖性佝偻病；(vii) 在骨中 -- 抗惊厥剂治疗、骨纤维生成不良、囊性纤维性骨炎、骨软化、骨质疏松症、骨质减少、骨硬化、肾性骨营养不良、佝偻病；(viii) 在肠中 -- 糖皮质激素拮抗、特发性高钙血症、吸收不良综合症、脂肪痢、热带口炎性腹泻；以及 (ix) 自体免疫病症。

67. 如权利要求 64 所述的用途，其中所述疾病选自癌症、皮肤病症（例如，牛皮癣）、甲状旁腺病症（例如，甲状旁腺功能亢进和继发性甲状旁腺功能亢进）、骨病症（例如，骨质疏松症）以及自体免疫病症。

68. 如权利要求 67 所述的用途，其中所述疾病是继发性甲状旁腺功能亢进。

69. 如权利要求 68 所述的用途，其中所述患者患有慢性肾病 (CKD)。

70. 如权利要求 69 所述的用途，其中所述 CKD 是 3 期或 4 期。

71. 如权利要求 70 所述的用途，其中所述患者是维生素 D 缺乏的。

72. 如权利要求 63 至 71 中任一项所述的用途，其中所述患者是人类。

73. 如权利要求 72 所述的用途，其中所述人类是成年人。

稳定化修饰释放维生素 D 制剂和施用其的方法

[0001] 相关申请的交叉引用

[0002] 特此要求 2013 年 3 月 15 日提交的美国临时专利申请序列号 61/801,896 依照 35U.S.C. § 119(e) 的权益并且其公开内容以引用的方式并入本文中。

技术领域

[0003] 本公开一般涉及控制释放医药组合物。更特别地,本发明涉及用于递送供肠吸收用的维生素 D 化合物(诸如 25-羟基维生素 D 化合物)的控制释放制剂,其随着时间是贮存稳定的。

背景技术

[0004] 称为 25-羟基维生素 D₂和 25-羟基维生素 D₃(统称作“25-羟基维生素 D”)的维生素 D 代谢物是有助于维持血流中钙和磷的正常水平的脂溶性类固醇激素原。激素原 25-羟基维生素 D₂从维生素 D₂(麦角钙化醇)产生并且 25-羟基维生素 D₃从维生素 D₃(胆钙化醇)产生,主要由位于肝中的一种或多种酶产生。这两种激素原也可以在肝外部从某些细胞(诸如肠上皮细胞)中的维生素 D₂和维生素 D₃(统称作“维生素 D”)产生,这些细胞含有与肝中所发现的那些相同或相似的酶。

[0005] 25-羟基维生素 D 激素原在肾中进一步代谢成有效的维生素 D 激素。激素原 25-羟基维生素 D₂代谢成 1 α , 25-二羟基维生素 D₂;同样地,25-羟基维生素 D₃代谢成 1 α , 25-二羟基维生素 D₃(钙三醇)。从 25-羟基维生素 D 激素原产生这些活性激素也可以在肾外部在含有所需酶的细胞中发生。

[0006] 可以施用 25-羟基维生素 D₂和/或 25-羟基维生素 D₃的控制释放制剂以治疗 25-羟基维生素 D 不足和缺乏,而没有 25-羟基维生素 D 的管腔内、细胞内以及血液水平的超生理激增和其后果;不会引起所施用的 25-羟基维生素 D 的实质上增加的分解代谢;以及不会引起与维生素 D 补充相关的严重副作用,即,维生素 D 毒性。控制释放制剂有效降低 PTH 水平而没有血清钙和血清磷的不合需要的增加,并且因此适用于治疗继发性甲状旁腺功能亢进,例如,在 CKD 患者中。参看国际专利申请号 PCT/US2007/061521 和 PCT/US2008/061579 以及美国专利申请号 12/109,983,以引用的方式并入本文中。

[0007] 控制释放的组合物经由在 DBP 上输送提供 25-羟基维生素 D 的实质上增加的吸收并且经由在乳糜微粒中输送提供减少的吸收。这些组合物还提供在 24 小时给药后时段期间 25-羟基维生素 D 的实质上恒定的血液水平的维持。通过提供 25-羟基维生素 D₂/25-羟基维生素 D₃的逐渐、持续以及直接释放和优先吸收至循环 DBP(而不是乳糜微粒),可以减少或消除血液、管腔内以及细胞内 25-羟基维生素 D 浓度尖峰,即,超生理水平和相关不当的分解代谢。此外,通过提供逐渐和持续释放,可以比施用立即释放制剂更加可预测的方式增加和维持 25-羟基维生素 D 的血清水平,从而允许一致的剂量并且减少或消除频繁的患者监测的需要。

[0008] 为了将 25-羟基维生素 D 的控制释放制剂的效益递送至患者,需要稳定化医药组

合物,其持续延长的时间段,例如在运送和储存之后保持制剂的所需溶解特性。

发明内容

[0009] 本发明包含一种控制释放维生素 D 制剂,其包含维生素 D 化合物和纤维素化合物。

[0010] 本发明还包含一种储存稳定化制剂,其用于在摄取这种制剂的受试者的胃肠道中维生素 D 化合物的控制释放。在一个方面,稳定化制剂包含 25-羟基维生素 D₂和 25-羟基维生素 D₃中的一者或两者以及稳定剂或稳定化合物,例如,纤维素化合物。具有所叙述的稳定剂的本发明的稳定化制剂与不含这类试剂的所公开的制剂相比可以具有改善或相对改善的“储存稳定性”或老化后稳定性,以及一种或多种额外特征,包括改善的物理、化学以及生物特性。所要求的制剂因此适合作为与老化的不稳定制剂相比具有长贮存期以及改善的生物利用度的治疗剂。

[0011] 在一个实施方案中,稳定化制剂包括 25-羟基维生素 D₂和 25-羟基维生素 D₃中的一者或两者、亲脂性基质(例如,蜡基质)以及稳定剂(例如,纤维素化合物)。在一个方面,稳定化制剂包括 25-羟基维生素 D₂和 25-羟基维生素 D₃中的一者或两者、蜡基质以及纤维素稳定剂。在另一个方面,制剂包括 25-羟基维生素 D₂和 25-羟基维生素 D₃中的一者或两者、蜡基质以及有效量的纤维素化合物以维持本文所描述的有利的稳定化程度。

[0012] 在一种类型的实施方案中,稳定化制剂包含有包含 25-羟基维生素 D₂和 25-羟基维生素 D₃中的一者或两者的活性剂加载的蜡基质与纤维素稳定剂的混合物,其中这种制剂在暴露于 25℃和 60%相对湿度的储存条件至少一个月之后在体外溶解期间释放的 25-羟基维生素 D 的量在所有溶解测试时间点与在对新鲜产品进行的体外溶解期间的相同溶解时间点释放的量相比变化 30%或更小。

[0013] 在一种类型的实施方案中,制剂是用于维生素 D 化合物的控制释放的改善制剂。在一个方面,改善包括将稳定剂混入用于在摄取制剂的受试者的胃肠道中维生素 D 化合物的控制释放的制剂中。在另一个方面,改善包括混入用于在摄取制剂的受试者的胃肠道中维生素 D 化合物的控制释放的制剂中的有效量的纤维素化合物以提供本文所描述的有利的稳定性程度。

[0014] 在一个实施方案中,本发明包含一种稳定的持续释放维生素 D 制剂,其包含 25-羟基维生素 D₂或 25-羟基维生素 D₃或其组合和持续释放赋形剂,其中所述制剂在 T₀下具有溶解型态 X,其根据公式 $X = T_0 \pm 30\%$ 经过选自例如室温和环境湿度、或 25℃和 60% RH、或 40℃和 75% RH 的储存条件保持这种型态。

[0015] 其它方面和优点从以下具体实施方式的评述结合图式将为本领域的一般技术人员显而易见。尽管组合物和方法容许有各种形式的实施方案,但下文的描述包括特定实施方案,条件是本发明是说明性的,并且不意图将本发明限于本文所描述的特定实施方案。

[0016] 对于本文所描述的组合物和方法,预期任选的特征,包括(但不限于)组分、其组成范围、替代物、条件以及步骤,选自本文所提供的各种方面、实施方案以及实施例。

附图说明

[0017] 图 1 示出了根据本公开的制剂在 25℃和 60%相对湿度下储存 0 至 24 个月之后的溶解型态。溶解时间(小时)在 x 轴上描绘并且所溶解的 25-羟基维生素 D₃的平均百分

比在 y 轴上示出。图 1A、1B 以及 1C 示出了分别包含 30 μg 、60 μg 以及 90 μg 25-羟基维生素 D₃ 的制剂的溶解型态。

[0018] 图 2 示出了根据本公开的制剂在 40°C 和 75% 相对湿度下储存 0 至 6 个月之后的溶解型态。溶解时间 (小时) 在 x 轴上描绘并且所溶解的 25-羟基维生素 D₃ 的平均百分比在 y 轴上示出。图 2A、2B 以及 2C 示出了分别包含 30 μg 、60 μg 以及 90 μg 25-羟基维生素 D₃ 的制剂的溶解型态。

[0019] 图 3 示出了制剂在 25°C 和 60% 相对湿度下储存 0 至 12 个月之后的溶解型态。溶解时间 (小时) 在 x 轴上描绘并且所释放的 25-羟基维生素 D₃ 的平均标示量 % 在 y 轴上示出。图 3A 示出了不含纤维素化合物的比较性制剂的溶解型态。图 3B 示出了根据本公开的稳定化制剂的溶解型态。

[0020] 图 4 示出了实施例 4 中所描述的用根据本公开的制剂处理的患者的处理组 (PK 群体) 的所得平均基线调整骨化二醇浓度。

[0021] 图 5 示出了实施例 4 中所描述的用根据本公开的制剂处理的患者的处理组 (PK 群体) 的骨化二醇浓度的所得汇总基线调整 PK 参数。

[0022] 图 6 示出了实施例 4 中所描述的用根据本公开的制剂处理的患者在 6 周处理 (PK 群体) 期间的所得平均基线调整血清 1, 25-二羟基维生素 D 水平。

[0023] 图 7 示出了实施例 4 中所描述的用根据本公开的制剂处理的患者的处理组 (PK 群体) 的血清 1, 25-二羟基维生素 D 的所得基线调整重复剂量 PK 参数的汇总。

[0024] 图 8 示出了实施例 4 中所描述的用根据本公开的制剂处理的患者在 6 周处理 (PK 群体) 期间的血浆 iPTH 水平的所得平均基线百分比。

[0025] 图 9 示出了实施例 4 中所描述的用根据本公开的制剂处理的患者的处理组 (PK 群体) 的血浆 iPTH 的所得基线调整重复剂量 PK 参数的汇总。

[0026] 图 10 和 11 示出了实施例 4 中所描述的用根据本公开的制剂处理的患者的 PK 群体中血浆 iPTH 相对于基线调整骨化二醇和 1, 25-二羟基维生素 D 暴露 ($\text{AUC}_{0-6\text{周}}$) 在 EOT 处从基线的变化百分比。

具体实施方式

[0027] 如本文所用的术语“控制释放”和“修饰释放”可互换使用并且指的是所施用的维生素 D 化合物以偏离立即释放的方式释放。如本文所用的术语“持续释放”和“延长释放”可互换使用并且指的是所施用的维生素 D 化合物相比可比的立即释放制剂经过更长的时间段释放,使得维生素 D 化合物的血清浓度相比可比的立即释放制剂持续更长的时间段保持升高超过基线。前述术语任选地包括延迟释放特征。举例来说,控制释放制剂的延迟释放类型的特征将为 C_{max} 在某个时间处大于立即释放制剂的 C_{max} 。作为另一个实例,25-羟基维生素 D 化合物的释放将优选地在使得 25-羟基维生素 D 的总血清或血液水平持续延长的时间段,例如 4 至 24 小时或甚至更长时间维持或升高高于给药前水平的速率下。

[0028] 除非另有规定,否则如本文所用的术语“纤维素化合物”可以包括纤维素 ($\text{C}_6\text{H}_{10}\text{O}_5$) 或纤维素衍生物。“纤维素醚”是已经进行化学修饰以使得纤维素分子中的羟基部分或完全醚化的纤维素衍生物。举例来说,可以用作稳定剂的纤维素衍生物的实例包括 (但不限于) 纤维素糖醛酸 (celluloronic acid)、羧甲基纤维素、乙基纤维素、羟乙基纤维素、羟丙

基纤维素、羟丙基甲基纤维素、甲基纤维素、聚阴离子纤维素以及其组合。对应于例如分子量、粘度、溶解度以及水合的变化变化的不同等级的每种纤维素化合物或稳定剂也由这些术语所涵盖。

[0029] 预期适合于预防和 / 或治疗用途的任何维生素 D 化合物以及其组合包括于本文所描述的制剂中。维生素 D、25- 羟基维生素 D、1, 25- 二羟基维生素 D 以及其它维生素 D 代谢物和类似物也适用作医药组合物中的活性化合物。特定实例包括 (但不限于) 维生素 D₃ (胆钙化醇)、维生素 D₂ (麦角钙化醇)、25- 羟基维生素 D₃、25- 羟基维生素 D₂、25- 羟基维生素 D₄、25- 羟基维生素 D₅、25- 羟基维生素 D₇、1 α , 25- 二羟基维生素 D₃、1 α , 25- 二羟基维生素 D₂、1 α , 25- 二羟基维生素 D₄ 以及维生素 D 类似物 (包括所有羟基和二羟基形式), 包括 1, 25- 二羟基 -19- 去甲 - 维生素 D₂ 和 1 α - 羟基维生素 D₃。在一种类型的实施方案中, 维生素 D 化合物包括一种或多种羟基形式, 诸如 25- 羟基维生素 D₃ 与 25- 羟基维生素 D₂ 的组合。

[0030] 特别预期用于本文所公开的制剂中的维生素 D 化合物的类型可以包括 25- 羟基维生素 D₂、25- 羟基维生素 D₃ 或其组合。特别预期 25- 羟基维生素 D₃。如本文所用的术语 25- 羟基维生素 D 指的是 25- 羟基维生素 D₃、25- 羟基维生素 D₂、25- 羟基维生素 D₄、25- 羟基维生素 D₅ 或 25- 羟基维生素 D₇ 中的一者或多者, 并且预期在针对此的任何提及内容中优选实施方案是 25- 羟基维生素 D₃ 和 25- 羟基维生素 D₂ 中的一者或多者, 优选 25- 羟基维生素 D₃。因此, 在本文所描述的任何和所有制剂中, 特定地预期活性剂可以包括 25- 羟基维生素 D₂ 和 25- 羟基维生素 D₃ 中的一者或两者, 特别是 25- 羟基维生素 D₃。在本文的公开内容中, 维生素 D 化合物 (或其组合) 也被称作制剂的 “活性” 部分 (或 “活性” 剂), 区别于控制释放基质、稳定剂以及其它赋形剂。在本文中关于使用 25- 羟基维生素 D₃ 作为活性剂的样品所报导的药物动力学测试中, 提及 25- 羟基维生素 D 应解释为意指 25- 羟基维生素 D₃, 并且与 (例如, t_{max} 、 C_{max} 、AUC) 相关的所有药物动力学 (PK) 结果应理解为基于 25- 羟基维生素 D₃。

[0031] 如本文所用的 “稳定化” 制剂指的是展现稳定的体外溶解型态 (根据本文进一步描述的参数中的任一者) 和维生素 D 化合物在体内持续初始制造之后, 例如实际上架储存或加速的稳定性储存条件之后的一段时间的控制释放 (例如, 持续释放) 的制剂。活性成分的释放可以使用适合的体外溶解方法来测量, 诸如本领域中已知的方法之一。原则上, 美国药典 (United States Pharmacopeia), USP 29-NF 24, Dissolution<711> 物理测试和测定 (physical tests and determinations), United States Pharmacopeial Convention, Inc., Rockville, MD, 2006, 第 2673-2682 页; 欧洲药典 2.9.3 (European Pharmacopoeia 2.9.3) 固体剂型的溶解测试 (Dissolution Test for Solid Dosage Forms); 或日本药典 6.10 (Japanese Pharmacopoeia 6.10) 溶解测试 (Dissolution Test) 中所描述的溶解研究中的任一者可以用于判定制剂是否稳定。出于本发明的目的, 体外溶解方法是美国药典 (United States Pharmacopeia), USP 29-NF 24, Dissolution<711> 物理测试和测定 (physical tests and determinations), United States Pharmacopeial Convention, Inc., Rockville, MD, 2006, 第 2673-2682 页, 使用装置 2 (桨板法), 如下文的实施例中所描述。

[0032] 如本文所用的 t_{max} (或 T_{max}) 定义为在施用根据本发明的制剂之后在给药间隔内活性化合物的血浆浓度达到其最大值的时间。当施用单一的 25- 羟基维生素 D 化合物, 例

如 25-羟基维生素 D₃ 时, 除非另有规定, 否则 $t_{\max}$ 定义为在施用制剂之后在给药间隔内血清 25-羟基维生素 D₃ 的血浆浓度达到其最大值的时间。

[0033] 与 NKF K/DOQI 准则一致, 如本文所用的维生素 D 充足定义为血清 25-羟基维生素 D 水平 $\geq 30\text{ng/mL}$, 维生素 D 不足定义为 $16\text{--}30\text{ng/mL}$ 的血清 25-羟基维生素 D, 轻度维生素 D 缺乏定义为 $5\text{--}15\text{ng/mL}$ 的血清 25-羟基维生素 D, 并且重度维生素 D 缺乏定义为低于 5ng/mL 的血清 25-羟基维生素 D。

[0034] 在禁止对人体实施的方法取得专利权的司法管辖区中, 将组合物“施用”于人类受试者的含义应限于开立人类受试者将通过任何技术(例如, 经口、吸入、局部应用、注射、插入, 等等)自行施用的管制物质。与定义可取得专利权的主题的法律或法规一致的最宽泛的合理解释是所预期的。在不禁止对人体实施的方法取得专利权的司法管辖区中, 组合物的“施用”包括对人体实施的方法以及前述活动。

[0035] 应特定地了解, 本文所叙述的任何数值包括从下限值至上限值的所有值, 即, 介于所列举的最低值与最高值之间的数值的所有可能组合都被视为在本申请中明确陈述。举例来说, 如果浓度范围或有益作用范围被陈述为 1% 至 50%, 那么意图在本说明书中明确列举诸如 2% 至 40%、10% 至 30% 或 1% 至 3% 等等的值。作为另一个实例, 约 20% 的陈述浓度意图包括从 19.5% 直至 20.5% 的值。这些仅仅是特定预期的实例。

[0036] 本文公开了用于在摄取制剂的受试者的胃肠道中维生素 D 化合物的控制释放的制剂。这种制剂将包括如本文所描述的维生素 D 化合物、可释放地结合维生素 D 化合物并且可控地释放维生素 D 化合物的基质组分(例如, 亲脂性基质)、以及稳定剂(例如, 纤维素化合物)。

[0037] 根据本文的公开内容的稳定化制剂在储存一定时间段之后在体外溶解中释放的 25-羟基维生素 D 的量与刚在制造之后和储存之前的相同制剂的溶解实质上没有不同。举例来说, 在一个实施方案中, 制剂在暴露于 25°C 和 60% 相对湿度的储存条件两个月之后在体外溶解期间释放的 25-羟基维生素 D 的量在四小时后的任何给定溶解时间点与在使制剂暴露于储存条件之前(即, 新鲜生产的产品)进行的体外溶解期间的相同溶解时间点释放的量相比变化 30% 或更小。

[0038] 下表提供了在 25°C 和 60% RH 下和替代地在 40°C 和 75% RH 下储存持续初始制造后的各种时间之后和在溶解测试期间的各种时间处, 本发明的实施方案所预期的有利的储存稳定性程度的实例。储存稳定性程度用从标称活性效力的最大偏差, 即, 从 LC 的最大变化% 来表示。还提供了最大偏差的替代性实施方案。

[0039]

时 间 (h)	1个月	3个月	6个月	9个月	12个月	18个月	24个月
在 25℃和 60% RH 下储存							
2	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%
4	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%
6	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%
8	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%
12	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%
在 40℃和 75% RH 下储存							

[0040]

2	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%
4	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%
6	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%
8	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%
12	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%	30%、或 25%、或 20%、或 15%、或 10%

[0041] 在一种类型的实施方案中,制剂在整个溶解测试中的多个时间点处,例如至少在 2 小时与 4 小时时间点处、任选地又在 6 小时时间点处、进一步任选地又在 8 小时时间点处以及进一步任选地又在 12 小时时间点处将具有在上文刚才的表格中所描述的有利的稳定性程度,以使得在储存之后的溶解型态遵循新鲜产品的溶解型态。或者,制剂至少在 2、6 以及 12 小时时间点处将具有在上文刚才的表格中所描述的有利的稳定性程度。或者,制剂至少在 4、8 以及 12 小时时间点处将具有在上文刚才的表格中所描述的有利的稳定性程度。或者,制剂至少在 2、4 以及 6 小时时间点处将具有在上文刚才的表格中所描述的有利的稳定性程度。或者,制剂至少在 4、6、8 以及 12 小时时间点处,或在 4 小时和此后的所有时间处将具有在上文刚才的表格中所描述的有利的稳定性程度。

[0042] 在上文刚才的表格中所描述的任何和所有实施方案中,预期偏差关于新鲜产品可

以是正向的（更多释放）或负向的（更少释放）。在一种类型的实施方案中，预期偏差在多个时间点处将处于负向（更少释放）方向。此外，在一种类型的实施方案中，预期溶解释放中的偏差如果在制剂中没有稳定剂的存在，那么在多个时间点将为负向的（更少释放）。

[0043] 在本文所预期的任何实施方案中，制剂的溶解释放型态可以具有本文下面所提供的实例中的任一者的特征。举例来说，制剂的特征可以为提供维生素 D 化合物的以下释放的溶解释放型态：在 2 小时处小于 30%、在 6 小时处大于 45% 以及在 12 小时处大于 80%，并且进一步任选地在 6 小时处小于 60%。

[0044] 在另一种类型的实施方案中，制剂的特征可以为提供维生素 D 化合物的以下释放的体外溶解型态：在 100 至 140 分钟处小于 30%、在 5 至 7 小时处大于 45% 以及在 11 至 13 小时处大于 80%。在另一种类型的实施方案中，制剂的特征可以为提供维生素 D 化合物的以下释放的体外溶解型态：在 2 小时处小于 30%、在 6 小时处大于 45% 以及在 12 小时处大于 80%。在这些类型的实施方案中，任选地，维生素 D 化合物的释放在 5 至 7 小时处小于 60%，或在 6 小时处小于 60%。

[0045] 在另一种类型的实施方案中，制剂的特征可以为提供维生素 D 化合物的以下释放的体外溶解型态：在 2 小时处约 20% 至约 40%、在 6 小时处至少 35% 以及在 12 小时处至少 70%。在另一种类型的实施方案中，制剂的特征可以为提供维生素 D 化合物的以下释放的体外溶解型态：在 2 小时处约 25% 至约 35%、在 6 小时处至少 40% 以及在 12 小时处至少 75%。在这些类型的实施方案中，任选地，维生素 D 化合物的释放为例如在 6 小时处 75% 或更小，或在 6 小时处 65% 或更小，或在 6 小时处 60% 或更小。

[0046] 在本文所描述的任何实施方案中，稳定化制剂的特征可以为在将剂型施用于人类患者之后至少 4 小时、或至少 8 小时、或至少 12 小时、或至少 18 小时、或至少 20 小时、或至少 24 小时、或至少 28 小时的 $t_{\max}$ ，例如在 4 至 96 小时的范围内，或在 18 至 30 小时的范围内，或在 13 至 28 小时的范围内，或为例如 28 小时。

[0047] 在本文所预期的任何实施方案中，包含 25-羟基维生素 D 的制剂的特征可以为当施用于成年人时提供每微克 25-羟基维生素 D 在约 0.0133ng/mL 至约 0.04ng/mL 的范围内的基线调整 $C_{\max}$ 。

[0048] 在本文所预期的任何方法中，这种方法可以包括将包含 25-羟基维生素 D 化合物的稳定化持续释放剂型施用于人类患者，其包括将有效量的制剂施用于患者以提供至少约 0.2ng/mL 并且任选地小于 110ng/mL 并且进一步任选地 24ng/mL 或更小的基线调整 $C_{\max}$ ，例如在约 0.2 至约 24ng/mL 的范围内。

[0049] 在本文所预期的任何方法中，这种方法可以包括将包含 25-羟基维生素 D 化合物的稳定化持续释放剂型施用于人类患者，其包括将有效量的制剂施用于患者以提供至少 52ng · h/mL 并且任选地小于 34,500ng · h/mL 并且进一步任选地约 12,000ng · h/mL 或更小的基线调整 $AUC_{0-\infty}$ ，例如在约 52ng · h/mL 至约 12,000ng · h/mL 的范围内。

[0050] 在本文所描述的任何实施方案中，预期稳定化制剂在储存之后可以与新鲜制成的产品生物等效。因此，举例来说，稳定化制剂在储存之后可以提供在新鲜产品的 90% 置信区间内、或在平均值的 80% 至 125% 内、或在平均值的 80% 至 120% 内的活性剂（或血清总 25-羟基维生素 D）的曲线下面积 AUC（例如， $AUC_{0-\infty}$ 或 AUC_{0-t} ）。另外或在替代方案中，稳定化制剂在储存之后可以提供在新鲜产品的 90% 置信区间内、或在平均值的 80% 至 125%

内、或在平均值的 80% 至 120% 内的活性剂（或血清总 25- 羟基维生素 D）的最大血清浓度 $C_{\max}$ （例如， $C_{\max}$ 绝对值，或相较于基线的 $C_{\max}$ ）。

[0051] 在一个实施方案中，稳定化制剂包含 25- 羟基维生素 D₂ 和 25- 羟基维生素 D₃ 中的一者或两者、蜡基质以及纤维素化合物。在一个方面，稳定化制剂包含 25- 羟基维生素 D₂ 和 25- 羟基维生素 D₃ 中的一者或两者、蜡基质以及纤维素稳定剂。在另一个方面，制剂包含 25- 羟基维生素 D₂ 和 25- 羟基维生素 D₃ 中的一者或两者、蜡基质以及有效量的纤维素化合物以提供如本文所描述的有利的稳定性程度，例如，就上文刚才的表格来说或与下文所描述的任何实施例一致。举例来说，这种量可以有效提供在暴露于 25℃ 和 60% 相对湿度的储存条件至少一个月之后在体外溶解期间的某个溶解时间点释放的活性剂的量与在使制剂暴露于储存条件之前进行的体外溶解期间的相同溶解时间点释放的量之间 30% 或更小的差异，而缺乏稳定剂的比较性制剂将导致在相同储存条件之后溶解释放的更大差异。

[0052] 在一个方面，制剂是用于在摄取制剂的受试者的胃肠道中维生素 D 化合物的控制释放的改善制剂。在一个实施方案中，改善包括将纤维素稳定剂混入用于在摄取制剂的受试者的胃肠道中维生素 D 化合物的控制释放的制剂中。在另一个实施方案中，改善包括混入用于在摄取制剂的受试者的胃肠道中维生素 D 化合物的控制释放的制剂中的有效量的纤维素化合物以提供如本文所描述的有利的稳定性程度，例如，就上文刚才的表格来说或与下文所描述的任何实施例一致。举例来说，这种量可以有效提供在暴露于 25℃ 和 60% 相对湿度的储存条件至少一个月之后在体外溶解期间的某个溶解时间点释放的活性剂的量与在使制剂暴露于储存条件之前进行的体外溶解期间的相同溶解时间点释放的量之间 30% 或更小的差异，而缺乏稳定剂的比较性制剂将导致在相同储存条件之后溶解释放的更大差异。

[0053] 稳定剂可以包括纤维素化合物。用于本公开的稳定化制剂中的纤维素化合物和稳定剂的实例可以包括（但不限于）纤维素糖醛酸、羧甲基纤维素、乙基纤维素、羟乙基纤维素、羟丙基纤维素、羟丙基甲基纤维素、甲基纤维素、聚阴离子纤维素以及其组合。还预期泊洛沙姆（poloxamer）（例如，泊洛沙姆 407）、聚（氧化乙烯）聚合物（例如，陶氏（Dow's）POLYOX 聚合物）、聚维酮（povidone）以及煅制二氧化硅（例如，AEROSIL 200, Evonik Industries AG, Essen, Germany）中的一者或多者。稳定剂，例如纤维素化合物，优选地以排除任何额外包衣或外壳的制剂的总重量计按制剂的至少约 5%（wt%）的量存在。举例来说，纤维素化合物可以按制剂的至少 5wt%、或制剂的至少 10wt%、或制剂的至少 15wt%、或制剂的大于 5wt%、或制剂的大于 10wt%、或制剂的大于 15wt% 的量存在。适合的范围包括 5wt% 至 30wt%、10wt% 至 20wt%、10wt% 至 15wt%、5wt% 至 15wt% 以及 7.5wt% 至 12.5wt%。实例包括约 5wt%、约 6wt%、约 7wt%、约 8wt%、约 9wt%、约 10wt%、约 11wt%、约 12wt%、约 13wt%、约 14wt% 以及约 15wt%。应了解，本文所提及的稳定剂是稳定溶解释放型态（并且因此也稳定体内释放型态）对抗在储存条件，例如典型上架储存条件期间随着时间的实质性变化的试剂。在本领域中已知作为用于防止活性组分本身降解的防腐剂的其它试剂并不意图涵盖于术语“稳定剂（stabilizing agent/stabilizer）”内，不过这类防腐剂也预期用于本发明的制剂中。

[0054] 在一种类别的实施方案中，纤维素化合物是纤维素醚。纤维素醚的实例包括（但不限于）甲基纤维素、羟丙基甲基纤维素、羟乙基甲基纤维素、羟乙基纤维素、羟丙基纤维

素以及其组合。

[0055] 特别预期羟丙基甲基纤维素 (HPMC)。HPMC 的特征可以为个别地和以组合形式特定预期的以下特征中的一者或多者。HPMC 中的甲氧基组分%可以在 19 至 24 的范围内。羟丙基组分%可以在 7 至 12 的范围内。表观粘度 (于水中的 2% 溶液, 在 20℃ 下) 可以为至少 50,000cP 或至少 80,000cP, 或在约 80 至 120,000cP、或 3000 至 120,000cP、或 11,000 至 120,000cP、或 80,000 至 120,000cP 的范围内。特别地, 表观粘度 (于水中的 2% 溶液, 在 20℃ 下) 可以在 80,000 至 120,000cP 的范围内。pH (于水中的 1% 溶液) 可以在 5.5 至 8.0 的范围内。举例来说, 具有所有前述特性, 包括在 80,000 至 120,000cP 的范围内的表观粘度 (于水中的 2% 溶液, 在 20℃ 下) 的适合的羟丙基甲基纤维素是 METHOCCEL K100M CR (Dow Wolff Cellulosics, Midland, Michigan)。

[0056] 在一种类型的实施方案中, 纤维素化合物将在基质的主要组分的熔点下, 例如在 65℃ 下或在 60℃ 至 75℃ 的范围内不溶于基质制剂中。

[0057] 在一种类型的实施方案中, 纤维素化合物将是亲水性的。

[0058] 包含 25- 羟基维生素 D₂ 和 25- 羟基维生素 D₃ 中的一者或多者以及纤维素化合物的根据本公开的医药制剂与缺乏纤维素化合物的制剂相比具有意外改善的稳定性。在一个实施方案中, 根据本公开的稳定化制剂包含有包含 25- 羟基维生素 D₂ 和 25- 羟基维生素 D₃ 中的一者或两者的活性剂加载的亲脂性基质与纤维素稳定剂的混合物, 其中这种制剂在暴露于 25℃ 和 60% 相对湿度的储存条件至少一个月之后在体外溶解期间释放的 25- 羟基维生素 D 的量在任何给定溶解时间点与在对新鲜制成的产品进行的体外溶解期间的相同溶解时间点释放的量相比变化 30% 或更小。

[0059] 如下文的实施例中所示, 未进行稳定化的制剂展现在将组合物储存一定时间段之后释放的活性成分的量的变化。未稳定化制剂在暴露于储存条件之后释放的 25- 羟基维生素 D 的量在给定溶解时间点与在对新鲜制成的产品进行的体外溶解期间的相同溶解时间点释放的量相比可以变化超过 30%。变化可以是在给定时间点处溶解速率的增大或减小, 并且这类变化产生曲线与初始溶解型态的形状不同的溶解型态。在如本文所描述的储存之后, 例如在 25℃ 和 60% RH 下储存 3 个月或更长时间之后, 未稳定化制剂与根据本公开的稳定化制剂相比还展现不同的体内作用。在如本文所描述的储存之后, 例如在 25℃ 和 60% RH 下储存 3 个月或更长时间之后, 稳定化制剂展示不同的临床药物动力学参数, 诸如改善的生物利用度。根据本公开的稳定化制剂可以具有储存不稳定的基础制剂, 与促使制剂如本文所描述储存稳定的稳定剂组合。

[0060] 可释放地结合并且可控地释放活性组分的基质可以是例如亲脂性基质, 包括蜡基质。蜡基质可以提供在室温下呈固体或半固体并且在体温下呈固体、半固体或液体, 优选地在体温下呈半固体或液体的制剂。在一个方面, 蜡基质包含控制释放剂、乳化剂以及吸收增强剂。

[0061] 适合使用的控制释放剂的实例包括 (但不限于) 蜡, 包括合成蜡、微晶蜡、石蜡、巴西棕榈蜡以及蜂蜡; 聚乙氧基化蓖麻油衍生物、氢化植物油、单山嵛酸甘油酯、二山嵛酸甘油酯或三山嵛酸甘油酯; 长链醇, 诸如硬脂醇、鲸蜡醇以及聚乙二醇; 以及任何前述者的混合物。非消化性蜡状物质, 诸如硬石蜡是优选的。

[0062] 控制释放剂可以按制剂的至少 5wt% 或制剂的大于约 5wt% 的量存在。举例来说,

取决于所使用的控制释放剂,控制释放剂可以占制剂的至少 5wt%、或制剂的至少 10wt%、或制剂的至少 15wt%、或制剂的至少 20wt%、或制剂的至少 25wt%、或制剂的大于 5wt%、或制剂的大于 10wt%、或制剂的大于 15wt%、或制剂的大于 20wt%、和 / 或制剂的大于 25wt%。控制释放剂可以按 50wt%或更小、40wt%或更小、35wt%或更小、或 30wt%或更小的量存在。适合的范围包括 5wt%至 40wt%、10wt%至 30wt%以及 15wt%至 25wt%。实例包括约 15wt%、约 16wt%、约 17wt%、约 18wt%、约 19wt%、约 20wt%、约 21wt%、约 22wt%、约 23wt%、约 24wt%以及约 25wt%。

[0063] 适合用于制剂中的乳化剂的实例包括(但不限于)具有小于 7 的 HLB 的亲脂剂,诸如混合脂肪酸甘油单酯;混合脂肪酸甘油二酯;脂肪酸甘油单酯与甘油二酯的混合物;亲脂性聚甘油酯;甘油酯,包括单油酸甘油酯、二油酸甘油酯、单硬脂酸甘油酯、二硬脂酸甘油酯、单棕榈酸甘油酯以及二棕榈酸甘油酯;脂肪酸甘油乳酸酯;丙二醇酯,包括单棕榈酸丙二醇酯、单硬脂酸丙二醇酯以及单油酸丙二醇酯;脱水山梨糖醇酯,包括单硬脂酸脱水山梨糖醇酯、倍半油酸脱水山梨糖醇酯;脂肪酸和其皂,包括硬脂酸、棕榈酸以及油酸;以及其混合物;单油酸甘油酯、二油酸甘油酯、单硬脂酸甘油酯、二硬脂酸甘油酯、单棕榈酸甘油酯以及二棕榈酸甘油酯;脂肪酸甘油乳酸酯;丙二醇酯,包括单棕榈酸丙二醇酯、单硬脂酸丙二醇酯以及单油酸丙二醇酯;脱水山梨糖醇酯,包括单硬脂酸脱水山梨糖醇酯、倍半油酸脱水山梨糖醇酯;脂肪酸和其皂,包括硬脂酸、棕榈酸以及油酸;以及其混合物。

[0064] 优选的类脂剂选自甘油酯和其衍生物。优选的甘油酯选自由重链或长链甘油酯、辛酰己酰聚乙二醇甘油酯以及其混合物组成的群组。

[0065] 优选的中链甘油酯包括(但不限于)中链甘油单酯、中链甘油二酯、辛酸/癸酸甘油三酯、单月桂酸甘油酯、单硬脂酸甘油酯、辛酸/癸酸甘油酯、单辛酸甘油酯、单二辛酸甘油酯、辛酸/癸酸亚油酸甘油三酯以及辛酸/癸酸/琥珀酸甘油三酯。

[0066] 具有低熔点的甘油单酯优选用于制造制剂。优选的甘油单酯包括(但不限于)单硬脂酸甘油酯、单棕榈酸甘油酯、单油酸甘油酯、单辛酸甘油酯、单癸酸甘油酯、单月桂酸甘油酯等等,优选单硬脂酸甘油酯(GMS)。GMS 是天然乳化剂。GMS 是油溶性的,但难溶于水。GMS 具有 3.8 的 HLB 值。举例来说,亲脂性乳化剂可以按约 10wt%至约 40wt%或约 20wt%至约 25wt%的范围内的量存在。其它实例包括约 20wt%、约 21wt%、约 22wt%、约 23wt%、约 24wt%以及约 25wt%。

[0067] 适合的吸收增强剂的实例包括(但不限于)辛酰己酰聚乙二醇甘油酯,诸如聚乙烯糖基化甘油酯,也称为聚乙烯醇化甘油酯或 PEG 化甘油酯。可以在组合物中采用的 PEG 化甘油酯包括(但不限于)甘油单酯、甘油二酯以及甘油三酯与聚乙二醇单酯和二酯的混合物、聚乙烯糖基化杏仁甘油酯、聚乙烯糖基化玉米甘油酯以及聚乙烯糖基化辛酸/癸酸甘油三酯。吸收增强剂可以具有 13 至 18 或 13 至 15 的 HLB 值。

[0068] 一种优选的吸收增强剂以商标名 GELUCIRE(Gattefossé Corporation, Paramus, New Jersey, USA)已知。GELUCIRE 是众所周知的赋形剂,其为甘油脂肪酸酯和 PEG 酯的家族,也称为聚乙烯醇化甘油酯。GELUCIRE 用于各种应用中,包括制备持续释放医药组合物。GELUCIRE 化合物是惰性的半固体蜡状物质,其为两亲性的并且以不同的物理特征可用,诸如熔点、HLB 以及于各种溶剂中的溶解度。GELUCIRE 性质上是表面活性的并且分散或溶解于水性介质中,形成胶束、微球或囊泡。GELUCIRE 由其熔点/HLB 值来

鉴别。熔点以摄氏度表示。可以选择不同等级的 GELUCIRE 赋形剂之一或混合物以达成熔点和 / 或 HLB 值的所需特征。优选的 GELUCIRE 组合物是 GELUCIRE 44/14, 即, 具有 44℃ 的熔点和 14 的 HLB 的月桂酰聚乙二醇甘油酯与月桂酰聚氧甘油酯的混合物。举例来说, 吸收增强剂可以按约 5wt% 至约 20wt% 或约 8wt% 至约 15wt% 的量存在。其它实例包括约 8wt%、约 9wt%、约 10wt%、约 11wt%、约 12wt%、约 13wt%、约 14wt% 以及约 15wt%。

[0069] 蜡基质的低熔点提供了在高于蜡基质的熔点约 0℃ 至约 50℃ 的温度下并入医药活性成分, 例如维生素 D 化合物, 诸如 25-D₂、25-D₃ 或两者, 然后将熔体 (溶液和 / 或分散体) 填充于适合的胶囊中的方式。胶囊可以是与熔体填充的温度相容的任何种类, 包括软或硬明胶胶囊, 和动物或植物明胶胶囊。熔体在冷却至室温后在胶囊内凝固。

[0070] 在一个方面, 稳定化制剂可以进一步包含用于 25-羟基维生素 D₂ 和 / 或 25-羟基维生素 D₃ 的油性媒剂。可以使用任何医药学上可接受的油。实例包括动物 (例如, 鱼)、植物 (例如, 大豆) 以及矿物油。油优选地将容易溶解所使用的 25-羟基维生素 D 化合物。优选的油性媒剂包括非消化性油, 诸如矿物油, 特别是液体石蜡, 和角鲨烯。举例来说, 油性媒剂可以按制剂的约 10wt% 至约 50wt%、或约 15wt% 至约 45wt%、或约 20wt% 至约 40wt%、或约 30wt% 至约 40wt% 的范围内的浓度存在。在一种类型的实施方案中, 适合的液体石蜡的特征可以为以下参数中的一者或多者: 比重, 约 0.88 至 0.89; 运动粘度 (40℃), 约 64cSt 至约 70cSt; 分子量, 424; 石蜡烃%, 约 59; 以及倾点, -24℃。可以优化蜡基质与油性媒剂之间的比率以达成维生素 D 化合物的所需释放速率。因此, 如果使用较重的油组分, 那么可以使用相对较少的蜡基质, 并且如果使用较轻的油组分, 那么可以使用相对较多的蜡基质。

[0071] 优选地设计根据本发明的稳定化控制释放组合物以含有例如每单位剂量 1 至 1000 μg 浓度的 25-羟基维生素 D₂ 和 / 或 25-羟基维生素 D₃, 并且以一定方式制备以便经过延长的时间段实现 25-羟基维生素 D₂/25-羟基维生素 D₃ 的控制或实质上恒定释放, 任选地释放至人类或动物的胃肠道的回肠中。示例性剂量包括每单位剂量 1 μg 至 1000 μg、1 μg 至 600 μg、1 μg 至 400 μg、1 μg 至 200 μg、1 μg 至 100 μg、5 μg 至 90 μg、30 μg 至 80 μg、20 μg 至 60 μg、30 μg 至 60 μg、35 μg 至 50 μg、5 μg 至 50 μg 以及 10 μg 至 25 μg, 例如, 20 μg、25 μg、30 μg、40 μg、50 μg、60 μg、70 μg、80 μg、90 μg 以及 100 μg。

[0072] 在一种优选类别的实施方案中, 控制释放制剂在给药后的最初 24 小时内释放至少 70%、更优选地至少 80% 的维生素 D 化合物。

[0073] 有利地, 可以根据上文所描述的实施方案以例如每天 1 至 100 μg 的剂量, 与其它治疗剂一起施用 25-羟基维生素 D₂、25-羟基维生素 D₃ 或其组合, 例如经口。在一种类型的实施方案中, 将选择剂量以在给药间隔内提供约 1 至 3ng/ml 的血清 25-羟基维生素 D₃ 的平均升高。

[0074] 在实施方案中, 可以施用本文所描述的制剂以升高并且优选地还维持血液 1, 25-二羟基维生素 D 水平处于 25pg/mL、30pg/mL 或更高, 例如 25-65pg/mL, 持续延长的时段, 例如至少一个月、至少三个月、至少六个月或更长时间。

[0075] 在一个方面, 可以将本文所描述的制剂施用于患者以降低或维持下降的血清甲状旁腺激素水平, 优选地以使 PTH 水平降低至少 30% 的量, 或者以使 PTH 的血清水平降至 CKD 分期的目标范围 (例如, 对于 3 期为 35-70pg/mL (等效于 3.85-7.7pmol/L), 对于 4 期为 70-110pg/mL (等效于 7.7-12.1pmol/L), 并且对于 5 期为 150-300pg/mL (等效于

16.5–33.0pmol/L) (在 K/DOQI 准则 1 号中定义)) 所需的量。

[0076] 在另一个方面, 可以将根据本文的公开内容的制剂施用于罹患继发性慢性肾病 (例如, 3 期或 4 期, 或 3 期、4 期或 5 期) 的甲状旁腺功能亢进的患者以降低血清 PTH 水平。

[0077] 本文所描述的剂量预期用于本文所描述的治疗方法中的任一者。应了解, 在特定情况下维生素 D 化合物的实际优选量将根据所配制的特定组合物、应用模式以及所治疗的特定部位而变化。剂量可以使用常规考虑因素来确定, 例如, 通过激素与已知药剂的差异活性的惯常比较, 例如借助于适当的常规药理方案。

[0078] 用于每个特定患者的特定剂量可以取决于多种因素, 例如, 年龄、体重、一般健康状况、性别、饮食、施用时间和模式、排泄速率, 以及组合使用的药物和应用疗法的特定病症的严重性。

[0079] 需要维生素 D 补充的患者包括健康受试者和处于维生素 D 不足或缺乏风险下的受试者, 例如, 患有 1 期、2 期、3 期、4 期或 5 期 CKD 的受试者; 不饮用维生素 D 强化牛奶的婴儿、儿童以及成人 (例如, 乳糖不耐的受试者、牛奶过敏的受试者、不喝牛奶的素食者、以及母乳喂养的婴儿); 患有佝偻病的受试者; 深色皮肤的受试者 (例如, 在美国, 相较于 4% 的白人女性, 42% 的年龄介于 15 岁与 49 岁之间的非裔美国女性是维生素 D 缺乏的); 老年人 (其合成维生素 D 的能力降低并且也更可能待在室内); 制度化的成人 (其可能待在室内, 包括患有阿尔茨海默氏病 (Alzheimer's disease) 或精神疾病的受试者); 遮盖所有暴露的皮肤受试者 (诸如某些宗教或文化的成员); 总是使用防晒霜的受试者 (例如, 应用防晒因子 (SPF) 值为 8 的防晒霜使维生素 D 的产生减少 95%, 并且更高的 SPF 值可以进一步减少维生素 D); 患有脂肪吸收不良综合症的受试者 (包括 (但不限于) 囊性纤维化、胆汁淤积性肝病、其它肝病、胆囊疾病、胰酶缺乏、克罗恩氏病 (Crohn's disease)、炎性肠病、口炎性腹泻或脂泻病, 或手术去除胃和 / 或肠的一部分或全部); 患有炎性肠病的受试者; 患有克罗恩氏病的受试者; 已经切除小肠的受试者; 患有牙龈疾病的受试者; 服用增加维生素 D 的分解代谢的药物的受试者, 包括苯妥英 (phenytoin)、磷苯妥英 (fosphenytoin)、苯巴比妥 (phenobarbital)、卡马西平 (carbamazepine) 以及利福平 (rifampin); 服用减少维生素 D 吸收的药物的受试者, 包括考来烯胺 (cholestyramine)、考来替泊 (colestipol)、奥利司他 (orlistat)、矿物油以及脂肪替代品; 服用抑制维生素 D 活化的药物的受试者, 包括酮康唑 (ketoconazole); 服用减少钙吸收的药物的受试者, 包括皮质类固醇; 肥胖的受试者 (沉积于体脂肪层中的维生素 D 有较小的生物可用性); 患有骨质疏松症的受试者; 具有低骨矿物质密度和骨质疏松症的患者; 和 / 或绝经后女性。根据医学研究所 (Institute of Medicine) 对维生素 D 的膳食参考摄入量 (Dietary Reference Intakes for vitamin D) 所作的报告, 食物消耗数据表明较年轻与较年长女性的维生素 D 的中值摄入量都低于当前推荐; 数据表明超过 50% 的较年轻和较年长女性并不消耗推荐量的维生素 D。

[0080] 从本文所描述的本发明方法中任选地排除罹患肾性骨营养不良 (包括骨软化和囊性纤维性骨炎) 的受试者的治疗处理。

[0081] 在其它方面, 本发明的组合物和方法适用于预防或治疗处理维生素 D 反应性疾病, 即, 维生素 D、25-羟基维生素 D 或活性维生素 D (例如, 1, 25-二羟基维生素 D) 防止疾病发作或进展, 或减轻疾病的征象或症状的疾病。这类维生素 D 反应性疾病包括癌症 (例如, 乳癌、肺癌、皮肤癌、黑素瘤、结肠癌、结肠直肠癌、直肠癌、前列腺癌以及骨癌)。已经观测到

1, 25-二羟基维生素D在体外诱导许多细胞的细胞分化和/或抑制许多细胞的细胞增殖。维生素D反应性疾病还包括自体免疫疾病,例如,I型糖尿病、多发性硬化、类风湿性关节炎、多肌炎、皮炎、硬皮病、纤维化、格雷夫氏病(Grave's disease)、桥本氏病(Hashimoto's disease)、急性或慢性移植排斥反应、急性或慢性移植抗宿主疾病、发炎性肠病、克罗恩氏病、全身性红斑狼疮、修格兰氏综合症(Sjogren's Syndrome)、湿疹以及牛皮癣;皮炎,包括异位性皮炎、接触性皮炎、过敏性皮炎和/或慢性皮炎。维生素D反应性疾病还包括其它发炎性疾病,例如,哮喘、慢性阻塞性肺病、多囊性肾病、多囊性卵巢综合症、胰腺炎、肾炎、肝炎和/或感染。还已报导维生素D反应性疾病包括高血压和心血管疾病。因此,本发明预期预防或治疗处理处于以下疾病风险下或罹患以下疾病的受试者:心血管疾病,例如,患有动脉粥样硬化、动脉硬化、冠状动脉疾病、脑血管疾病、外周血管疾病、心肌梗塞、心肌缺血、脑缺血、中风、充血性心脏衰竭、心肌病的受试者;肥胖或其它体重异常;脂质异常(例如,高脂血症;脂代谢异常,包括相关的糖尿病性脂代谢异常和混合性脂代谢异常;低 α 脂蛋白血症;高甘油三酯血症;高胆固醇血症;以及低HDL(高密度脂蛋白));代谢异常(例如,代谢综合症;II型糖尿病;I型糖尿病;高胰岛素血症;葡萄糖耐量减低;胰岛素抵抗;糖尿病并发症,包括神经病、肾病、视网膜病、糖尿病足溃疡以及白内障);和/或血栓症。

[0082] 可以得益于维生素D化合物的水平调节的疾病包括(但不限于):(i)在甲状旁腺中——甲状旁腺功能减退、假性甲状旁腺功能减退、继发性甲状旁腺功能亢进;(ii)在胰腺中——糖尿病;(iii)在甲状腺中——髓样癌;(iv)在皮肤中——牛皮癣、伤口愈合;(v)在肺中——肉状瘤病和结核病;(vi)在肾中——慢性肾病、低磷酸盐血症VDRR、维生素D依赖性佝偻病;(vii)在骨中——抗惊厥剂治疗、骨纤维生成不良、囊性纤维性骨炎、骨软化、骨质疏松症、骨质减少、骨硬化、肾性骨营养不良、佝偻病;(viii)在肠中——糖皮质激素拮抗、特发性高钙血症、吸收不良综合症、脂肪痢、热带口炎性腹泻;以及(ix)自体免疫病症。

[0083] 在本发明的实施方案中,得益于维生素D化合物的水平调节的疾病选自癌症、皮肤病症(例如,牛皮癣)、甲状旁腺病症(例如,甲状旁腺功能亢进和继发性甲状旁腺功能亢进)、骨病症(例如,骨质疏松症)以及自体免疫病症。

[0084] 制剂可以通过充分处于一般技术人员的能力范围内的程序来制备。举例来说,必要时可以使基质组分(例如,蜡和油性媒剂)熔化以提供可流动液体,从而使得更容易获得均匀混合物。将活性剂(例如,25-羟基维生素D₂和/或25-羟基维生素D₃)添加至液体载剂中,例如,溶解于诸如无水乙醇的醇中,并且混合这些成分以提供均匀混合物。在一种类型的实施方案中,可以在掺合所有基质组分(例如,蜡和油)之后并且在与活性剂组合之前添加稳定剂。可以在稍后分成单位剂型,诸如填充的明胶胶囊之前冷却并储存混合物。

[0085] 在一种类型的方法中,将一部分油性媒剂、控制释放剂以及乳化剂加热至相对高的温度(例如,65℃)并且在添加吸收增强剂之前混合,继而进行额外混合直至均质,然后冷却至中间的高温(例如,50℃至55℃)。在一个独立容器中,将抗氧化剂防腐剂和剩余的油性媒剂混合并且加热至中间的高温(例如,50℃),然后与蜡混合物组合并混合直至获得均质溶液。接下来,边混合边添加稳定剂。接下来,将维生素D化合物于醇中的溶液与均质蜡状溶液组合,混合直至获得均质溶液,优选地填充至胶囊中,然后冷却至室温。在另一种优选方法中,在55℃至60℃的温度下加热一部分油性媒剂、控制释放剂以及乳化剂并且在添加吸收增强剂之前混合,继而进行额外混合直至均质。在一个独立容器中,将抗氧化剂防

腐剂、剩余的油性媒剂以及稳定剂混合并且加热至 55℃至 60℃的温度,然后与蜡混合物组合并混合直至获得均质溶液。接下来,将维生素 D 化合物于醇中的溶液与均质蜡状溶液组合,混合直至获得均质溶液,优选地填充至胶囊中,然后冷却至室温。

[0086] 在施用于需要治疗的患者之前将制剂优选地放置于胶囊中。这类胶囊可以是硬的或软的,并且特别预期软胶囊。可以使用标准胶囊填充机将制剂填充至明胶胶囊中,诸如通过使制剂熔化并且将其注射填充至软胶囊外壳中。示例性软胶囊外壳包括 VEGICAPS 和 OPTISHELL 技术 (Catalent, Somerset, NJ, USA)。在替代方案中,可以通过任何其它适合的工艺将制剂制成单位剂型,例如以得到片剂、香囊、糖衣丸、栓剂,等等。

[0087] 在一种类型的实施方案中,准备制剂并且通过经口递送而施用。在另一种类型的实施方案中,准备制剂并且作为栓剂,例如直肠栓剂而施用。

[0088] 除非另有规定,否则制剂以及使用和制造方法预期包括实施方案,其包括下文进一步描述的额外任选的要素、特征以及步骤中的一者或多者的任何组合。

[0089] 因此,在一种类型的实施方案中,制剂进一步包括防腐剂,诸如抗氧化剂。丁基化羟基甲苯 (BHT) 是优选的。

[0090] 在另一种类型的实施方案中,维生素 D 化合物与一种或多种其它治疗剂组合施用。

[0091] 如果维生素 D 化合物与一种或多种其它治疗剂组合施用,那么所施用的组合中的每种化合物的特性将取决于所处理的特定疾病病况。举例来说,我们可以选择与一种或多种钙盐(预期为钙补充剂或饮食性磷酸盐结合剂)、双膦酸盐、拟钙剂、烟酸、铁、磷酸盐结合剂、胆钙化醇、麦角钙化醇、活性维生素 D 固醇、血糖和高血压控制剂、各种抗肿瘤剂以及 CYP24 和可以使维生素 D 药剂降解的其它细胞色素 P450 酶的抑制剂一起施用 25-羟基维生素 D₂和 / 或 25-羟基维生素 D₃(例如,经口)。另外,我们可以选择与胆钙化醇、麦角钙化醇、活性维生素 D 固醇、血糖和高血压控制剂、各种抗肿瘤剂以及 CYP24 和可以使维生素 D 药剂降解的其它细胞色素 P450 酶的抑制剂一起静脉内施用 25-羟基维生素 D₂和 / 或 25-羟基维生素 D₃。实际上,在疾病病况的治疗处理是所需目标的情况下使用较高剂量的本发明化合物,而较低剂量一般用于预防目的,应了解,如本领域的技术人员所熟知,在任何给定情况下所施用的特定剂量将根据所施用的特定化合物、所治疗的疾病、受试者的状况以及可以改变药物的活性或受试者的反应的其它相关医学实情来调整。

[0092] 如上文所描述,将制剂优选地填充至明胶胶囊中,但其也可以按纯的形式施用,或具有一个或多个外包衣层,诸如肠溶包衣。还预期可以将制剂压成片剂,并且在这类情况下可以包括一种或多种压片赋形剂。

[0093] 在本文所描述的组合物和方法中,优选步骤、优选组分、其优选组成范围以及前述者的优选组合可以选自本文所提供的各种特定实例。举例来说,优选制剂包括 25-羟基维生素 D(例如,约 30 μg、约 60 μg 或约 90 μg 25-羟基维生素 D₃)、约 2wt%(例如,2.32wt%)无水乙醇、约 10wt%(例如,9.75wt%)GELUCIRE 44/14、约 20wt%(例如,20.00wt.%)硬石蜡、约 23wt%(例如,22.55wt%)GMS、约 35wt%(例如,35.36wt%)液体石蜡或矿物油、约 10wt% HPMC,以及任选地,少量防腐剂(例如,0.02wt% BHT)。这种制剂的变化将包括约 15%(例如,15.29wt%)HPMC 和约 30wt%(例如,29.88wt%)液体石蜡或矿物油。

[0094] 实施例

[0095] 以下实施例说明特定制剂和其制备方法。提供这些实施例用于说明并且不意图限制本发明的范围。

[0096] 使用如 USP 29-NF 24 通则 <711>Dissolution 中所描述的 USP 装置 2(桨板法), 使用下文所描述的溶解介质进行实施例中的体外溶解测试。一般来说, 方法根据以下步骤进行。将规定体积的溶解介质 ($\pm 1\%$) 放置于指定装置的容器中, 组装这个装置, 使溶解介质平衡至 $37 \pm 0.5^\circ\text{C}$, 并且移走温度计。将剂量单位放置于装置中, 小心地从剂量单位的表面排除气泡, 并且立即以指定速率操作装置。在每个规定时间处, 从溶解介质的表面与旋转叶片的顶部之间的中段区域, 距容器壁不小于 1cm 处抽取样本。将抽取用于分析的等分试样用 37°C 下等体积的新鲜溶解介质替换。保持容器被覆盖为时测试的持续时间, 并且在适合的时间检验处于测试下的混合物的温度。使用适合的检测法进行分析, 在这种情况下是超高效液相色谱法 (UPLC)。

[0097] 在每个时间点测试每种制剂的六个胶囊。溶解介质是 0.05M pH 6.8 磷酸盐缓冲液 / 1% 十二烷基硫酸钠溶解介质 ($37 \pm 0.5^\circ\text{C}$), 并且以每分钟 100 转操作装置。在 2、4、6、8 以及 12 小时获取样品, 并且使用 UPLC 测定每个样品的 25-羟基维生素 D 含量。

[0098] 实施例 1-25-羟基维生素 D 的未稳定化持续释放制剂的体外溶解

[0099] 测试由 $90\text{ }\mu\text{g}$ 25-羟基维生素 D_3 、19.98wt% 硬石蜡、37.85wt% GMS、9.76wt% GELUCIRE 44/14、2.36wt% 无水乙醇、29.88wt% 液体石蜡以及 0.02wt% BHT 的混合物制成的制剂 (比较性制剂 1) 的溶解。这种制剂不包含纤维素化合物。在 $T = 0$ 处以及在 5°C 和环境湿度下制剂控制储存直至 12 个月之后所释放的 25-羟基维生素 D_3 的平均量, 以每种剂型的标称药物负荷的平均百分比 (平均标示量%、LC%) 计算, 汇总于下表中。已确定在测试之前, 在 15°C 至 30°C 的范围内的温度和环境湿度下将样品储存约 3 个月的时段。因此, 应具有代表时间零点的样品被标记为 $T = 0_p$ (伪时间零点), 并且应了解, 标称 1 个月、3 个月、6 个月、9 个月以及 12 个月老化的样品也经历刚描述的约 3 个月老化时段。为了提供更精确的基线, 制备一批新鲜的相同类型的样品并且在没有任何老化的情况下测试; 这个数据被标记为 $T = 0_f$ 以指示新鲜样品。还报导了变异系数 (CV%)。从由 $T = 0_p$ 和 $T = 0_f$ 批次释放的 25-羟基维生素 D_3 的初始量的变化百分比分别在方括号和双方括号中提供。

[0100]

在 5°C/环境湿度下储存之后的溶解							
时间 (小时)	伪 $T=0_p$	新鲜 $T=0_r$	1 个月 (CV %) [从 $T=0_p$ 的 变化%] [[从 $T=0_r$ 的变化%]]	3 个月 (CV %) [从 $T=0_p$ 的 变化%] [[从 $T=0_r$ 的变化%]]	6 个月 (CV %) [从 $T=0_p$ 的 变化%] [[从 $T=0_r$ 的变化%]]	9 个月 (CV %) [从 $T=0_p$ 的 变化%] [[从 $T=0_r$ 的变化%]]	12 个月 (CV %) [从 $T=0_p$ 的 变化%] [[从 $T=0_r$ 的变化%]]
2	6.1	22.1	8.9	15.7	9.1	15.2	12.7
	(29.6)	(17.2)	(13.4)	(27.4)	(23)	(47.2)	(16.8)
			[45.9]	[157.4]	[49.2]	[149.2]	[108.2]
			[[59.7]]	[[29.0]]	[[58.8]]	[[31.2]]	[[42.5]]
4	14.5	52.0	20.7	22.3	22.9	25.2	24.7
	(15.7)	(4.6)	(19.1)	(15.6)	(7.1)	(19.2)	(13.5)
			[42.8]	[53.8]	[57.9]	[73.8]	[70.3]
			[[60.2]]	[[57.1]]	[[56.0]]	[[51.5]]	[[52.5]]

[0101]

6	27.6 (21.2)	77.9 (4.6)	35.7 (9.6) [29.3] [[54.2]]	33.5 (2.6) [21.4] [[57.0]]	34.1 (7.1) [23.6] [[56.2]]	36.2 (20.5) [31.2] [[53.5]]	34.8 (14.6) [26.1] [[55.3]]
8	45.7 (23.6)	96.8 (2.9)	53.0 (9.9) [16.0] [[45.2]]	47.4 (3.7) [3.7] [[51.0]]	46.8 (6) [2.4] [[51.7]]	47.8 (18.6) [4.6] [[50.6]]	46.4 (8.9) [1.5] [[52.1]]
12	89.7 (15.6)	112.3 (1.6)	100.0 (4.8) [11.5] [[11.0]]	78.9 (8.1) [12.0] [[29.7]]	76.9 (5.7) [14.3] [[31.5]]	74.1 (17.3) [17.4] [[34.0]]	78.8 (5.3) [12.2] [[29.8]]

[0102] 测试在 25℃和 60%相对湿度下储存 0 至 12 个月之后比较性制剂 1 的溶解。结果汇总于下表中。

[0103]

在 25℃/60%相对湿度下储存之后的溶解							
溶解时间 (小时)	伪 T=0 _p	新 鲜 T=0 _f	1 个月 (CV %) [从 T=0 _p 的变化 %] [[从 T=0 _f 的	3 个月 (CV %) [从 T=0 _p 的变化 %] [[从 T=0 _f 的	6 个月 (CV %) [从 T=0 _p 的变化 %] [[从 T=0 _f 的	9 个月 (CV %) [从 T=0 _p 的变化 %] [[从 T=0 _f 的	12 个月 (CV %) [从 T=0 _p 的变化 %] [[从 T=0 _f 的

[0104]

			变化%]]	变化%]]	变化%]]	变化%]]	变化%]]
2	6.1	22.1	7.6	10.8	8.5	10.8	13.5
	(29.6)	(17.2)	(7.7)	(15.7)	(19.2)	(15.8)	(24.7)
			[24.6]	[77.0]	[39.3]	[77.0]	[121.3]
			[[65.6]]	[[51.1]]	[[61.5]]	[[51.1]]	[[38.9]]
4	14.5	52.0	18.7	22.8	17.9	21.4	24.5
	(15.7)	(4.6)	(18.6)	(23.7)	(11.9)	(5.5)	(17.4)
			[29.0]	[57.2]	[23.4]	[47.6]	[69.0]
			[[64.0]]	[[56.2]]	[[65.6]]	[[58.8]]	[[52.9]]
6	27.6	77.9	27.1	30.7	23.8	27.0	30.0
	(21.2)	(4.6)	(22.7)	(29.6)	(11.6)	(7.3)	(15.7)
			[1.8]	[11.2]	[13.8]	[2.2]	[8.7]
			[[65.2]]	[[60.6]]	[[69.4]]	[[65.3]]	[[61.5]]
8	45.7	96.8	37.1	40.6	28.5	32.3	35.6
	(23.6)	(2.9)	(18.1)	(29.9)	(13.2)	(6.4)	(14.7)
			[18/8]	[11.2]	[37.6]	[29.3]	[22.1]
			[[61.7]]	[[58.1]]	[[70.6]]	[[66.6]]	[[63.2]]
12	89.7	112.3	61.6	53.0	38.5	38.9	44.2
	(15.6)	(1.6)	(16.6)	(32.2)	(12.2)	(6)	(12.2)
			[31.3]	[40.9]	[57.1]	[56.6]	[50.7]
			[[45.1]]	[[52.8]]	[[65.7]]	[[65.4]]	[[60.6]]

[0105] 测试在 40℃和 75%相对湿度下储存 0、1、3 以及 6 个月之后比较性制剂 1 的溶解。结果汇总于下表中。

[0106]

在 40℃/75%相对湿度下储存之后的溶解					
溶解时间 (小时)	伪 $T=0_p$	新 鲜 $T=0_r$	1 个月 (CV%) [从 $T=0_p$ 的 变化%] [[从 $T=0_r$ 的 变化%]]	3 个月 (CV%) [从 $T=0_p$ 的 变化%] [[从 $T=0_r$ 的 变化%]]	6 个月 (CV%) [从 $T=0_p$ 的变 化%] [[从 $T=0_r$ 的变 化%]]
2	6.1 (29.6)	22.1 (17.2)	11.7 (50) [91.8] [[47.1]]	16.9 (36.3) [177.0] [[23.5]]	1.8 (75) [70.5] [[91.9]]
4	14.5 (15.7)	52.0 (4.6)	52.0 (45.1) [258.6] [[0]]	59.8 (31.3) [312.4] [[15.0]]	36.2 (21.8) [149.7] [[30.4]]
6	27.6 (21.2)	77.9 (4.6)	87.0 (21.5) [215.2] [[11.7]]	97.8 (24) [254.3] [[25.5]]	76.7 (12.3) [177.9] [[1.5]]
8	45.7 (23.6)	96.8 (2.9)	107.3	110.9	101.2

[0107]

			(8.1)	(13)	(6.1)
			[134.8]	[142.7]	[121.4]
			[[10.8]]	[[14.6]]	[[4.5]]
12	89.7	112.3	118.7	115.1	112.6
	(15.6)	(1.6)	(1.7)	(3.7)	(2.1)
			[32.3]	[28.3]	[25.5]
			[[5.7]]	[[2.5]]	[[0.3]]

[0108] 在不打算受任何特定理论约束的情况下, 据信在 40℃ 下储存之后溶解程度相较于伪 T = 0 值的增加是归因于上文针对所测试的伪 T = 0 样品所描述的老化效应与在 40℃ 下储存时制剂的温度依赖性相变的组合。

[0109] 使根据比较性制剂 1 的老化产品热固化, 然后进行溶解测试。固化由应用热处理组成并且已经显示使医药制剂稳定 (参看例如美国专利号 6, 645, 527)。将比较性制剂 1 (老化样品) 在 40℃ 下加热 72 小时以固化, 然后在室温下储存 8 周。在室温下储存 0、2、4 以及 8 周之后测试 25-羟基维生素 D₃ 从固化制剂的释放。结果汇总于下表中。

[0110]

在 40℃ 下固化 72 小时之后的溶解				
溶解时间 (小时)	T=0	2 周	4 周	8 周
		LC %	LC %	LC %
		[变化%]	[变化%]	[变化%]
2	17.4	12.4	11.4	8.2
		[28.7]	[34.5]	[52.9]
4	53.3	46.4	40.1	26.6
		[12.9]	[24.8]	[50.1]
6	86.2	76.2	69.0	44.8
		[11.6]	[20.0]	[48.0]

[0111]

8	103.8	102.0 [1.7]	95.8 [7.7]	66.6 [35.8]
12	115.7	110.5 [4.5]	119.8 [3.5]	103.3 [10.7]

[0112] 实施例 2-25- 羟基维生素 D 的稳定化控制释放制剂的体外溶解

[0113] 在室温下储存 0 至 11 周之后测试包含 90 μ g 25- 羟基维生素 D₃、19.88wt% 硬石蜡、15.29wt% 羟丙基甲基纤维素、22.55wt% GMS、9.76wt% GELUCIRE 44/14、2.36wt% 无水乙醇、29.88wt% 液体石蜡以及 0.02wt% BHT 的持续释放制剂（实施例制剂 A）的溶解。结果汇总于下表中。

[0114]

在室温/环境湿度下储存之后的溶解				
溶解时间(小时)	T=0	3 周	11 周	
		LC %	LC %	
		[变化%]	[变化%]	
2	15.45	14.20 [8.1%]	12.08 [21.8%]	
4	36.3	38.80 [6.9%]	37.13 [2.3%]	
6	56.9	62.70 [10.2%]	59.51 [4.6%]	
8	71.1	71.90 [1.1%]	69.76 [1.9%]	
12	89.4	91.20 [2.0%]	89.90 [0.6%]	

[0115] 在室温下储存 0 至 26 周之后测试包含 90 μ g 25- 羟基维生素 D₃、19.88wt% 硬石蜡、10.00wt% 羟丙基甲基纤维素、22.55wt% GMS、9.76wt% GELUCIRE 44/14、2.36wt% 无水乙醇、35.17wt% 液体石蜡以及 0.02wt% BHT 的持续释放制剂（实施例制剂 B）的溶解。

结果汇总于下表中。

[0116]

在室温/环境湿度下储存之后的溶解				
溶解时间 (小时)	T=0	6 周	13 周	26 周
		LC %	LC %	LC %
		[变化%]	[变化%]	[变化%]
2	30.15	25.40	25.20	21.10
		[15.8%]	[16.4%]	[30.0%]
4	58.55	51.90	51.80	45.20
		[11.4%]	[11.5%]	[22.8%]
6	72.1	74.40	73.00	67.63
		[3.2%]	[1.2%]	[6.2%]
8	80.55	84.30	84.50	77.30
		[4.7%]	[4.9%]	[4.0%]
12	91.8	94.10	94.40	91.16
		[2.5%]	[2.8%]	[0.7%]

[0117] 实施例制剂 B 在室温下储存至少 26 周之后展示实质上稳定的溶解型态。

[0118] 使用 25℃ 和 60% 相对湿度以及 40℃ 和 75% 相对湿度的储存条件测试包含 30 μg (实施例制剂 C)、60 μg (实施例制剂 D) 或 90 μg (实施例制剂 E) 的 25-羟基维生素 D₃ 的稳定化制剂的稳定性。实施例制剂 C 至 E 的组成汇总于下表中：

[0119]

组分	量
25-羟基维生素 D ₃	30 μg、60 μg 或 90 μg
石蜡	20.00 wt%
矿物油	35.36 wt%

[0120]

羟丙基甲基纤维素 K100M CR (METHOCEL)	10.00 wt%
单硬脂酸甘油酯	22.55 wt%
月桂酰聚乙二醇甘油酯和聚氧甘油 酯 (GELUCIRE 44/14)	9.75 wt%
无水乙醇	2.32 wt%
BHT	0.02 wt%
软胶囊外壳 (VEGICAPS)	

[0121] 制剂在 25℃ 和 60% 相对湿度下储存至少 24 个月之后展现实质上稳定的溶解型态 (图 1)。溶解结果 (LC% 和 CV%) 汇总于下表中。

[0122]

在 25℃/60% 相对湿度下储存之后的溶解								
时 间 (小 时)	T=0	1 个月	3 个月	6 个月	9 个月	12 个月	18 个月	24 个月
	LC %	LC %	LC %	LC %	LC %	LC %	LC %	LC %
	(CV %)	(CV %)	(CV %)	(CV %)	(CV %)	(CV %)	(CV %)	(CV %)
30 µg 25-羟基维生素 D ₃ (实施例制剂 C)								
2	10.1 (16.1)	12.9 (25.2)	14.0 (48.5)	9.6 (38.3)	10.5 (18.2)	13.5 (35.8)	10.6 (26.5)	7.0 (47.8)
4	43.6 (12.7)	48.8 (10.9)	45.9 (29.9)	36.8 (25)	37.2 (11.1)	50.2 (14.8)	39.3 (22.9)	39.6 (32.3)
6	83.1 (5.7)	73.4 (9.2)	72.4 (7.5)	71.4 (6.8)	66.7 (10.6)	70.6 (11.5)	70.1 (7.2)	69.3 (12.6)
8	96.4 (6.5)	89.6 (4.4)	88.4 (4.7)	88.4 (5.7)	85.2 (4.9)	85.4 (9)	84 (5.1)	85.7 (8.2)
12	115.8 (4.5)	104.2 (1.9)	105.6 (1.4)	106.1 (1.6)	101.5 (1.5)	100.8 (3.9)	100.2 (4.5)	103 (2.6)

[0123]

60 μg 25-羟基维生素 D_3 (实施例制剂 D)								
2	17.5 (20)	16.3 (27.4)	16.1 (25.3)	17.7 (34.7)	11.2 (20.2)	14.3 (29.1)	16.1 (25.8)	12.4 (52.3)
4	53.6 (19.6)	55.1 (18.8)	53.8 (12.8)	55.3 (17.9)	43.7 (14)	51 (22.5)	52.9 (16.7)	41 (36.6)
6	83.9 (7.5)	78.7 (8.3)	79.9 (6.6)	78.4 (4.7)	72.2 (7.1)	75 (13)	72 (9.9)	64.7 (29.6)
8	99.2 (3.9)	94.3 (5.2)	97.2 (4.8)	92.5 (3.3)	87 (5.5)	88.9 (6.3)	84.9 (12.3)*	81.3 (21.7)
12	104.8 (3.3)	108.7 (1.8)	111.9 (1.1)	104.5 (0.5)	103.1 (0.8)	104.7 (1.4)	99.8 (4.6)*	101.7 (8)
90 μg 25-羟基维生素 D_3 (实施例制剂 E)								
2	14.9 (19.9)	14.9 (8.6)	13.3 (41.2)	13.5 (23.4)	14.3 (30.4)	15 (35.1)	9.5 (37.1)	8.5 (53.2)
4	49.9 (16.4)	46.9 (10.2)	52.4 (18.5)	49.7 (16.4)	45.9 (25.6)	51.8 (14)	36.8 (34.5)	34.4 (24.9)
6	89.4 (7.2)	71.4 (4.1)	81.1 (5.6)	74.2 (11.1)	71.6 (17.6)	77 (4.9)	64.4 (10.3)	64.5 (15.1)
8	101.7 (2.5)	84.9 (2.8)	96.1 (2.3)	90.8 (6.4)	89 (9.4)	91.6 (3.3)	77.4 (15.7)	83.6 (11.2)
12	103 (2.1)	99.3 (2.4)	110 (1.3)	104.4 (1.1)	100.5 (2.4)	104.6 (0.3)	96.8 (5)	102.8 (3.4)

[0124] 4 个重复替代六个

[0125] 在老化之后释放的 25-羟基维生素 D_3 的量相较于所释放的初始量之间的变化百分比汇总于下表中。

[0126]

时 间 (h)	1个月 变化%	3个月 变化%	6个月 变化%	9个月 变化%	12个月 变化%	18个月 变化%	24个月 变化%
30 μg 25-羟基维生素 D ₃ (实施例制剂 C)							
2	27.7%	38.6%	5.0%	4.0%	33.7%	5.0%	30.7%
4	11.9%	5.3%	15.6%	14.7%	15.1%	9.9%	9.2%
6	11.7%	12.9%	14.1%	19.7%	15.0%	15.6%	16.6%
8	7.1%	8.3%	8.3%	11.6%	11.4%	12.9%	11.1%
12	10.0%	8.8%	8.4%	12.3%	13.0%	13.5%	11.1%
60 μg 25-羟基维生素 D ₃ (实施例制剂 D)							
2	6.9%	8.0%	1.1%	36.0%	18.3%	8.0%	29.1%
4	2.8%	0.4%	3.2%	18.5%	4.9%	1.3%	23.5%
6	6.2%	4.8%	6.6%	13.9%	10.6%	14.2%	22.9%
8	4.9%	2.0%	6.8%	12.3%	10.4%	14.4%	18.0%
12	3.7%	6.8%	0.3%	1.6%	0.1%	4.8%	3.0%
90 μg 25-羟基维生素 D ₃ (实施例制剂 E)							
2	0.0%	10.7%	9.4%	4.0%	0.7%	36.2%	43.0%
4	6.0%	5.0%	0.4%	8.0%	3.8%	26.3%	31.1%
6	20.1%	9.3%	17.0%	19.9%	13.9%	28.0%	27.9%
8	16.5%	5.5%	10.7%	12.5%	9.9%	23.9%	17.8%
12	3.6%	6.8%	1.4%	2.4%	1.6%	6.0%	0.2%

[0127] 实施例制剂 C 至 E 在 40℃ 和 75% RH 下储存至少 6 个月之后也展现实质上稳定的溶解型态 (图 2)。溶解结果汇总于下表中。

[0128]

在 40℃/75% 相对湿度下储存之后的溶解				
时间 (小时)	初始 LC % (CV %)	1个月 LC % (CV %)	3个月 LC % (CV %)	6个月 LC % (CV %)
30 μg 25-羟基维生素 D ₃ (实施例制剂 C)				

[0129]

2	10.1 (16.1)	11.3 (54.3)	13.5 (53.8)	11.1 (14.8)
4	43.6 (12.7)	46 (27.1)	44.4 (23.9)	40.9 (13.9)
6	83.1 (5.7)	72.7 (9.7)	62.8 (20.4)	68.7 (7.3)
8	96.4 (6.5)	88.7 (5)	76.5 (12.5)	82.5 (4.1)
12	115.8 (4.5)	103.1 (0.9)	93.4 (7.6)	96.4 (2.8)
60 µg 25-羟基维生素 D ₃ (实施例制剂 D)				
2	17.5 (20)	12.9 (40.7)	15.5 (37)	13.9 (40)
4	53.6 (19.6)	50.7 (18.5)	54.4 (12)	49.8 (16.3)
6	83.9 (7.5)	75.8 (9.7)	78.3 (10.6)	74.7 (8.1)
8	99.2 (3.9)	91.2 (7.9)	91.6 (9.1)	88.5 (6.5)
12	104.8 (3.3)	100.7 (5.1)	104.1 (6.5)	101.5 (2.3)
90 µg 25-羟基维生素 D ₃ (实施例制剂 E)				
2	14.9 (19.9)	18.5 (32.5)	10.2 (44.6)	8.3 (34.7)

[0130]

4	49.9 (16.4)	50.7 (12.8)	47 (14.6)	44.8 (10.6)
6	89.4 (7.2)	74.7 (8)	72.9 (5.2)	73 (3.4)
8	101.7 (2.5)	90.5 (5)	86.6 (4.8)	87.9 (3)
12	103 (2.1)	100.1 (1.4)	102.5 (1.6)	101.0 (1.9)

[0131] 在暴露于储存条件之后释放的 25-羟基维生素 D₃ 的量相较于所释放的初始量之间的变化百分比汇总于下表中。

[0132]

时间 (小时)	1 个月 变化%	3 个月 变化%	6 个月 变化%
30 µg 25-羟基维生素 D ₃ (实施例制剂 C)			
2	11.9%	33.7%	9.9%
4	5.5%	1.8%	6.2%
6	12.5%	24.4%	17.3%
8	8.0%	20.6%	14.4%
12	11.0%	19.3%	16.8%
60 µg 25-羟基维生素 D ₃ (实施例制剂 D)			
2	26.3%	11.4%	20.6%
4	5.4%	1.5%	7.1%
6	9.7%	6.7%	11.0%
8	8.1%	7.7%	10.8%
12	3.9%	0.7%	3.1%
90 µg 25-羟基维生素 D ₃ (实施例制剂 E)			
2	24.2%	31.5%	44.3%
4	1.6%	5.8%	10.2%

[0133]

6	16.4%	18.5%	18.3%
8	11.0%	14.8%	13.6%
12	2.8%	0.5%	1.9%

[0134] 在 25℃和 60%相对湿度下储存 12 个月之后评估不含纤维素化合物的比较性制剂 1 和包含羟丙基甲基纤维素的实施例制剂 E 的稳定性 (图 3)。溶解结果汇总于下表中。

[0135]

在 25℃/60%相对湿度下储存之后的溶解				
溶解时间 (小时)	比较性制剂 1		实施例制剂 E	
	初始	12 个月	初始	12 个月
	LC %	LC %	LC %	LC %
2	22.1	13.5	14.9	15.0
4	52.2	24.5	49.9	51.8
6	77.9	30.0	89.4	77.0
8	96.8	35.6	101.7	91.6
12	112.3	44.2	103.0	104.6

[0136] 在暴露于储存条件之后释放的 25-羟基维生素 D₃ 的量相较于所释放的初始量之间的变化百分比汇总于下表中。

[0137]

溶解时间 (小时)	比较性制剂 1	实施例制剂 E
	从初始的变化%	从初始的变化%
2	38.9%	0.7%
4	53.1%	3.8%
6	61.5%	13.9%
8	63.2%	9.9%
12	60.6%	1.6%

[0138] 实施例 3: 未稳定化和稳定化控制释放制剂的体内结果

[0139] 进行体内研究以评估 25-羟基维生素 D₃ 的未稳定化和稳定化控制释放制剂在人类受试者中的临床药物动力学。在研究 A 中, 具有 3 期或 4 期 CKD、继发性甲状旁腺功能亢进 (3 期: 70-1000pg/mL iPTH; 4 期: 110-1000pg/mL iPTH) 以及维生素 D 不足 (15ng/mL 至 29ng/mL 的血清总基线 25-羟基维生素 D) 的 28 位受试者接受单次口服剂量的包含 450 μg 或 900 μg 25-羟基维生素 D₃、20.00wt% 硬石蜡、37.85wt% GMS、9.75wt% GELUCIRE 44/14、2.32wt% 无水乙醇、30.06wt% 矿物油以及 0.02wt% BHT 的控制释放胶囊 (比较性制

剂 3) 或单次静脉内剂量的 448 μg 于乙醇溶液中的 25- 羟基维生素 D_3 。没有一种制剂包含纤维素化合物。

[0140] 在施用口服剂量之后 25- 羟基维生素 D_3 的血清浓度逐渐增加。25- 羟基维生素 D_3 的增加与剂量成比例并且在施用 900 μg 胶囊之后达到 32ng/mL 的近似平均最大观测血清浓度 (C_{max})。 C_{max} 出现的时间 (T_{max}) 约为给药后 13 小时。相比之下, 在施用静脉内剂量之后 25- 羟基维生素 D_3 的浓度快速增加。在施用静脉内剂量之后立即达到峰值血清水平 ($T_{\text{max}} = 0.5$ 小时) 并且达到 134ng/mL 的近似平均 C_{max} 。口服剂量的生物利用度约为 6% 至 11%。在施用口服剂量之后 25- 羟基维生素 D_3 的终末半衰期 ($t_{1/2}$) 约为 12 至 22 天。在任何处理组中都没有观测到对血清钙或磷、或尿钙的不良影响。

[0141] 在施用静脉内注射之后平均血清总 1, 25- 二羟基维生素 D 快速上升, 截止给药后 6 小时从处理前基线增加约 13pg/mL。相比之下, 在施用 900 μg 胶囊之后截止给药后 48 小时平均血清总 1, 25- 二羟基维生素 D 与剂量成比例地并且逐渐增加约 7pg/mL。

[0142] 在施用静脉内剂量之后血清 iPTH 经过最初 96 小时没有显示有意义的变化。相比之下, 对于接受 900 μg 胶囊的受试者, 在给药之后血清 PTH 逐渐下降, 从处理前基线达到约 20% 的最大抑制。对于所有处理组的观测药物动力学参数汇总于下表中。

[0143]

参数	450 μ g口服 (N=9)		900 μ g口服 (N=9)		448 μ g静脉内 (N=9)	
	n	平均值 (SD)	n	平均值 (SD)	n	平均值 (SD)
		中值 范围		中值 范围		中值 范围
PK/PD群体						
观测到的25-羟基维生素D ₃						
AUC _{0-42天} (ng·h/mL)	9	13353.12 (10606.47) 12196.45 888.39, 32885.95	9	21563.95 (9165.53) 17940.11 9292.88, 38631.91	9	43463.51 (12589.57) 47115.66 23340.59, 63006.78
AUC _{0-28天} (ng·h/mL)	9	13353.12 (10606.47) 12196.45 888.39, 32885.95	9	21563.95 (9165.53) 17940.11 9292.88, 38631.91	9	43463.51 (12589.57) 47115.66 23340.59, 63006.78
AUC _{0-12h} (ng·h/mL)	9	81511.71 (103037.08) 54967.57 4927.95, 333366.90	9	122901.73 (114168.13) 79902.04 25729.84, 378935.59	9	137955.58 (66746.71) 123580.87 39282.49, 243322.76
C _{max} (ng/mL)	9	25.18 (10.134) 20.52 15.35, 42.24	9	31.54 (15.765) 30.12 12.21, 67.01	9	133.99 (19.311) 133.68 91.71, 180.91
C _{24h} (ng/mL)	9	18.11 (7.846) 15.84 10.30, 29.80	9	19.08 (7.611) 21.37 7.30, 27.93	9	35.07 (12.330) 36.91 12.68, 53.39
t _{max} (h)	9	13.11 (9.597) 10.00 6.00, 36.00	9	13.56 (9.989) 10.00 2.00, 30.00	9	0.49 (0.638) 0.25 0.083, 2.00
λ_z (h ⁻¹)	9	0.0015 (0.0028) 0.0003 0.0001, 0.0087	9	0.0003 (0.0002) 0.0004 0.0001, 0.0005	9	0.0005 (0.0002) 0.0004 0.0002, 0.0008
R ²	9	0.89 (0.130) 0.96 0.662, 1.000	9	0.90 (0.169) 0.99 0.523, 0.998	9	0.91 (0.090) 0.93 0.730, 1.000
t _{1/2} (h)	9	2477.72 (2581.24) 2483.61 79.24, 8615.11	9	3228.63 (2734.74) 1937.32 1300.13, 9646.71	9	1775.86 (779.13) 1694.69 871.46, 3297.78
[0144]						
V _d (L/kg)	9	49.42 (18.30) 50.93 23.20, 72.76	9	45.06 (19.38) 40.080 20.77, 87.51	9	20.35 (7.42) 19.550 13.04, 32.68
CL (L/kg·h)	9	0.0499 (0.0155) 0.0182 0.0030, 0.2029	9	0.0155 (0.0119) 0.0125 0.0026, 0.0389	9	0.0095 (0.0065) 0.0081 0.0041, 0.0255
F	NA	0.306 (NA) NA NA	NA	0.247 (NA) NA NA	NA	1.000 (NA) NA NA

[0145] 对于所有处理组的基线调整药物动力学参数汇总于下表中。

[0146]

参数	450 μg口服 (N=9)			900 μg口服 (N=9)			448 μg静脉内 (N=9)		
	n	平均值	(SD)	n	平均值	(SD)	n	平均值	(SD)
		中值	范围		中值	范围		中值	范围
47]									
AUC _{0-42h} (ng•h/mL)	9	1394.89 (1911.41) 605.42 48.87, 4956.68		8	4525.43 (3123.29) 4801.54 148.07, 8843.74		9	19609.07 (5319.01) 18764.48 11066.02, 28611.05	
AUC _{0-24h} (ng•h/mL)	9	1257.30 (2047.74) 48.87 -325.43, 4956.68		8	4274.27 (3488.40) 4801.54 -877.99, 8843.74		9	19609.07 (5319.01) 18764.48 11066.02, 28611.05	
AUC _{0-inf} (ng•h/mL)	6	3318.90 (4606.89) 547.25 50.78, 9878.03		8	6791.49 (5224.54) 6872.86 285.04, 14979.17		9	34543.75 (22103.97) 26962.25 16868.97, 89126.53	
C _{max} (ng/mL)	9	6.90 (4.266) 5.70 2.93, 14.87		8	14.17 (9.884) 12.30 2.55, 35.59		9	110.33 (14.536) 111.08 76.63, 127.40	
C _末 (ng/mL)	9	2.36 (2.257) 2.05 0.16, 5.49		8	2.64 (1.784) 3.01 0.42, 5.40		9	11.40 (5.648) 9.01 5.84, 22.86	
t _{max} (h)	9	13.11 (9.597) 10.00 6.00, 36.00		8	15.00 (9.621) 10.00 8.00, 30.00		9	0.49 (0.638) 0.25 0.083, 2.00	
λ _z (h ⁻¹)	6	0.018 (0.359) 0.0042 0.0008, 0.0910		7	0.0020 (0.0013) 0.0016 0.0008, 0.0037		9	0.0011 (0.0005) 0.0010 0.0004, 0.0021	
R ²	6	0.92 (0.101) 0.96 0.743, 0.999		6	0.99 (0.020) 0.99 0.948, 1.000		9	0.92 (0.086) 0.95 0.720, 0.999	
t _{1/2} (h)	6	307.86 (336.42) 165.72 7.61, 914.23		6	522.96 (320.80) 530.00 189.84, 879.31		9	745.86 (437.65) 663.43 337.37, 1834.71	
V _d (L/ng)	6	340.42 (269.11) 249.77 80.51, 771.79		6	82.92 (29.70) 77.11 39.96, 127.06		9	32.94 (11.00) 29.70 24.28, 58.95	
CL (L/ng•h)	6	4.588 (7.525) 2.119 0.101, 19.692		6	0.141 (0.080) 0.1200 0.0668, 0.2860		9	0.036 (0.014) 0.037 0.011, 0.059	
F	NA	0.064 (NA) NA NA		NA	0.109 (NA) NA NA		NA	1.000 (NA) NA NA	

[0148] 在研究 B 中, 具有约 24ng/mL (范围 11ng/mL 至 45ng/mL) 的平均基线血清 25- 羟基维生素 D 的 20 位健康受试者接受单次口服剂量的包含 900 μ g 25- 羟基维生素 D₃、20.00wt% 硬石蜡、10.00wt% HPMC、22.55wt% GMS、9.75wt% GELUCIRE 44/14、2.32wt% 无

水乙醇、35.36wt%矿物油以及 0.02wt% BHT 的稳定化控制释放胶囊（实施例制剂 F）或单次静脉内剂量的 448 μg 于乙醇溶液中的 25-羟基维生素 D₃。

[0149] 25-羟基维生素 D₃水平的逐渐增加通过在施用稳定化口服制剂之后与静脉内剂量相比延长的 T_{max} 来展示。在施用稳定化口服制剂之后的药物动力学型态展示 25-羟基维生素 D₃浓度的逐渐增加,其中平均 T_{max} 为 28 小时,而避免大多数受试者中血液水平的快速增加。施用静脉内剂量引起所有受试者中 25-羟基维生素 D₃浓度的快速增加。避免 25-羟基维生素 D₃水平的快速增加通过处理组之间所观测到的 C_{max}的明显差异来突出强调。相较于在静脉内剂量之后 153ng/mL 的 C_{max},在口服剂量之后 C_{max}为 58ng/mL。

[0150] 尽管口服剂量约高两倍,但在施用控制释放胶囊之后暴露于 25-羟基维生素 D₃比在静脉内剂量之后约低两倍,得到约 25%的生物利用度。t_{1/2}、清除率 (CL) 以及分布体积 (Vd) 在处理组之间似乎是类似的。t_{1/2}和 CL 的值与所报导的 25-羟基维生素 D₃的延长的消除一致。另外,Vd 值表明 25-羟基维生素 D₃维持于全身循环中,可能高度结合至 DBP。对于所有处理组的观测药物动力学参数汇总于下表中。

[0151]

参数	900 µg CTAP101 胶囊 (N=10)	448 µg CTAP101 注射 (N=10)
AUC_{0-∞} (ng·h/mL)		
平均值 (SD)	21545.20 (7054.02)	25274.44 (7206.93)
中值	19904.00	25810.85
最小值, 最大值	10176.40, 35885.02	8434.02, 35382.55
AUC₀₋₁₂ (ng·h/mL)		
平均值 (SD)	77945.13 (55896.15)	55234.52 (27268.64)
中值	58974.22	51247.29
最小值, 最大值	19504.43, 194796.33	22979.18, 119865.38
C_{max} (ng/mL)		
平均值 (SD)	57.657 (39.3810)	133.029 (20.8620)
中值	37.925	152.890
最小值, 最大值	24.43, 146.86	125.94, 185.33
t_{max} (h)		
平均值 (SD)	28.100 (27.4000)	0.272 (0.2910)
中值	21.000	0.167
最小值, 最大值	4.00, 96.00	0.05, 1.00
t_{1/2} (h)		
平均值 (SD)	1389.40 (1144.48)	660.23 (415.82)
中值	1042.60	607.65
最小值, 最大值	557.32, 4173.67	238.46, 1733.68
λ_e (h⁻¹)		
平均值 (SD)	0.00072 (0.00036)	0.00136 (0.00071)
中值	0.00067	0.00115
最小值, 最大值	0.00017, 0.00124	0.00040, 0.00291
CL (L/h)		
平均值 (SD)	0.0064 (0.0027)	0.0098 (0.0046)
中值	0.0066	0.0087
最小值, 最大值	0.0018, 0.0098	0.0037, 0.0195
Vd (L)		
平均值 (SD)	9.27 (0.97)	7.50 (1.19)
中值	9.39	7.24
最小值, 最大值	7.93, 10.49	6.02, 9.77
R²		
平均值 (SD)	0.80 (0.24)	0.92 (0.075)
中值	0.88	0.94
最小值, 最大值	0.25, 0.99	0.74, 1.0
F		
平均值 (SD)	0.42 (0.14)	N/A
中值	0.59	N/A
最小值, 最大值	0.20, 0.71	N/A

[0152] *个别受试者的生物利用度的平均值

[0153] 缩写 :N/A, 不适用

[0154] 对于所有处理组的基线调整药物动力学参数汇总于下表中。

[0155]

参数	900 µg CTAP101 胶囊 (N=10)	448 µg CTAP101 注射 (N=10)
AUC₀₋₂₄ (ng·h/mL)		
平均值 (SD)	6891.81 (6678.97)	13583.95 (3908.42)
中值	4360.23	14853.46
最小值, 最大值	1017.88, 20340.68	5302.50, 17194.59
AUC_{0-∞} (ng·h/mL)		
平均值 (SD)	9418.00 (9410.58)	17735.09 (5249.38)
中值	5420.04	18229.25
最小值, 最大值	1179.07, 28031.64	9820.16, 25534.45
C_{max} (ng/mL)		
平均值 (SD)	35.867 (39.3886)	133.653 (20.7925)
中值	14.910	133.785
最小值, 最大值	6.50, 120.52	103.88, 166.34
t_{max} (h)		
平均值 (SD)	28.100 (27.4001)	0.272 (0.2914)
中值	21.000	0.167
最小值, 最大值	4.00, 96.00	0.05, 1.00

[0156]

t_{1/2} (h)		
平均值 (SD)	270.61 (215.00)	264.08 (82.23)
中值	194.00	269.57
最小值, 最大值	107.90, 832.70	132.46, 382.99
λ_e (h⁻¹)		
平均值 (SD)	0.00362 (0.00182)	0.00292 (0.00112)
中值	0.00363	0.00257
最小值, 最大值	0.00083, 0.00624	0.00181, 0.00523
CL (L/h)		
平均值 (SD)	0.027 (0.0063)	0.028 (0.0093)
中值	0.028	0.025
最小值, 最大值	0.012, 0.033	0.018, 0.046
Vd (L)		
平均值 (SD)	8.78 (3.08)	9.74 (2.02)
中值	8.08	9.47
最小值, 最大值	5.06, 14.17	6.54, 13.27
R²		
平均值 (SD)	0.83 (0.22)	0.92 (0.072)
中值	0.88	0.94
最小值, 最大值	0.25, 1.0	0.74, 1.0
F		
平均值 (SD)	0.25 (0.24)	N/A
中值	0.16	N/A
最小值, 最大值	0.037, 0.75	N/A

[0157] *个别受试者的生物利用度的平均值

[0158] 缩写 :N/A, 不适用

[0159] 研究展示, 稳定化控制释放制剂改变 25- 羟基维生素 D₃ 的吸收速率, 得到血清 25- 羟基维生素 D₃ 水平的更逐渐增加, 同时维持分布和消除特征。稳定化制剂与研究 A 中

相同剂量的未稳定化制剂相比展示改善的药物动力学参数,诸如增加的 T_{max} 、AUC 以及生物利用度。

[0160] 在研究C中,具有3期CKD($eGFR$ 25–70mL/min/1.73m²)、SHPT(>70pg/mL血浆iPTH)以及维生素D不足(10ng/mL至29ng/mL的血清总基线25-羟基维生素D)的78位受试者接受每日口服剂量的包含30 μ g、60 μ g或90 μ g 25-羟基维生素D₃、20.00wt%硬石蜡、10.00wt% HPMC、22.55wt% GMS、9.75wt% GELUCIRE 44/14、2.32wt%无水乙醇、35.36wt%矿物油以及0.02wt% BHT的稳定化控制释放制剂(来自实施例2的实施例制剂C、D以及E)或安慰剂,持续6周。

[0161] 平均基线血清25-羟基维生素D₃浓度跨越处理组是可比的并且在约16至20ng/mL的范围内。在用25-羟基维生素D₃处理之后,血清25-羟基维生素D₃的平均水平在重复每日施用25-羟基维生素D₃之后逐渐地并且以与剂量成比例的方式增加并且截止6周开始接近稳态(图4)。对于施用30 μ g、60 μ g以及90 μ g 25-羟基维生素D₃的组,平均基线调整 C_{max} 值分别约为28、60以及86ng/mL。如背景调整 $AUC_{0-6周}$ 所评估的对25-羟基维生素D₃的平均暴露跨越剂量组是与剂量成比例的。在最后一个剂量之后,平均血清25-羟基维生素D₃水平缓慢下降,但截止研究结束对于所有组都保持高于基线。测得平均 $t_{1/2}$ 约为25天至50天之间。25-羟基维生素D₃的基线调整药物动力学参数汇总于下表中。

[0162]

	安慰剂	30 μg	60 μg	90 μg
基线 (ng/mL)				
平均值 (SD)	16.4 (8.2)	16.2 (7.3)	19.8 (8.7)	18.4 (9.8)
中值	12.9	17.2	21.2	16.7
最小值, 最大值	4.4, 30.4	5.0, 25.8	5.8, 32.5	6.7, 38.9
C_{max} (ng/mL)				
平均值 (SD)	4.1 (3.5)	27.8 (8.2)	60.3 (19.0)	85.7 (26.9)
中值	3.1	28.1	60.8	76.0
最小值, 最大值	0.6, 13.8	10.8, 43.4	30.3, 89.5	55.4, 146.4
AUC₀₋₆ (ng·d/mL)				
平均值 (SD)	45.9 (60.0)	709.2 (246.3)	1531.4 (374.8)	2134.3 (584.3)
中值	32.1	6843.0	1573.0	1963.8
最小值, 最大值	-60.1, 222.3	307.8, 1249.0	712.7, 2221.8	1377.5, 3207.3
t_{max} (d)				
平均值 (SD)	NA	37.8 (10.4)	41.1 (5.2)	42.6 (5.3)
中值	NA	42.50	43.0	43.0
最小值, 最大值	NA	8.0, 44.0	29.0, 45.0	35.0, 57.0
t_{1/2} (d)				
平均值 (SD)	NA	25.8 (16.3)	33.1 (9.3)	50.1 (51.0)
中值	NA	24.1	31.6	37.7
最小值, 最大值	NA	5.2, 52.6	17.4, 52.3	23.2, 224.0

[0163] 平均基线血清 1, 25- 二羟基维生素 D 浓度跨越处理组是可比的并且逐渐增加, 类似于对血清 25- 羟基维生素 D₃浓度的作用。平均值 $\pm$ SD 基线调整 C_{max} 值在 60 μg 和 90 μg 组 (分别为 18.4 ± 6.24 和 $19.9 \pm 14.30\text{ng/mL}$) 中与安慰剂和 30 μg 组 (分别为 5.7 ± 6.35 和 $6.4 \pm 7.66\text{ng/mL}$) 相比较。如基线调整 AUC₀₋₆ 所评估的对 1, 25- 二羟基维生素 D 的平均暴露跨越 25- 羟基维生素 D₃剂量组是与剂量成比例的。1, 25- 二羟基维生素 D 的基线调整药物动力学参数汇总于下表中。

[0164]

	安慰剂	30 μ g	60 μ g	90 μ g
	N=23	N=12	N=16	N=14
基线 (pg/mL)				
平均值 (SD)	20.8 (10.11)	18.3 (7.53)	20.6 (7.62)	20.6 (7.29)
中值	17.0	17.0	18.0	21.0
最小值, 最大值	7.0, 41.4	5.1, 30.7	8.2, 33.6	9.3, 34.5
C_{max} (pg/mL)				
平均值 (SD)	7.6 (5.71)	6.4 (7.66)	18.4 (6.24)	19.9 (14.30)
中值	4.9	5.0	18.4	18.9
最小值, 最大值	1.9, 22.6	-6.3, 21.0	7.3, 29.9	-11.6, 48.3
AUC_{0-6 h} (g·d/mL)				
平均值 (SD)	11.5 (112.97)	100.6 (185.38)	249.9 (198.83)	371.1 (290.81)
中值	16.2	23.0	298.7	352.2
最小值, 最大值	-267.1, 219.8	-145.4, 452.3	-191.7, 563.6	-5.8, 1235.8
t_{max} (d)				
平均值 (SD)	24.4 (15.55)	16.8 (16.09)	26.4 (11.52)	25.5 (13.88)
中值	23.0	12.0	23.0	23.00
最小值, 最大值	2.0, 45.0	1.0, 44.0	8.0, 44.0	1.0, 44.0

[0165] 25-羟基维生素 D₃的稳定化控制释放制剂与安慰剂相比使所有活性剂组中显著更大数目的受试者中的血清总 25-羟基维生素 D 水平增至 ≥ 30 ng/mL。类似地, 稳定化制剂与安慰剂相比从基线显著降低平均血浆 iPTH。

[0166] 每天施用稳定化控制释放制剂中的 25-羟基维生素 D₃与所施用的剂量成比例地增加平均血清总 25-羟基维生素 D。最低施用剂量 (30 μ g) 在处理结束时使血清总 25-羟基维生素 D 从处理前基线 (21.7 ± 1.8 ng/mL) 增加 15.6 ± 1.7 (SE), 并且最高剂量 (90 μ g) 使血清总 25-羟基维生素 D 从 21.8 ± 1.2 ng/mL 增加 61.1 ± 6.1 ng/mL。相比之下, 在组合安慰剂组中观测到在处理结束时 1.2 ± 0.7 ng/mL 的降低。在处理组与安慰剂组之间的差异对于所研究的所有三个剂量水平都是显著的 ($p < 0.0001$)。在处理结束时 30 μ g 剂量组中的平均血清 25-羟基维生素 D 水平是 37.3 ± 1.8 ng/mL (稍高于 30 ng/mL 的 K/DOQI 指定最低充足水平), 指示了 30 μ g 是最低有效剂量。

[0167] 在处理结束时达成 ≥ 30 ng/mL 的血清总 25-羟基维生素 D 水平的经过处理的受试者的百分比在 30 μ g、60 μ g 以及 90 μ g 剂量组中与安慰剂中的 0% 相比为 92.3%、100.0% 以及 100.0%。在活性剂与安慰剂处理之间反应率的这些差异全部是显著的 ($p < 0.001$)。

[0168] 平均血浆 iPTH 在处理结束时与 25-羟基维生素 D₃ 的施用剂量成比例地降低。最低施用剂量 (30 μg) 使 iPTH 从处理前基线降低 20.2±5.8(SE)%, 并且最高剂量 (90 μg) 使 iPTH 降低 35.9±4.2%。在组合安慰剂组中在处理结束时观测到 17.2±7.8% 的增加。在接受 25-羟基维生素 D₃ 与安慰剂的组之间的差异对于所研究的所有三个剂量水平都是显著的 (p<0.005), 并且其与在安慰剂对照研究中使用更强效和钙血口服维生素 D 激素替代疗法 (例如, 度骨化醇 (doxercalciferol)、帕立骨化醇 (paricalcitol) 以及钙三醇) 的更长处理所观测到的差异有利地比较。

[0169] 达成 iPTH 在 EOT 时从处理前基线确认降低 (即, 两次连续测量) 至少 20% 或 30% 的接受 25-羟基维生素 D₃ 的受试者的百分比随着剂量而增加直至 60 μg。在 60 μg 与 90 μg 处理组中观测到类似的反应率, 指示了在这项研究中对于 90 μg 剂量没有观测到 iPTH 降低的进一步效益。30 μg、60 μg 以及 90 μg 剂量组分别与组合安慰剂组中的 9.7% 相比, 对于 iPTH 的确认 20% 降低的反应率为 38.5%、70.6% 以及 76.5%。对于 20% 降低所观测到的反应率的差异仅仅在 60 μg 和 90 μg 剂量组中是显著的 (p<0.005) 并且对于 30% 降低在所有三个剂量组中都是显著的 (p<0.05)。这个数据支持了在稳定化控制释放制剂中每天 30 μg 的 25-羟基维生素 D₃ 是最低有效剂量的结论。

[0170] 25-羟基维生素 D₃ 的稳定化制剂对于经过校正的白蛋白校正血清钙、血清磷以及尿钙排泄没有临床上显著的影响。在 6 周处理时段期间对血清钙或血清磷或尿钙不存在不良影响。

[0171] 药物动力学分析揭示, 25-羟基维生素 D₃ 的稳定化制剂经过 6 周跨越三个剂量组以与剂量成比例的方式增加 25-羟基维生素 D₃ 暴露 (AUC 和 C_{max}), 其中 t_{1/2} 没有差异。在施用 6 周之后, 三个处理组不完全达到稳态。然而, 稳态建模展示, 稳态将在所有剂量组中截止 7-9 周已经达成。

[0172] 来自这项研究的数据清楚展示, 25-羟基维生素 D₃ 的稳定化控制释放制剂有效升高血清总 25-羟基维生素 D 至 30ng/mL 的最低充足水平并且降低血浆 iPTH。研究还显示, 25-羟基维生素 D₃ 的稳定化制剂在所调查的剂量下对血清钙或磷没有临床上有意义的影响。

[0173] 实施例 4: 在具有继发性甲状旁腺功能亢进和维生素 D 不足的 CKD 受试者中修饰释放骨化二醇的药物动力学和药效学型态

[0174] 在 2 个群组的受试者中进行稳定化持续释放 25-羟基维生素 D₃ (骨化二醇, 25D₃) 胶囊的多中心、随机、双盲、安慰剂对照、重复剂量、安全性、功效以及 PK/PD 研究。募集具有 3 期 CKD (eGFR 为 25-70mL/min/1.73m²)、维生素 D 不足 (血清 25-羟基维生素 D ≥ 10 并且 ≤ 29ng/mL)、SHPT (血浆 iPTH > 70pg/mL) 并且不需要常规血液透析的年龄 18 岁至 85 岁的男性和女性受试者用于这项研究。将在第一个群组中符合条件的受试者以 1:1:1 的比率随机分成 3 个处理组: 2 个组分别接受 60 或 90 μg 每日口服剂量的胶囊, 并且 1 个组接受匹配的安慰剂胶囊。将群组 2 中的受试者以 1:1 的比率随机分成 2 个处理组: 1 个组每日接受 30 μg 胶囊并且另一个接受安慰剂。每个群组中的受试者完成 6 周处理并且进入 6 周追踪期, 在此期间每周收集 PK 和 PD 样品。在 6 周处理和 6 周追踪期间每周监测血清钙 (Ca)、磷 (P)、25D₃、总 1, 25-二羟基维生素 D (1, 25D) 以及血浆 iPTH。ANCOVA 模型检查 25D₃ 暴露与 1, 25D 和 iPTH 从基线的变化的相关性。所包括的协变量有基线 eGFR、体重和身高、性别、年

龄、种族、糖尿病状态,以及 1, 25D 或 iPTH 的基线浓度。

[0175] 图 4 示出了处理组 (PK 群体) 的所得平均基线调整骨化二醇浓度。血清骨化二醇的平均水平逐渐地并且以与剂量成比例的方式增加并且截止 6 周开始接近稳态。在追踪 6 周之后,在所有活性剂处理组中水平下降但仍保持高于基线。

[0176] 图 5 示出了处理组 (PK 群体) 的骨化二醇浓度的所得汇总基线调整 PK 参数。

[0177] 图 6 示出了在 6 周处理 (PK 群体) 期间的所得平均基线调整血清 1, 25- 二羟基维生素 D 水平。与施用安慰剂的那些受试者相比,在施用活性剂胶囊的那些受试者中平均基线调整血清总 1, 25- 二羟基维生素 D 水平随着时间而增加。

[0178] 图 7 示出了处理组 (PK 群体) 的血清 1, 25- 二羟基维生素 D 的所得基线调整重复剂量 PK 参数的汇总。

[0179] 图 8 示出了在 6 周处理 (PK 群体) 期间血浆 iPTH 水平的所得平均基线百分比。与组合安慰剂组中的 17% 增加相比,活性剂胶囊使所有剂量组 (分别为 30、60 以及 90 μ g) 中的平均血浆 iPTH 从基线显著降低 21%、33% 以及 39%。

[0180] 图 9 示出了处理组 (PK 群体) 的血浆 iPTH 的所得基线调整重复剂量 PK 参数的汇总。

[0181] 图 10 和 11 示出了在 PK 群体中血浆 iPTH 相对于基线调整骨化二醇和 1, 25- 二羟基维生素 D 暴露 ($AUC_{0-6周}$) 在 EOT 处从基线的变化百分比。血浆 iPTH 从基线至 EOT 的降低百分比随着在处理期间血清骨化二醇和总 1, 25- 二羟基维生素 D 暴露 (表示为基线调整 $AUC_{0-6周}$) 增加而增加。

[0182] 稳定化持续释放 25-羟基维生素 D₃ 胶囊使大多数受试者中的 25D 水平正常化并且显著降低所有剂量组 (30、60 以及 90 μ g) 中的 iPTH。稳定化持续释放 25-羟基维生素 D₃ 胶囊在暴露中以剂量依赖性增加逐渐地增加血清 25D₃ 和血清 1, 25D 水平。25D₃ 与总 1, 25D 暴露都与血浆 iPTH 从基线的变化显著地并且反向相关。在两种模型中只有 eGFR 是显著的协变量。这些发现展示,稳定化持续释放 25-羟基维生素 D₃ 胶囊可靠地使 25D 水平正常化,增加血清 1, 25D 水平并且抑制升高的血浆 iPTH,而在所调查的剂量下对血清 Ca 和 P 没有临床上有意义的影响。

[0183] ***

[0184] 给出前面的描述仅仅是为了理解清楚,并且来自于其的理解不应有不必要的限制,因为在本发明的范围内的修改可以为本领域的一般技术人员显而易见。

[0185] 在本说明书和以上权利要求书通篇,除非上下文另有要求,否则词语“包含”应理解为意味着包括规定的整数或步骤或者整数或步骤的组,但不排除任何其它整数或步骤或者整数或步骤的组。

[0186] 在说明书通篇,除非另有描述,否则在组合物被描述为包括组分或物质的情况下,预期这些组合物也可以基本上由所叙述的组分或物质的任何组合组成,或由所叙述的组分或物质的任何组合组成。同样地,除非另有描述,否则在方法被描述为包括特定步骤的情况下,预期这些方法也可以基本上由所叙述的步骤的任何组合组成,或由所叙述的步骤的任何组合组成。本文说明性地公开的发明内容可以在不存在本文未特定公开的任何要素或步骤的情况下实施。

[0187] 本文所公开的方法和其个别步骤的实施可以人工地和 / 或借助于电子设备来进

行。尽管工艺已经参考特定实施方案来描述,但本领域的一般技术人员将容易地了解,可以使用执行与这些方法相关的动作的其它方式。举例来说,除非另有描述,否则在不脱离方法的范围或精神的情况下可以改变各种步骤的次序。另外,可以将个别步骤中的一些步骤组合,省略,或进一步细分成额外的步骤。

[0188] 本文所引用的所有专利、公布以及参考文献特此以引用的方式完全并入。在本公开与所并入的专利、公布以及参考文献之间相矛盾的情况下,应以本公开为准。

[0189] 鉴于前面的描述所预期的实施方案包括以下编号的段落中所描述的那些。

[0190] 1. 一种维生素 D 化合物的控制释放制剂,其包含 25-羟基维生素 D₂和 25-羟基维生素 D₃中的一者或两者,所述制剂包含可释放地结合并且可控地释放所述维生素 D 化合物的基质,所述基质包含纤维素衍生物。

[0191] 2. 一种稳定化制剂,其用于在摄取所述制剂的受试者的胃肠道中维生素 D 化合物的控制释放,所述制剂包含以下的混合物:

[0192] 25-羟基维生素 D₂和 25-羟基维生素 D₃中的一者或两者;

[0193] 以及有效量的稳定剂,任选地是纤维素化合物,以维持在两个月暴露于 25℃和 60%相对湿度的储存条件之后在体外溶解测试期间在四小时后的任何给定时间点释放的维生素 D 化合物的量与在使所述制剂暴露于所述储存条件之前进行的体外溶解期间的相同溶解时间点释放的量之间小于 30%的差异。

[0194] 3. 一种稳定化制剂,其用于维生素 D 化合物的控制释放,所述制剂包含以下的混合物:

[0195] 25-羟基维生素 D₂和 25-羟基维生素 D₃中的一者或两者;

[0196] 蜡基质;以及

[0197] 稳定剂,任选地是纤维素化合物。

[0198] 4. 一种稳定化制剂,其用于在摄取所述制剂的受试者的胃肠道中维生素 D 化合物的控制释放,所述制剂包含以下的混合物:

[0199] 25-羟基维生素 D₂和 25-羟基维生素 D₃中的一者或两者;

[0200] 蜡基质;以及

[0201] 稳定剂,任选地是纤维素稳定剂。

[0202] 5. 一种稳定化制剂,其用于维生素 D 的控制释放,所述制剂包含以下的混合物:

[0203] 25-羟基维生素 D₂和 25-羟基维生素 D₃中的一者或两者;

[0204] 蜡基质;以及

[0205] 有效量的稳定剂,任选地是纤维素化合物,以维持在持续两个月暴露于 25℃和 60%相对湿度的储存条件之后在体外溶解测试期间在四小时后的任何给定时间点释放的维生素 D 化合物的量与在使所述制剂暴露于所述储存条件之前进行的体外溶解期间的相同溶解时间点释放的量之间小于 30%的差异。

[0206] 6. 一种稳定化制剂,其用于在摄取所述制剂的受试者的胃肠道中维生素 D 化合物的控制释放,所述制剂包含以下的混合物:

[0207] 包含 25-羟基维生素 D₂和 25-羟基维生素 D₃中的一者或两者的活性剂加载的蜡基质;以及

[0208] 纤维素稳定剂;

[0209] 其中所述制剂在两个月暴露于 25℃ 和 60% 相对湿度的储存期之后在体外溶解期间释放的 25-羟基维生素 D 的量在任何给定溶解时间点与在使所述制剂暴露于所述储存条件之前进行的体外溶解期间的相同溶解时间点释放的量相比在不存在所述纤维素稳定剂的情况下变化 30% 或更小。

[0210] 7. 在用于在摄取所述制剂的受试者的胃肠道中维生素 D 化合物的控制释放的制剂中, 所述改善包括将纤维素稳定剂混入所述制剂中。

[0211] 8. 在用于在摄取所述制剂的受试者的胃肠道中维生素 D 化合物的控制释放的制剂中, 所述改善包括混入所述制剂中的有效量的纤维素化合物以维持在暴露于 25℃ 和 60% 相对湿度的储存条件至少一个月之后在体外溶解期间释放的 25-羟基维生素 D 的量在四小时后的任何给定溶解时间点与在使所述制剂暴露于所述储存条件之前进行的体外溶解期间的相同溶解时间点释放的量相比小于 30% 的变化。

[0212] 9. 如前述段落中任一项所述的制剂, 其中所述纤维素化合物或纤维素稳定剂包含纤维素醚。

[0213] 10. 如段落 9 所述的制剂, 其中所述纤维素醚选自自由以下组成的群组: 甲基纤维素、羟丙基甲基纤维素、羟乙基甲基纤维素、羟乙基纤维素以及羟丙基纤维素。

[0214] 11. 如段落 9 所述的制剂, 其中所述纤维素化合物或纤维素稳定剂是羟丙基甲基纤维素。

[0215] 12. 如前述段落中任一项所述的制剂, 其中所述制剂在暴露于 25℃ 和 60% 相对湿度的储存条件持续 2 个月之后在体外溶解期间释放的 25-羟基维生素 D 的量在四小时后的任何给定溶解时间点与在使所述制剂暴露于所述储存条件之前进行的体外溶解期间的相同溶解时间点释放的量相比变化 30% 或更小。

[0216] 13. 如前述段落中任一项所述的制剂, 其中所述制剂在暴露于 40℃ 和 75% 相对湿度的储存条件持续一个月之后在体外溶解期间释放的 25-羟基维生素 D 的量在四小时后的任何给定溶解时间点与在使所述制剂暴露于所述储存条件之前进行的体外溶解期间的相同溶解时间点释放的量相比变化 30% 或更小。

[0217] 14. 如前述段落中任一项所述的制剂, 其中所述基质包含有包含控制释放剂、乳化剂以及吸收增强剂的蜡基质。

[0218] 15. 如段落 14 所述的制剂, 其中所述控制释放剂包含石蜡。

[0219] 16. 如段落 14 或 15 所述的制剂, 其中所述乳化剂具有小于 7 的 HLB 值。

[0220] 17. 如段落 16 所述的制剂, 其中所述乳化剂包含单硬脂酸甘油酯。

[0221] 18. 如段落 14 至 17 中任一项所述的制剂, 其中所述吸收增强剂具有在约 13 至约 18 的范围内的 HLB 值。

[0222] 19. 如段落 18 所述的制剂, 其中所述吸收增强剂是月桂酰聚乙二醇甘油酯与月桂酰聚氧甘油酯的混合物。

[0223] 20. 如前述段落中任一项所述的制剂, 其中所述维生素 D 化合物包含 25-羟基维生素 D₃。

[0224] 21. 如前述段落中任一项所述的制剂, 其进一步包含油性媒剂。

[0225] 22. 如段落 21 所述的制剂, 其中所述油性媒剂包含矿物油。

[0226] 23. 如段落 22 所述的制剂, 其中所述制剂包含约 20wt% 石蜡、约 20wt% 至约

25wt%单硬脂酸甘油酯、约 10wt%月桂酰聚乙二醇甘油酯与月桂酰聚氧甘油酯的混合物、约 30wt%至约 35wt%矿物油、以及约 10wt%至约 15wt%羟丙基甲基纤维素。

[0227] 24. 如前述段落中任一项所述的制剂,其中所述制剂包含单硬脂酸甘油酯。

[0228] 25. 如前述段落中任一项所述的制剂,其中所述制剂包含一种或多种聚乙二醇化甘油酯。

[0229] 26. 一种呈胶囊、片剂、香囊、糖衣丸或栓剂形式的持续释放剂型,其包含如前述段落中任一项所述的制剂。

[0230] 27. 如段落 26 所述的剂型,其包含胶囊或片剂。

[0231] 28. 如段落 27 所述的剂型,其包含胶囊。

[0232] 29. 如段落 26 所述的剂型,其包含口服胶囊、片剂、香囊、糖衣丸。

[0233] 30. 如前述段落中任一项所述的稳定化剂型,其特征为提供维生素 D 化合物的以下释放的溶解型态:

[0234] 在 2 小时处小于 30%;

[0235] 在 6 小时处大于 45%;以及

[0236] 在 12 小时处大于 80%。

[0237] 31. 如段落 26 所述的稳定化剂型,其中在 6 小时处维生素 D 化合物的所述释放小于 60%。

[0238] 32. 一种包含维生素 D 化合物的稳定化持续释放口服剂型,其特征为提供维生素 D 化合物的以下释放的体外溶解型态:

[0239] 在 100 至 140 分钟处小于 30%;

[0240] 在 5 至 7 小时处大于 45%;以及

[0241] 在 11 至 13 小时处大于 80%。

[0242] 33. 如段落 32 所述的剂型,其中维生素 D 化合物的所述释放为

[0243] 在 2 小时处小于 30%;

[0244] 在 6 小时处大于 45%;以及

[0245] 在 12 小时处大于 80%。

[0246] 34. 如段落 32 或 33 所述的剂型,其中在 5 至 7 小时处维生素 D 化合物的所述释放小于 60%。

[0247] 35. 如段落 34 所述的剂型,其中在 6 小时处维生素 D 化合物的所述释放小于 60%。

[0248] 36. 一种包含维生素 D 化合物的稳定化持续释放口服剂型,其特征为提供维生素 D 化合物的以下释放的体外溶解型态:

[0249] 在 2 小时处约 20%至约 40%;

[0250] 在 6 小时处至少 35%;以及

[0251] 在 12 小时处至少 70%。

[0252] 37. 如段落 36 所述的剂型,其中维生素 D 化合物的所述释放为在 2 小时处约 25%至约 35%;

[0253] 在 6 小时处至少 40%;以及

[0254] 在 12 小时处至少 75%。

[0255] 38. 如段落 36 或 37 所述的剂型,其中维生素 D 化合物的所述释放为在 6 小时处

75%或更小。

[0256] 39. 如段落 38 所述的剂型,其中维生素 D 化合物的所述释放为在 6 小时处 65%或更小。

[0257] 40. 如段落 39 所述的剂型,其中维生素 D 化合物的所述释放为在 6 小时处 60%或更小。

[0258] 41. 一种包含维生素 D 化合物的稳定化持续释放剂型,其特征为在将所述剂型施用于人类患者之后至少 4 小时的 t_{max} 。

[0259] 42. 如段落 41 所述的剂型,其中所述 t_{max} 为至少 8 小时。

[0260] 43. 如段落 42 所述的剂型,其中所述 t_{max} 为至少 12 小时。

[0261] 44. 如段落 43 所述的剂型,其中所述 t_{max} 为至少 18 小时。

[0262] 45. 如段落 44 所述的剂型,其中所述 t_{max} 为至少 20 小时。

[0263] 46. 如段落 45 所述的剂型,其中所述 t_{max} 为至少 24 小时。

[0264] 47. 如段落 46 所述的剂型,其中所述 t_{max} 为至少 28 小时。

[0265] 48. 如段落 41 所述的剂型,其中所述 t_{max} 在 4 至 96 小时的范围内。

[0266] 49. 如段落 48 所述的剂型,其中所述 t_{max} 在 18 至 30 小时的范围内。

[0267] 50. 如段落 49 所述的剂型,其中所述 t_{max} 在 13 至 28 小时的范围内。

[0268] 51. 如段落 50 所述的剂型,其中所述 t_{max} 为约 28 小时。

[0269] 52. 一种包含 25-羟基维生素 D 化合物的稳定化持续释放剂型,所述剂型的特征为当施用于成年人时提供每微克 25-羟基维生素 D 在约 0.0133ng/mL 至约 0.04ng/mL 的范围内的基线调整 C_{max} 。

[0270] 53. 一种将包含 25-羟基维生素 D 化合物的稳定化持续释放剂型施用于人类患者的方法,其包括将有效量的所述剂型施用于所述患者以提供至少约 0.2ng/mL 并且小于 110ng/mL 的基线调整 C_{max} 。

[0271] 54. 如段落 53 所述的方法,其包括施用有效量的所述剂型以提供在约 0.2 至约 24ng/mL 的范围内的基线调整 C_{max} 。

[0272] 55. 一种将包含 25-羟基维生素 D 化合物的稳定化持续释放剂型施用于人类患者的方法,其包括将有效量的所述剂型施用于所述患者以提供至少 52ng · h/mL 并且小于 34500ng · h/mL 的基线调整 AUC_{0-inf} 。

[0273] 56. 如段落 55 所述的方法,其包括将有效量的所述剂型施用于所述患者以提供在约 52ng · h/mL 至约 12,000ng · h/mL 的范围内的基线调整 AUC_{0-inf} 。

[0274] 57. 一种维生素 D 补充的方法,其包括向有需要的受试者施用如前述段落中任一项所述的制剂或剂型。

[0275] 58. 一种治疗或预防受试者的维生素 D 反应性疾病的方法,其包括向所述受试者施用如前述段落中任一项所述的制剂或剂型。

[0276] 59. 如段落 58 所述的方法,其中所述疾病选自癌症(例如,乳癌、肺癌、皮肤癌、黑色素瘤、结肠癌、结肠直肠癌、直肠癌、前列腺癌以及骨癌);自体免疫疾病,例如,I 型糖尿病、多发性硬化、类风湿性关节炎、多肌炎、皮肌炎、硬皮病、纤维化、格雷夫氏病、桥本氏病、急性或慢性移植排斥反应、急性或慢性移植抗宿主疾病、发炎性肠病、克罗恩氏病、全身性红斑狼疮、修格兰氏综合症、湿疹以及牛皮癣;皮炎,包括异位性皮炎、接触性皮炎、过敏性

皮炎和 / 或慢性皮炎 ; 发炎性疾病, 例如, 哮喘、慢性阻塞性肺病、多囊性肾病、多囊性卵巢综合症、胰腺炎、肾炎、肝炎和 / 或感染 ; 高血压 ; 心血管疾病, 例如, 患有动脉粥样硬化、动脉硬化、冠状动脉疾病、脑血管疾病、外周血管疾病、心肌梗塞、心肌缺血、脑缺血、中风、充血性心脏衰竭、心肌病的受试者 ; 肥胖或其它体重异常 ; 脂质异常 (例如, 高脂血症 ; 脂代谢异常, 包括相关的糖尿病性脂代谢异常和混合性脂代谢异常 ; 低 α 脂蛋白血症 ; 高甘油三酯血症 ; 高胆固醇血症 ; 以及低 HDL (高密度脂蛋白)) ; 代谢异常 (例如, 代谢综合症 ; II 型糖尿病 ; I 型糖尿病 ; 高胰岛素血症 ; 葡萄糖耐量减低 ; 胰岛素抵抗 ; 糖尿病并发症, 包括神经病、肾病、骨质疏松症、视网膜病、糖尿病足溃疡以及白内障) ; 和 / 或血栓症。

[0277] 60. 如段落 59 所述的方法, 其中所述疾病选自 (i) 在甲状旁腺中 -- 甲状旁腺功能减退、假性甲状旁腺功能减退、继发性甲状旁腺功能亢进 ; (ii) 在胰腺中 -- 糖尿病 ; (iii) 在甲状腺中 -- 髓样癌 ; (iv) 在皮肤中 -- 牛皮癣、伤口愈合 ; (v) 在肺中 -- 肉状瘤病和结核病 ; (vi) 在肾中 -- 慢性肾病、低磷酸盐血性 VDDR、维生素 D 依赖性佝偻病 ; (vii) 在骨中 -- 抗惊厥剂治疗、骨纤维生成不良、囊性纤维性胃炎、骨软化、骨质疏松症、骨质减少、骨硬化、肾性骨营养不良、佝偻病 ; (viii) 在肠中 -- 糖皮质激素拮抗、特发性高钙血症、吸收不良综合症、脂肪痢、热带口炎性腹泻 ; 以及 (ix) 自体免疫病症。

[0278] 61. 如段落 60 所述的方法, 其中所述疾病选自癌症、皮肤病症 (例如, 牛皮癣)、甲状旁腺病症 (例如, 甲状旁腺功能亢进和继发性甲状旁腺功能亢进)、骨病症 (例如, 骨质疏松症) 以及自体免疫病症。

[0279] 62. 如段落 61 所述的方法, 其中所述疾病是继发性甲状旁腺功能亢进。

[0280] 63. 如段落 62 所述的方法, 其中所述受试者患有慢性肾病 (CKD)。

[0281] 64. 如段落 63 所述的方法, 其中所述 CKD 是 3 期或 4 期。

[0282] 65. 如段落 64 所述的方法, 其中所述患者是维生素 D 缺乏的。

[0283] 66. 如前述段落中任一项所述的方法, 其中所述患者是人类。

[0284] 67. 如段落 66 所述的方法, 其中所述人类是成年人。

[0285] 68. 一种组合物, 其实质上如本文所描述。

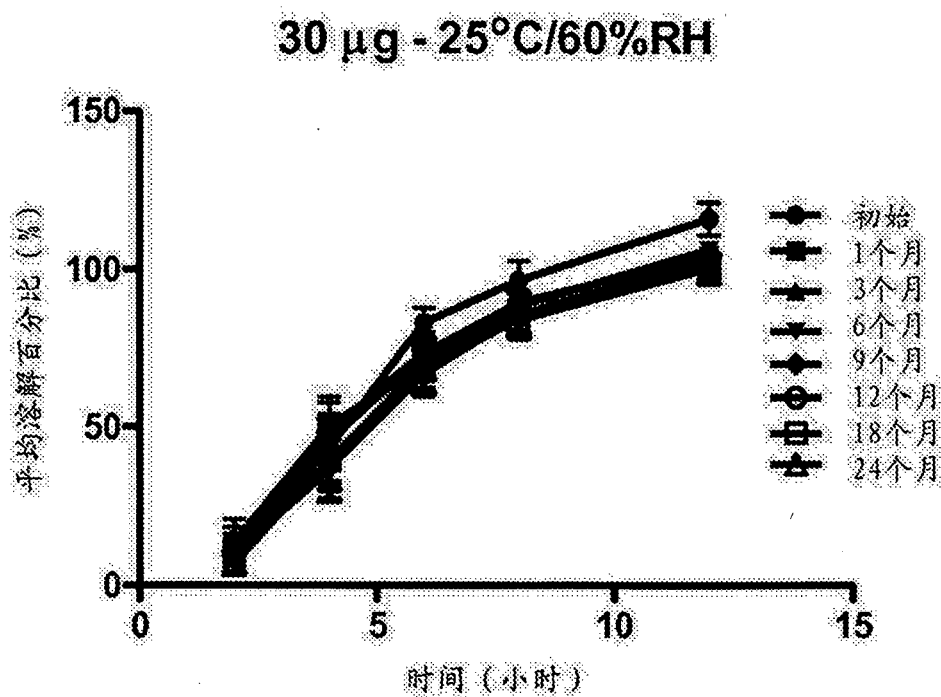


图 1A

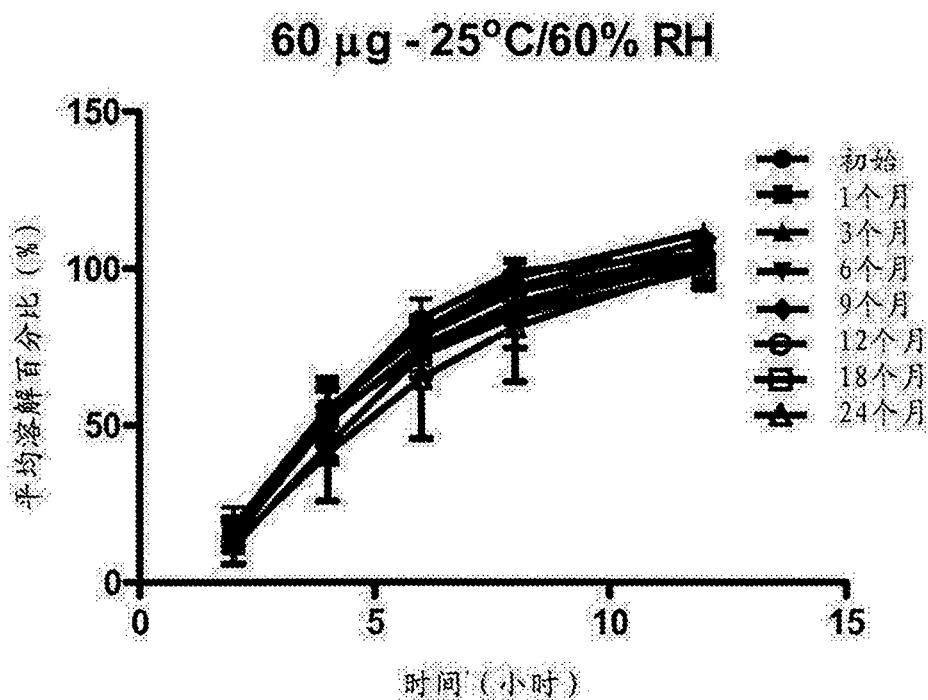


图 1B

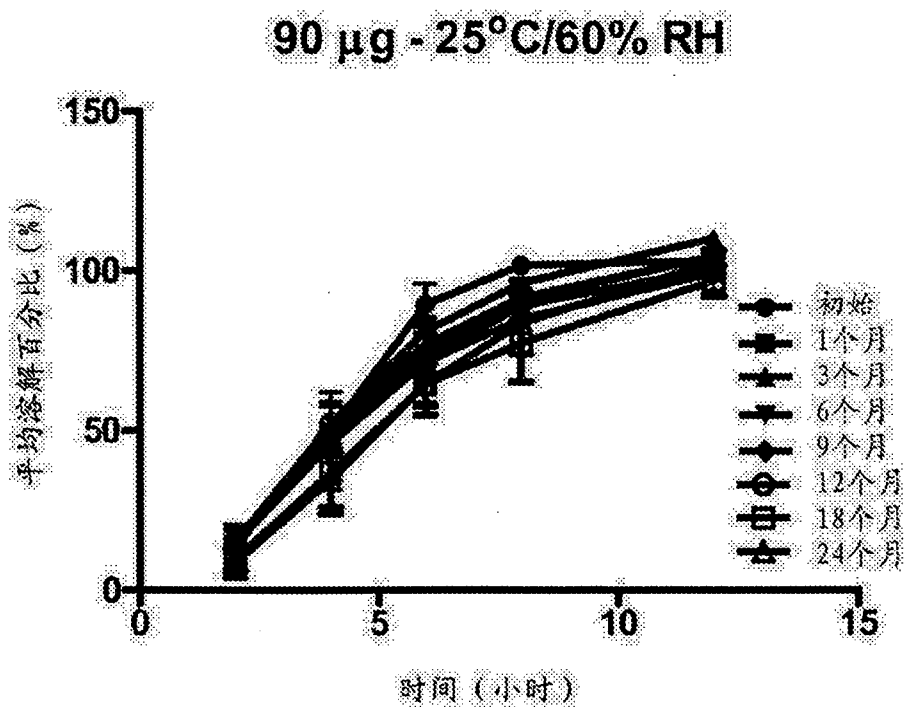


图 1C

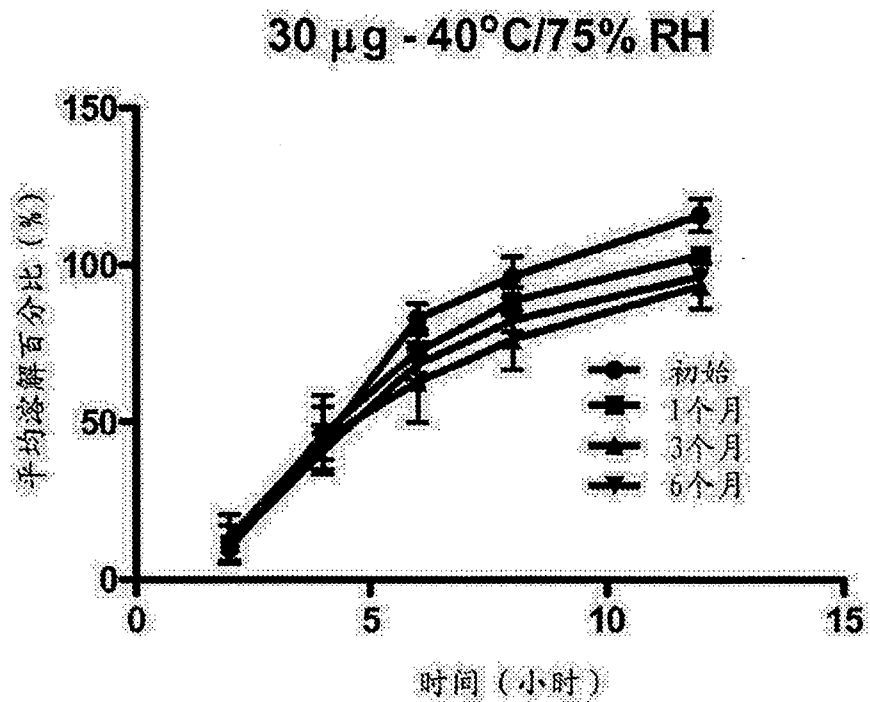


图 2A

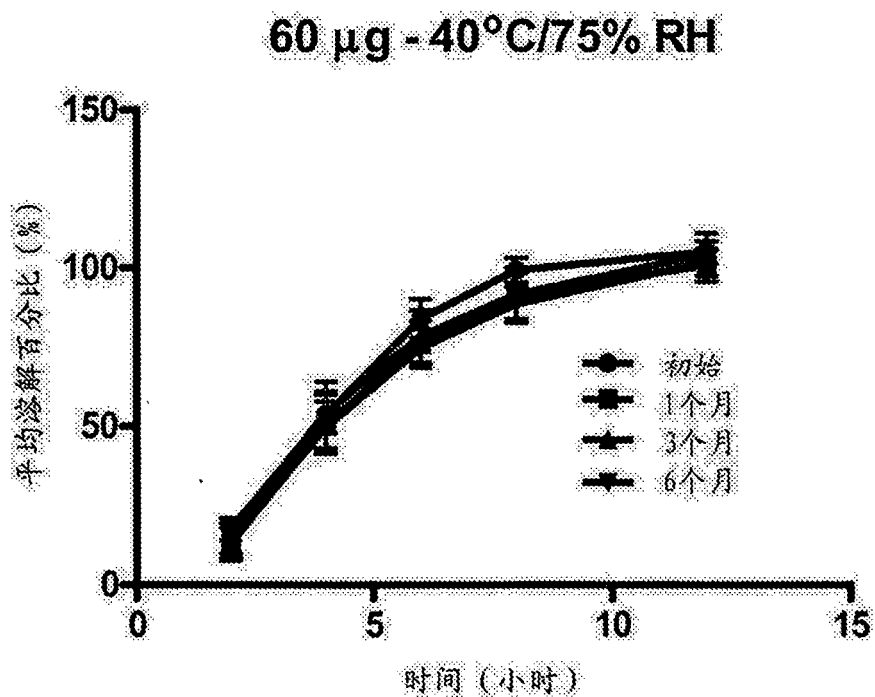


图 2B

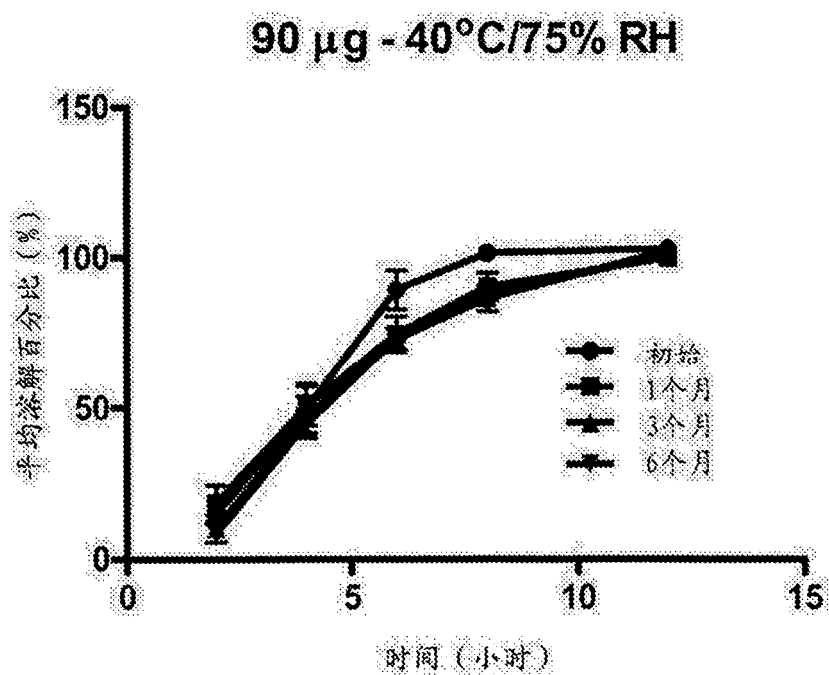


图 2C

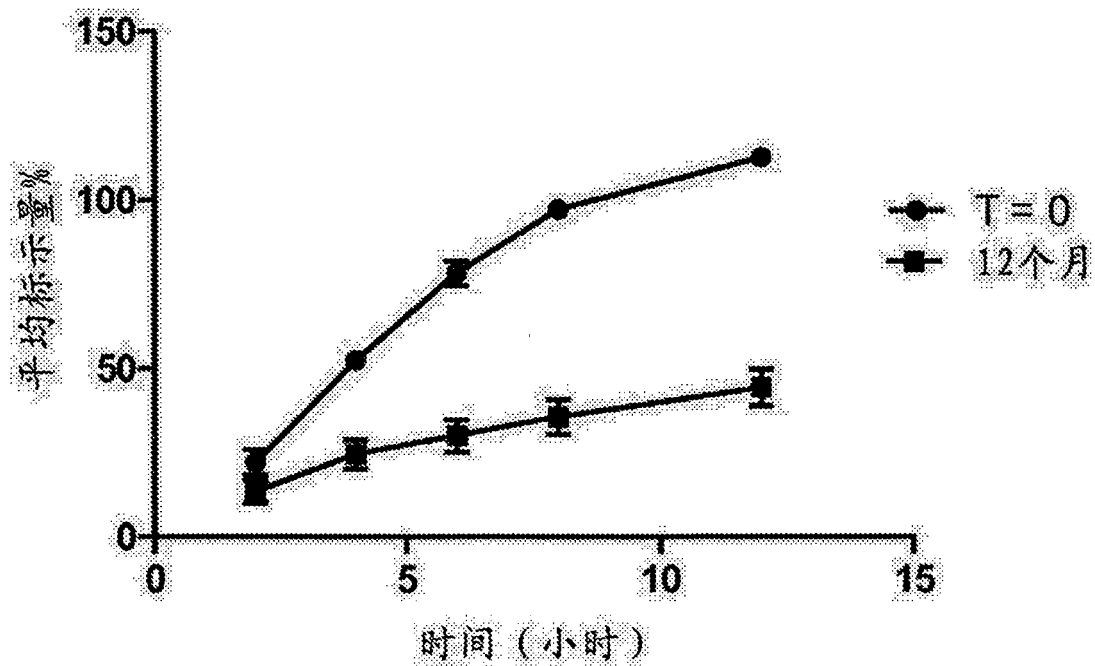


图 3A

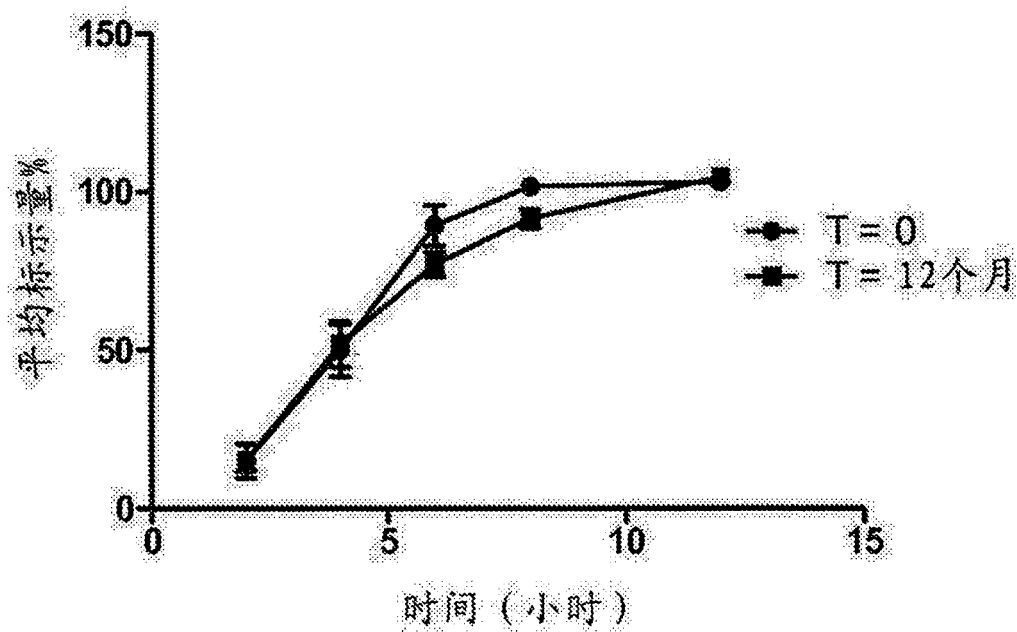


图 3B

图 3

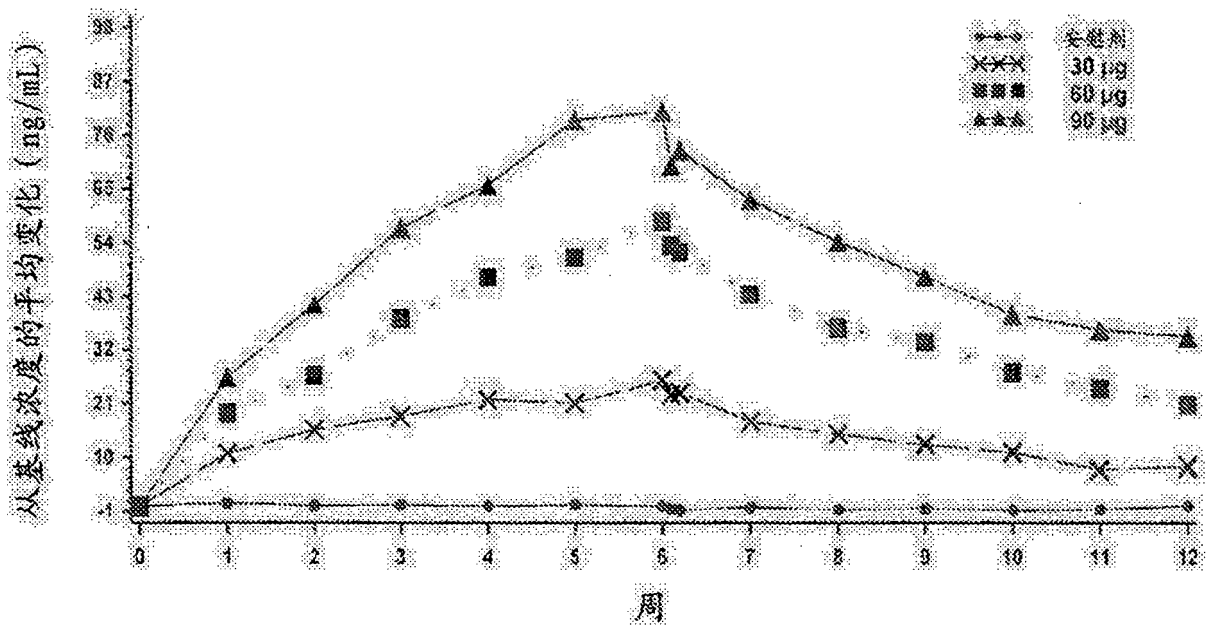


图 4

特征	安慰剂 N=29	30μg N=12	60μg N=16	90μg N=14
基线 (ng/mL)				
平均值 (SD)	16.23 (8.29)	16.21 (7.34)	19.79 (8.69)	18.37 (9.77)
中值	12.87	17.24	21.21	16.65
Min, Max	4.35, 30.43	5.02, 25.83	5.83, 32.45	6.67, 38.86
C _{max} (ng/mL) ^a				
平均值 (SD)	3.58 (3.61)	27.75 (8.21)	60.33 (18.97)	85.69 (26.90)
中值	2.97	28.13	60.77	76.04
Min, Max	-0.56, 13.83	10.75, 43.39	30.31, 89.54	55.44, 146.35
AUC _{0-∞} (ng·d/mL)				
平均值 (SD)	9.19 (85.66)	689.15 (238.14)	1477.80 (360.22)	2060.95 (588.86)
中值	22.62	657.19	1472.18	1896.27
Min, Max	-171.75, 214.62	393.97, 1208.29	685.75, 2141.08	1316.39, 3206.31
t _{max} (d) ^b				
平均值 (SD)	34.97 (30.79)	37.75 (10.41)	41.13 (5.24)	42.50 (5.06)
中值	23.00	42.50	43.00	43.00
Min, Max	1.00, 87.00	8.00, 44.00	28.00, 45.00	35.00, 56.00
t _{1/2} (d) ^c				
平均值 (SD)	- (-)	26.32 (13.98)	32.67 (8.59)	49.62 (51.09)
中值	-	24.06	30.85	36.32
Min, Max	-	5.16, 49.35	19.44, 48.11	23.15, 224.03

^a数据截至 50S
缩写: Min: 最小值; Max: 最大值

图 5

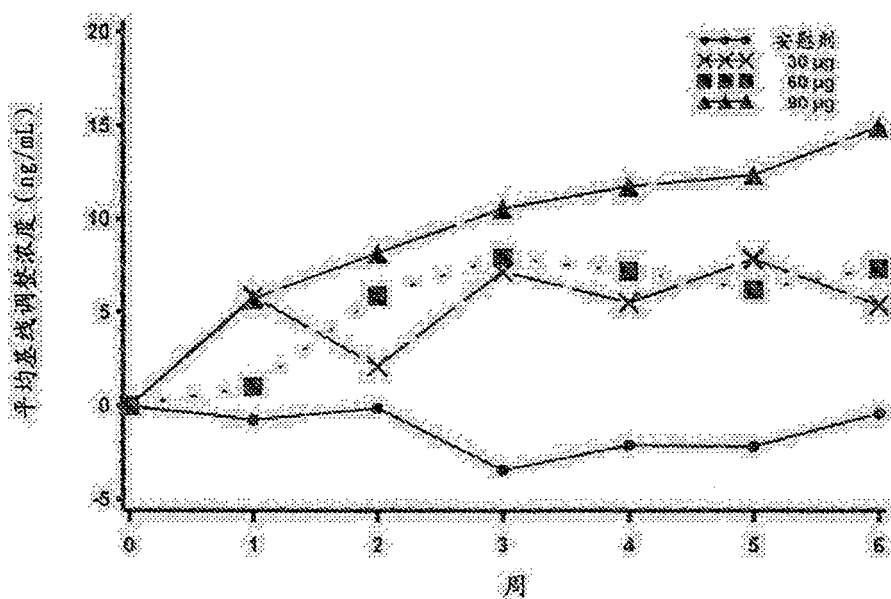


图 6

特征	安慰剂 N=29	30μg N=12	60μg N=16	90μg N=14
基线 (pg/mL)				
平均值 (SD)	23.14 (12.51)	18.47 (7.97)	20.96 (6.56)	21.38 (7.70)
中值	18.57	15.52	18.73	21.02
Min, Max	7.00, 52.07	5.07, 30.67	12.77, 39.63	10.70, 36.63
C _{max} (pg/mL) ¹				
平均值 (SD)	9.07 (7.99)	18.05 (20.24)	16.58 (9.30)	23.71 (13.63)
中值	7.30	9.95	17.35	20.92
Min, Max	-1.57, 34.13	3.53, 78.37	-10.33, 29.90	5.50, 46.30
AUC _{0-∞} (pg·d/mL)				
平均值 (SD)	44.08 (262.50)	252.70 (380.07)	198.86 (295.73)	396.03 (291.81)
中值	-12.17	165.83	290.33	393.36
Min, Max	-726.25, 509.95	-112.18, 1295.40	-593.93, 553.00	72.05, 1188.60
t _{max} (d) ¹				
平均值 (SD)	21.55 (16.86)	30.67 (8.12)	25.19 (10.81)	26.64 (13.30)
中值	23.00	30.00	22.50	23.00
Min, Max	1.00, 44.00	16.00, 42.00	8.00, 43.00	7.80, 44.00

¹数据直至EOS
缩写: Min: 最小值; Max: 最大值

图 7

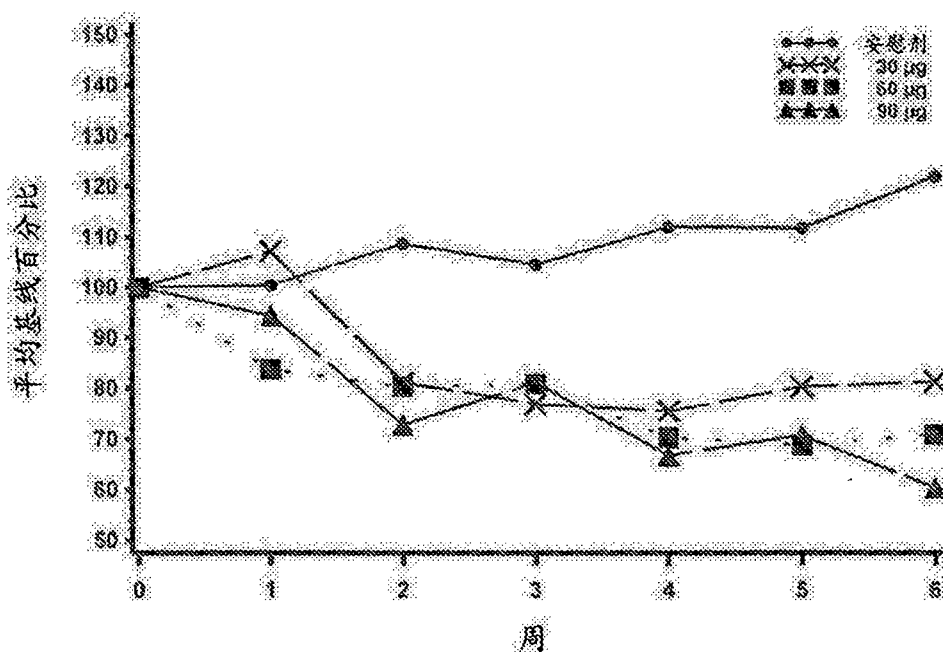


图 8

特征	安慰剂 N=29	30μg N=12	60μg N=16	90μg N=14
基线 ¹ (pg/mL)				
平均值 (SD)	144.62 (67.47)	156.28 (57.92)	118.46 (25.89)	155.88 (58.51)
中值	130.63	161.22	113.78	135.08
Min, Max	64.10, 323.27	81.03, 253.97	82.23, 167.85	96.33, 291.25
C _{min} (pg/mL)				
平均值 (SD)	-38.80 (33.35)	-67.84 (36.71)	-63.09 (21.57)	-86.04 (37.39)
中值	-32.63	-62.48	-63.33	-60.51
Min, Max	-133.03, -3.90	-140.27, -29.83	-104.77, -24.83	-184.10, -41.27
AUC _{0-24h} (pg·d/mL)				
平均值 (SD)	176.02 (1575.81)	-896.76 (1215.80)	-1322.53 (723.32)	-1560.91 (820.99)
中值	180.95	-1029.50	-1325.92	-1303.40
Min, Max	-3059.00, 4463.65	-2812.60, 1457.05	-2228.40, -177.45	-3743.70, -575.75
t _{max} (d)				
平均值 (SD)	21.14 (14.21)	32.08 (8.53)	29.38 (10.39)	32.29 (12.61)
中值	21.00	32.50	32.00	37.00
Min, Max	1.00, 44.00	15.00, 42.00	8.00, 43.00	8.00, 44.00

¹基线是随访1 (或2, 如果洗脱的话)、3以及4的平均值。

图 9

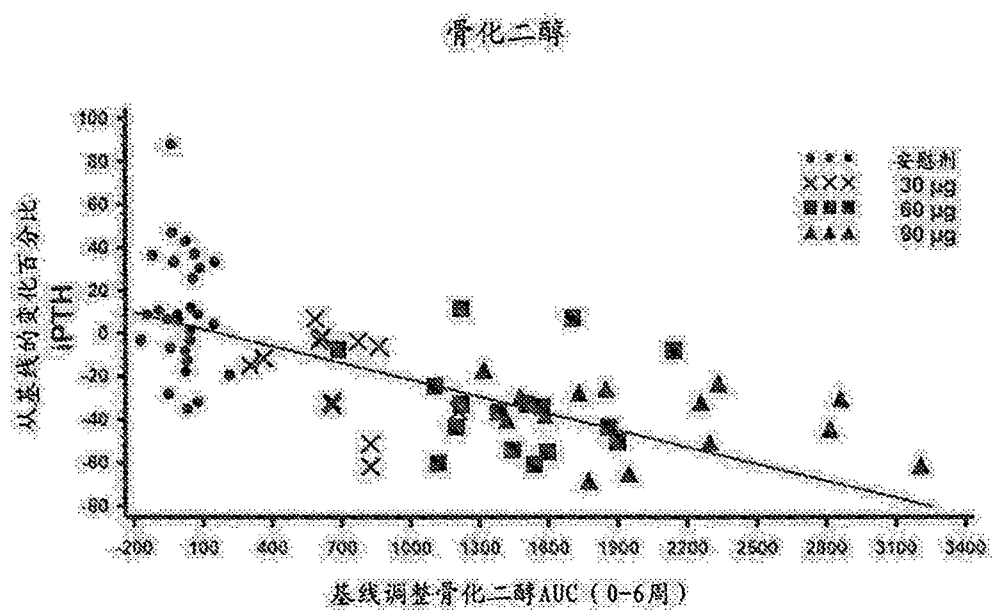


图 10

1,25-二羟基维生素D

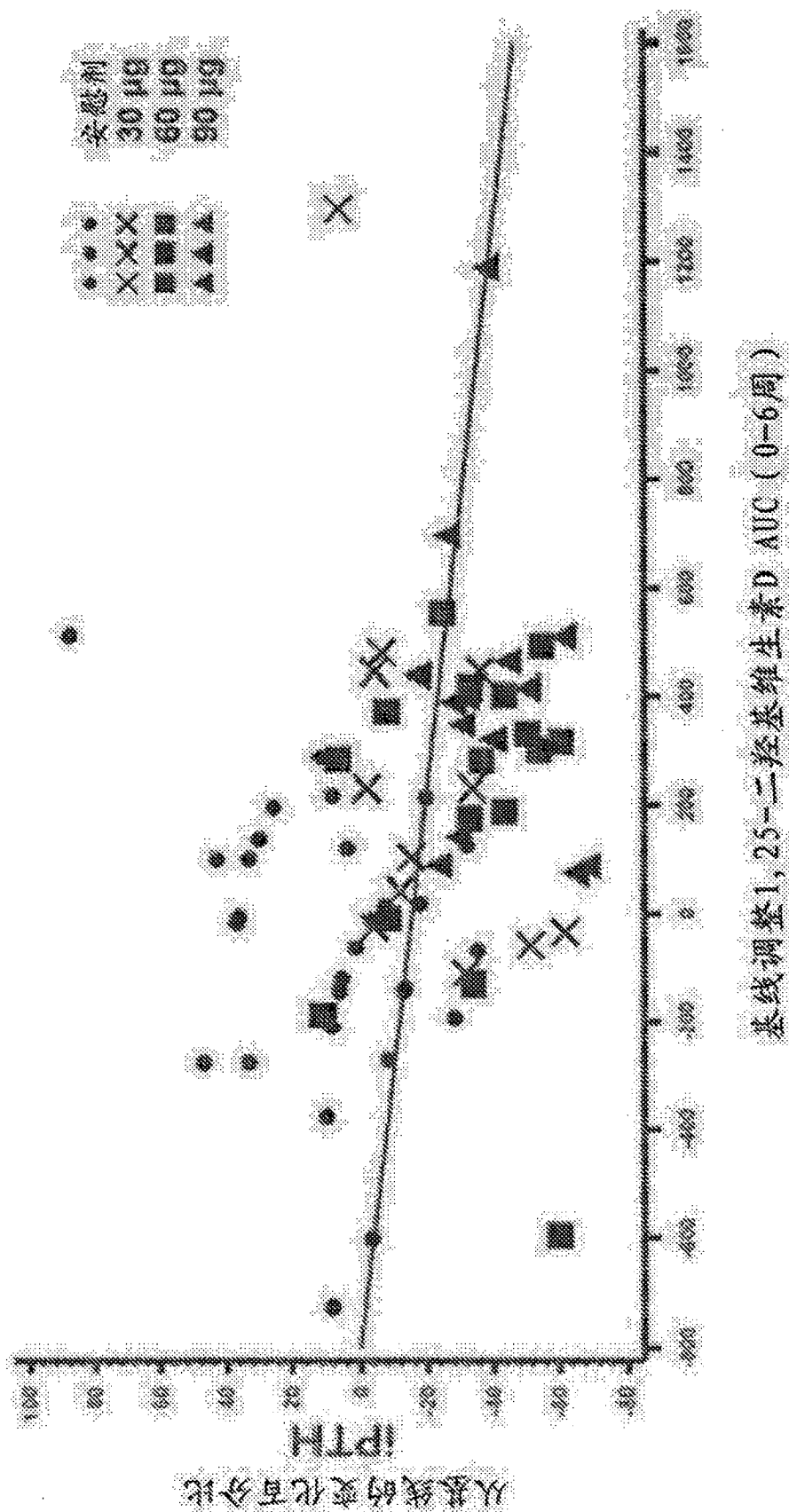


图 11

Abstract

A stabilized formulation for controlled release of a vitamin D compound is disclosed. The formulation comprises one or both of 25-hydroxyvitamin D₂ and 25-hydroxyvitamin D₃ and a cellulosic compound. The stabilized formulations exhibit a stable dissolution profile following exposure to storage conditions and demonstrate improved pharmacokinetic parameters compared to unstabilized formulations.