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 another aspect of the present disclosure, there is provided a stabilized formulation for sustained release of a vitamin D compound, said formulation comprising a mixture of:

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

a non-wax matrix; 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.

[0007c] 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.

[0007d] 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.

[0007e] 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

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 stabilized formulation for sustained release of a vitamin D compound, said formulation comprising a mixture of:

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

a non-wax matrix; 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.

12. 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.

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

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

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

16. The product for use according to claim 14 or use according to claim 15, 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.

17. The product for use or use according to any one of claims 14 to 16, 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.

18. The product for use according to claim 14 or use according to claim 15, wherein the vitamin-D responsive disease is hyperparathyroidism secondary to Chronic Kidney Disease.

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

20. The product for use or use according to any one of claims 14 to 19, wherein the patient is:

(a) human; or

(b) an adult human.

21. The product for use or use according to any one of claims 14 to 20, 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.