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 D_2 and 25-hydroxyvitamin D_3 (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 D_2 is produced from Vitamin D_2 (ergocalciferol) and 25-hydroxyvitamin D_3 is produced from Vitamin D_3 (cholecalciferol), primarily by one or more enzymes located in the liver. The two prohormones also can be produced outside of the liver from Vitamin D_2 and Vitamin D_3 (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 D_2 is metabolized into 1α,25-dihydroxyvitamin D_2; likewise, 25-hydroxyvitamin D_3 is metabolized into 1α,25-dihydroxyvitamin D_3 (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 D_2 and/or 25-hydroxyvitamin D_3 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 D_2/25-hydroxyvitamin D_3 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

[0007a] In an aspect of the present disclosure, there is provided a stabilized formulation for sustained release of a vitamin D compound, the formulation comprising a mixture of:

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

a stabilizing agent comprising a material selected from the group consisting of: cellulose compounds, poloxamers, poly(ethylene oxide) polymers, povidones, fumed silicas, and combinations thereof, wherein the stabilizing agent 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%), which is effective 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.

[0007b] In a further aspect of the present disclosure, there is provided a sustained release dosage form in the form of a capsule, tablet, sachet, dragee, or suppository comprising a formulation disclosed herein.

[0007c] In another aspect of the present disclosure, there is provided a product, which is a stabilized formulation for sustained release or a sustained release dosage form disclosed herein, for use in the treatment of a vitamin-D responsive disease.

[0007d] In a further aspect of the present disclosure, there is provided a use of a product, which is a stabilized formulation for sustained release or a sustained release dosage form disclosed herein, in the manufacture of a medicament for the treatment of a vitamin-D responsive disease.

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

[0009] The present disclosure 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 example, the stabilized formulation comprises one or both of 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3 and a stabilizing agent or stabilizing compound,

e.g. a cellulosic compound. The stabilized formulations of the present disclosure 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 example, the stabilized formulation includes one or both of 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3, a lipophilic matrix (e.g. a wax matrix), and a stabilizing agent (e.g., a cellulosic compound). In one example, a stabilized formulation includes one or both of 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3, a wax matrix, and a cellulosic stabilizing agent. In another example, the formulation includes one or both of 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3, 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 example, the stabilized formulation comprises a mixture of an active-loaded wax matrix comprising one or both of 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3 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 ^oC 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 example, the formulation is an improvement formulation for controlled release of a vitamin D compound. In one example, 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 example, 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 example, the present disclosure comprises a stable sustained release vitamin D formulation comprising 25-hydroxyvitamin D_2 or 25-hydroxyvitamin D_3 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 $X=T_0+/-30\%$ over storage conditions selected from room temperature and ambient humidity, or 25 ºC and 60% RH, or 40 ºC and 75% RH, for example.

[0014] Further examples 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 examples in various forms, the description hereafter includes specific examples with the understanding that the present disclosure is illustrative, and is not intended to limit the present disclosure to the specific examples 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 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 ºC and 60% relative humidity. The dissolution time in hours is depicted on the x-axis and the mean percent of 25-hydroxyvitamin D_3 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 D_3, respectively.

[0017] Figure 2 shows the dissolution profile of formulations according to the disclosure after storage for 0 to 6 months at 40 ºC and 75% relative humidity. The dissolution time in hours is depicted on the x-axis and the mean percent of 25-hydroxyvitamin D_3 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 D_3, respectively.

[0018] Figure 3 shows the dissolution profile of formulations after storage for 0 to 12 months at 25 ºC and 60% relative humidity. The dissolution time in hours is depicted on the x-axis and the mean % Label Claim of 25-hydroxyvitamin D_3 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 ($AUC_{0\text{-}6wk}$) 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 Cmax at a time greater than Cmax 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, celluloronic 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 D_3 (cholecalciferol), Vitamin D_2 (ergocalciferol), 25-hydroxyvitamin D_3, 25-hydroxyvitamin D_2, 25-hydroxyvitamin D_4, 25-hydroxyvitamin D_5, 25-hydroxyvitamin D_7, 1α,25-dihydroxyvitamin D_3, 1α,25-dihydroxyvitamin D_2, 1α,25-dihydroxyvitamin D_4, and vitamin D analogs (including all hydroxy and dihydroxy forms), including 1,25-dihydroxy-19-nor-vitamin D_2, and 1α-hydroxyvitamin D_3. In one type of embodiment, the vitamin D compound includes one or more hydroxy forms, such as a combination of 25-hydroxyvitamin D_3 and 25-hydroxyvitamin D_2.

[0029] A type of vitamin D compound particularly contemplated for use in the formulation disclosed herein can include 25-hydroxyvitamin D_2, 25-hydroxyvitamin D_3, or a combination thereof. 25-hydroxyvitamin D_3, is particularly contemplated. As used herein, the term 25-hydroxyvitamin D refers to one or more of 25-hydroxyvitamin D_3, 25-hydroxyvitamin D_2, 25-hydroxyvitamin D_4, 25-hydroxyvitamin D_5, or 25-hydroxyvitamin D_7, and it is contemplated that in any reference thereto a preferred embodiment is one or more of 25-hydroxyvitamin D_3 and 25-hydroxyvitamin D_2, preferably 25-hydroxyvitamin D_3. Thus, in any and all formulations described herein, it is specifically contemplated that the active can include one or both of 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3, particularly 25-hydroxyvitamin D_3. 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 D_3 as the active, references to 25-hydroxyvitamin D should be interpreted to mean 25-hydroxyvitamin D_3, and all pharmacokinetic (PK) results associated with (e.g., t_{max}, C_{max}, AUC) should be understood to be based on 25-hydroxyvitamin D_3.

[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 D_3, tmax is defined as the time for the plasma concentration of serum 25-hydroxyvitamin D_3 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 $\geq$ 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 ºC 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 $AUC_{0\text{-}inf}$ 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., $AUC_{0\text{-}inf}$ or $AUC_{0\text{-}t}$) 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 D_2 and 25-hydroxyvitamin D_3, a wax matrix, and a cellulosic compound. In one aspect, a stabilized formulation comprises one or both of 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3, a wax matrix, and a cellulosic stabilizing agent. In another aspect, the

formulation comprises one or both of 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3, 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, celluloronic 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 % methyoxyl 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 D_2 and 25-hydroxyvitamin D_3 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 D_2 and 25-hydroxyvitamin D_3 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 monocaprate, 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-D_2, 25-D_3, 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 D_2 and/or 25-hydroxyvitamin D_3. 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 D_2 and/or 25-hydroxyvitamin D_3 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 D_2/25-hydroxyvitamin D_3, 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 D_2, 25-hydroxyvitamin D_3 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 D_3 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 erythematosis, 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, 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 VDRR, vitamin D dependent rickets; (vii) in the bone--anticonvulsant treatment, fibrogenisis imperfecta ossium, osteitis fibrosa cystica, osteomalacia, osteoporosis, osteopenia, osteosclerosis, renal osteodytrophy, rickets; (viii) in the intestine--glucocorticoid antagonism, idopathic 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 D_2 and/or 25-hydroxyvitamin D_3) 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 D_2 and/or 25-hydroxyvitamin D_3 (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 D_2 and/or 25-hydroxyvitamin D_3 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 D_3), 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 (±1%)in the vessel of the specified apparatus, assemble the apparatus, equilibrate the Dissolution Medium to 37 ± 0.5°, 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 D_3, 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 D_3 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 D_3 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 D_3 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 D_3, 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 D_3, 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 D_3 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 D_3 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 D_3 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 D_3 (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 D_3 (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

[00105] The percent change between the amount of 25-hydroxyvitamin D_3 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 D_3 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 D_3, 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 D_3 in an ethanol solution. None of the formulations comprised a cellulosic compound.

[00107] The serum concentration of 25-hydroxyvitamin D_3 increased gradually following the administration of an oral dose. The increase in 25-hydroxyvitamin D_3 was dose proportional and reached an approximate mean maximum observed serum concentration (Cmax) of 32 ng/mL

following the administration of the 900 μg capsule. The time at which Cmax occurred (Tmax) was approximately 13 hours post-dose. In contrast, concentrations of 25-hydroxyvitamin D_3 increased rapidly following the administration of the i.v. dose. Peak serum levels were achieved immediately following administration of the i.v. dose (Tmax = 0.5 hours) and reached an approximate mean Cmax 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 D_3 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) Median Range	n	Mean (SD) Median Range	n	Mean (SD) Median Range
PK/PD Population						
Observed 25-hydroxyvitamin D_3						
$AUC_{0\text{-}42\ days}$ (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
$AUC_{0\text{-}last}$ (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
$AUC_{0\text{-}inf}$ (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	**450 µg po (N=9)** **n Mean (SD)** **Median** **Range**	**900 µg po (N=9)** **n Mean (SD)** **Median** **Range**	**448 µg iv (N=9)** **n Mean (SD)** **Median** **Range**
$AUC_{0-42\ days}$ (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-last} (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_{last} (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 D_3, 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 D_3 in an ethanol solution.

[00112] The gradual increase in 25-hydroxyvitamin D_3 levels was demonstrated by the prolonged Tmax 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 D_3 concentrations, with a mean Tmax 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 D_3 concentrations in all subjects. The avoidance of the rapid increase in 25-hydroxyvitamin D_3 levels was highlighted by the marked difference in the observed C_{max} between the treatment groups. The Cmax following the oral dose was 58 ng/mL, compared to a Cmax of 153 ng/mL following the i.v. dose.

[00113] The exposure to 25-hydroxyvitamin D_3 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 D_3. In addition, the Vd values suggested that 25-hydroxyvitamin D_3 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)
$AUC_{0\text{-}t}$ (ng·h/mL)		
Mean (SD)	21545.20 (7084.02)	25274.44 (7206.93)
Median	19904.00	25810.85
Minimum, Maximum	10176.40, 35885.02	8434.02, 35382.55
$AUC_{0\text{-}inf}$ (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
R^2		
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*		
Mean	0.42 (0.14)	N/A
Median	0.39	N/A
Minimum, Maximum	0.20, 0.71	N/A

*average 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 CTAP101 Capsules (N=10)	448 µg CTAP101 Injection (N=10)
AUC_{0-t} (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
AUC_{0-inf} (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 (27.4901)	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_z (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
R^2		
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
F		
Mean (SD)	0.25 (0.24)	N/A

Median	0.16	N/A
Minimum, Maximum	0.037, 0.75	N/A

[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 D_3, yielding a more gradual increase in serum 25-hydroxyvitamin D_3 levels while maintaining the distribution and elimination characteristics. The stabilized formulation demonstrated improved pharmacokinetic parameters, such as increased Tmax, 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/1.73m^2), 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 D_3, 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 D_3 concentrations were comparable across treatment groups and ranged from approximately 16 to 20 ng/mL. Following treatment with 25-hydroxyvitamin D_3, mean levels of serum 25-hydroxyvitamin D_3 increased gradually and in a dose-proportional manner following repeated daily administration of 25-hydroxyvitamin D_3 and began to approach steady-state by 6 weeks (Figure 4). The mean baseline adjusted Cmax values were approximately 28, 60 and 86 ng/mL for the groups administered 30 µg, 60 µg and 90 µg of 25-hydroxyvitamin D_3, respectively. Mean exposures to 25-hydroxyvitamin D_3, assessed as background adjusted $AUC_{0\text{-}6\ Weeks}$, were dose proportional across dose groups. Following the last dose, mean serum 25-hydroxyvitamin D_3 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 D_3 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
$AUC_{0\text{-}6\ Weeks}$ (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 D_3 concentrations. Mean ± SD baseline-adjusted Cmax 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 $AUC_{0\text{-}6\ weeks}$, were dose-proportional across the 25-hydroxyvitamin D_3 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
$AUC_{0\text{-}6\ Weeks}$(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 D_3 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 D_3 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 D_3. 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 ±

4.2%. An increase of 17.2 ± 7.8% was observed at end of treatment in the combined placebo groups. Differences between groups receiving 25-hydroxyvitamin $D_3$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 D_3 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 D_3 in a stabilized controlled release formulation is the minimum effective dose.

[00124] The stabilized formulations of 25-hydroxyvitamin D_3 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 D_3 increased 25-hydroxyvitamin D_3 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 D_3 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 D_3 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 D_3 (calcifediol, $25D_3$) 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/1.73m^2), vitamin D insufficiency (serum 25-hydroxyvitamin D $\geq$10 and $\leq$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 μg, 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 μg 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), $25D_3$, 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 $25D_3$ 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 μg, 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 ($AUC_{0\text{-}6wk}$) 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 $AUC_{0\text{-}6wk}$) increased.

[00136] The stabilized, sustained release 25-hydroxyvitamin D_3 capsules normalized 25D levels in the majority of subjects and significantly reduced iPTH in all dose groups (30, 60 and 90 μg). The stabilized, sustained release 25-hydroxyvitamin D_3 capsules increased serum $25D_3$ and serum 1,25D levels gradually with dose-dependent increases in exposure. Both $25D_3$ 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 D_3 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.

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[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 D_2 and 25-hydroxyvitamin D_3, 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 D_2 and 25-hydroxyvitamin D_3;

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 ^{o}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 D_2 and 25-hydroxyvitamin D_3;

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 D_2 and 25-hydroxyvitamin D_3;

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 D_2 and 25-hydroxyvitamin D_3;

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 D_2 and 25-hydroxyvitamin D_3; 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 D_3.

[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 Cmax 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 Cmax 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 $AUC_{0\text{-}inf}$ 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 $AUC_{0\text{-}inf}$ 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 erythematosis, 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 VDRR, vitamin D dependent rickets; (vii) in the bone--anticonvulsant treatment, fibrogenisis imperfecta ossium, osteitis fibrosa cystica, osteomalacia, osteoporosis, osteopenia, osteosclerosis, renal osteodytrophy, rickets; (viii) in the intestine--glucocorticoid antagonism, idopathic 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 stabilized formulation for sustained release of a vitamin D compound, the formulation comprising a mixture of:

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

a stabilizing agent comprising a material selected from the group consisting of: cellulose compounds, poloxamers, poly(ethylene oxide) polymers, povidones, fumed silicas, and combinations thereof, wherein the stabilizing agent 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%), which is effective 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.

2. The formulation of claim 1, comprising a matrix that releasably binds and controllably releases the one or both of 25-hydroxyvitamin D2 and 25-hydroxyvitamin D3.

3. The formulation of claim 1 or 2, comprising a lipophilic matrix comprising the one or both of 25-hydroxyvitamin D2 and 25-hydroxyvitamin D3.

4. The formulation of claim 3, wherein the lipophilic matrix comprises a wax.

5. The formulation of any one of the preceding claims, wherein the formulation is an oral formulation for sustained release of the vitamin D compound in the gastrointestinal tract of a subject which ingests the formulation.

6. The formulation of any one of the preceding claims, wherein the stabilizing agent comprises a cellulosic compound.

7. The formulation of claim 6, wherein the cellulosic compound comprises a cellulose ether.

8. The formulation according to claim 7, wherein the cellulose ether comprises one or more of methylcellulose, hydroxyl propyl methylcellulose, hydroxyl ethyl methylcellulose, hydroxyl ethyl cellulose, and hydroxyl propyl cellulose.

9. The formulation according to claim 8, wherein the cellulosic compound comprises hydroxypropyl methylcellulose.

10. The formulation according to any one of the preceding claims, wherein the vitamin D compound comprises 25-hydroxyvitamin D3.

11. A sustained release dosage form in the form of a capsule, tablet, sachet, dragee, or suppository comprising a formulation according to any of the preceding claims.

12. The sustained release dosage form according to claim 11, wherein the dosage form contains 5 to 80 µg of 25-hydroxyvitamin D3, preferably 30 µg or 60 µg of 25-hydroxyvitamin D3.

13. A product, which is a stabilized formulation for sustained release according to any one of claims 1-10 or a sustained release dosage form according to any one of claims 11-12, for use in the treatment of a vitamin-D responsive disease.

14. Use of a product, which is a stabilized formulation for sustained release according to any one of claims 1-10 or a sustained release dosage form according to any one of claims 11-12, in the manufacture of a medicament for the treatment of a vitamin-D responsive disease.

15. The product for use according to claim 13 or use according to claim 14, wherein the vitamin-D responsive disease:

(a) is selected from cancer, dermatological disorders, parathyroid disorders, bone disorders and autoimmune disorders; or

(b) is selected from psoriasis, hyperparathyroidism, secondary hyperparathyroidism and osteoporosis; or

(c) is secondary hyperparathyroidism.

16. The product for use or use according to any one of claims 13 to 15, wherein the patient:

(a) has chronic kidney disease (CKD); or

(b) has chronic kidney disease which is Stage 3 or 4; or

(c) has chronic kidney disease which is Stage 3 or 4 and vitamin D insufficiency; or

(d) has chronic kidney disease which is Stage 3 or 4 and vitamin D deficiency.

17. The product for use according to claim 13 or use according to claim 14, wherein the vitamin-D responsive disease is hyperparathyroidism secondary to Chronic Kidney Disease.

18. The product for use or use according to claim 17, wherein the vitamin-D responsive disease is hyperparathyroidism secondary to Chronic Kidney Disease Stage 3 or 4.

19. The product for use or use according to any one of claims 13 to 18, wherein the patient is:

(a) human; or

(b) an adult human.

20. The product for use or use according to any one of claims 13 to 19, wherein 5 to 80 μg of 25-hydroxyvitamin D3, preferably 30 μg or 60 μg of 25-hydroxyvitamin D3, is to be administered per day.

STABILIZED MODIFIED RELEASE VITAMIN D FORMULATION AND METHOD OF ADMINISTERING SAME

ABSTRACT

A stabilized formulation for controlled release of a vitamin D compound is disclosed. The formulation comprises one or both of 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3 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.

[Figure 1A]