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(71) Applicant: **Opko Renal, LLC**
Miami, FL 33137 (US)

(72) Inventors:
- **BISHOP, Charles W**
Miami, FL Florida 33141 (US)
- **CRAWFORD, Keith H**
Denver, CO Colorado 80202 (US)
- **MESSNER, Eric J**
Lake Forest, IL Illinois 60045 (US)

(74) Representative: **Barker Brettell LLP**
100 Hagley Road
Edgbaston
Birmingham B16 8QQ (GB)

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(54) TREATING VITAMIN D INSUFFICIENCY AND DEFICIENCY WITH 25-HYDROXYVITAMIN D2 AND 25-HYDROXYVITAMIN D3

(57) Methods and compositions for treating 25-hydroxyvitamin D insufficiency or deficiency in a patient are described herein. The method includes orally administering to the patient a sustained release formulation of 25-hydroxyvitamin D2, 25-hydroxyvitamin D3, or a combination of 25-hydroxyvitamin D2 and 25-hydroxyvitamin D3. The 25-hydroxyvitamin D is administered in combination with one or more agents selected from: one or more calcium salts, bisphosphonates, calcimimetics, nicotinic acid, iron, phosphate binders, glycemic control agents, hypertension control agents, and antineoplastic agents.

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Description

CROSS REFERENCE TO RELATED APPLICATION

[0001] The benefit under 35 U.S.C. §119(e) of U.S. Provisional Patent Application Serial No. 60/764,665 filed February 3, 2006, is hereby claimed.

[0002] 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 to Vitamin D hormones 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.

[0003] The prohormones are further metabolized in the kidneys into potent hormones. The prohormone 25-hydroxyvitamin D_2 is metabolized into a hormone known as 1α,25-dihydroxyvitamin D_3; likewise, 25-hydroxyvitamin D_3 is metabolized into 1α,25-dihydroxyvitamin D_3 (calcitriol). Production of these hormones from the prohormones also can occur outside of the kidney in cells which contain the required enzyme(s).

[0004] The Vitamin D hormones have essential roles in human health which are mediated by intracellular Vitamin D receptors (VDR). In particular, the Vitamin D hormones regulate blood calcium levels by controlling the absorption of dietary calcium by the small intestine and the reabsorption of calcium by the kidneys. Excessive hormone levels, whether transient or prolonged, can lead to abnormally elevated urine calcium (hypercalciuria), blood calcium (hypercalcemia) and blood phosphorus (hyperphosphatemia). The Vitamin D hormones also participate in the regulation of cellular differentiation and growth, PTH secretion by the parathyroid glands, and normal bone formation and metabolism. Further, Vitamin D hormones are required for the normal functioning of the musculoskeletal, immune and renin-angiotensin systems. Numerous other roles for Vitamin D hormones are being postulated and elucidated, based on the documented presence of intracellular VDR in nearly every human tissue.

[0005] The actions of Vitamin D hormones on specific tissues depend on the degree to which they bind to (or occupy) the intracellular VDR in those tissues. The prohormones 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3 have essentially identical affinities for the VDR which are estimated to be at least 100-fold lower than those of the Vitamin D hormones. As a consequence, physiological concentrations of 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3 have little, if any, biological actions without prior metabolism to Vitamin D hormones. However, supraphysiologic levels of 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3, in the range of 10 to 1,000 fold higher than normal, can sufficiently occupy the VDR to exert actions like the Vitamin D hormones.

[0006] Surges in blood or intracellular prohormone concentrations can promote excessive extrarenal hormone production, leading to local adverse effects on calcium and phosphorus metabolism. They also can inhibit hepatic prohormone production from Vitamin D, and promote catabolism of both Vitamin D and 25-hydroxyvitamin D in the kidney and/or other tissues. Blood levels of both the prohormones and the Vitamin D hormones are normally constant through the day, given a sustained, adequate supply of Vitamin D from sunlight exposure or an unsupplemented diet. Blood levels of 25-hydroxyvitamin D, however, can increase markedly after administration of currently available Vitamin D supplements, especially at doses which greatly exceed the minimum amounts required to prevent Vitamin D deficiency rickets or osteomalacia. Prohormone blood levels can also increase markedly after rapid intravenous administration of 25-hydroxyvitamin D_2 and/or 25-hydroxyvitamin D_3.

[0007] Production of 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3 declines when Vitamin D is in short supply, as in conditions such as Vitamin D insufficiency or Vitamin D deficiency (alternatively, hypovitaminosis D). Low production of 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3 leads to low blood levels of 25-hydroxyvitamin D. Inadequate Vitamin D supply often develops in individuals who are infrequently exposed to sunlight without protective sunscreens, have chronically inadequate intakes of Vitamin D, or suffer from conditions that reduce the intestinal absorption of fat soluble vitamins (such as Vitamin D). It has recently been reported that most individuals living in northern latitudes have inadequate Vitamin D supply. Left untreated, inadequate Vitamin D supply can cause serious bone disorders, including rickets and osteomalacia, and may contribute to the development of many other disorders including osteoporosis, non-traumatic fractures of the spine and hip, obesity, diabetes, muscle weakness, immune deficiencies, hypertension, psoriasis, and various cancers.

[0008] The Institute of Medicine (IOM) of the National Academy of Sciences has concluded that an Adequate Intake (AI) of Vitamin D for a healthy individual ranges from 200 to 600 IU per day, depending on the individual's age and sex [Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Dietary reference intakes: calcium, phosphorus, magnesium, vitamin D, and fluoride. Washington, DC: National Academy Press (1997)], incorporated by reference. The AI for Vitamin D was defined primarily on the basis of a serum 25-hydroxyvitamin D level sufficient to prevent Vitamin D deficiency rickets or osteomalacia (or ≥ 11 ng/mL). The IOM also established a Tolerable Upper Intake Level (UL) for Vitamin D of 2,000 IU per day, based on evidence that higher doses are associated with an increased risk of hypercalciuria, hypercalcemia and related sequelae, in-

cluding cardiac arrhythmias, seizures, and generalized vascular and other soft-tissue calcification.

[0009] Currently available oral Vitamin D supplements are far from ideal for achieving and maintaining optimal blood 25-hydroxyvitamin D levels. These preparations typically contain 400 IU to 5,000 IU of Vitamin D_3 or 50,000 IU of Vitamin D_2 and are formulated for quick or immediate release in the gastrointestinal tract. When administered at chronically high doses, as is often required for Vitamin D repletion, these products have significant and, often, severe limitations which are summarized below.

[0010] High doses of immediate release Vitamin D supplements produce marked surges in blood Vitamin D levels, thereby promoting: (a) storage of Vitamin D in adipose tissue, which is undesirable because stored Vitamin D is less available for later conversion to 25-hydroxyvitamin D; (b) catabolism of Vitamin D to metabolites which are less or no longer useful for boosting blood 25-hydroxyvitamin D levels, via 24- and/or 26-hydroxylation; and, (c) excessive intracellular 24- or 25-hydroxylation of Vitamin D, which leads to increased risk of hypercalciuria, hypercalcemia and hyperphosphatemia via mass-action binding to the VDR.

[0011] High doses of immediate release Vitamin D supplements also produce surges or spikes in blood and intracellular 25-hydroxyvitamin D levels, thereby promoting: (a) transiently excessive renal and extrarenal production of Vitamin D hormones, and leading to local aberrations in calcium and phosphorus homeostasis and increased risk of hypercalciuria, hypercalcemia and hyperphosphatemia; (b) catabolism of both Vitamin D and 25-hydroxyvitamin D by 24-and/or 26-hydroxylation in the kidney and other tissues; (c) down-regulation of hepatic production of Vitamin D prohormones, unnecessarily impeding the efficient repletion of Vitamin D insufficiency or deficiency; and, (d) local aberrations in calcium and phosphorus homeostasis mediated by direct binding to VDR.

[0012] Furthermore, high doses of immediate release Vitamin D supplements produce supraphysiologic, even pharmacological, concentrations of Vitamin D, e.g., in the lumen of the duodenum, promoting: (a) 25-hydroxylation in the enterocytes and local stimulation of intestinal absorption of calcium and phosphorus, leading to increased risk of hypercalciuria, hypercalcemia and hyperphosphatemia; and (b) catabolism of Vitamin D by 24- and 26- hydroxylation in the local enterocytes, causing decreased systemic bioavailability.

[0013] Vitamin D supplementation above the UL is frequently needed in certain individuals; however, currently available oral Vitamin D supplements are not well suited for maintaining blood 25-hydroxyvitamin D levels at optimal levels given the problems of administering high doses of immediate release Vitamin D compounds.

[0014] Administration of 25-hydroxyvitamin D_3 in an immediate release oral formulation has been tried as an alternative method of Vitamin D supplementation. This approach, which has been subsequently abandoned, caused problems as do the currently used Vitamin D supplements. Specifically, it produced surges or spikes in blood and intracellular 25-hydroxyvitamin D levels, thereby promoting (a) competitive displacement of Vitamin D hormones from the serum Vitamin D Binding Protein (DBP) and excessive delivery of the displaced hormones to tissues containing VDR, and (b) transiently excessive renal and extrarenal production of Vitamin D hormones, which together led to local aberrations in calcium and phosphorus metabolism. In addition, these surges in blood 25-hydroxyvitamin D levels promoted catabolism of both Vitamin D and 25-hydroxyvitamin D by 24-and/or 26-hydroxylation in the kidney and other tissues, down-regulation of hepatic production of Vitamin D prohormones, unnecessarily impeding the efficient repletion of Vitamin D insufficiency or deficiency, and, additional local aberrations in calcium and phosphorus homeostasis mediated by direct binding to VDR. Importantly, immediate release 25-hydroxyvitamin D_3 promoted its intestinal absorption via a mechanism substantially involving transport to the liver in chylomicrons, rather than bound to the serum DBP. Delivery of 25-hydroxyvitamin D to the liver via chylomicrons significantly increased the likelihood of its catabolism.

[0015] Clearly, an alternative approach to Vitamin D supplementation is needed given the problems encountered with both currently available oral Vitamin D supplements, and with previously used oral 25-hydroxyvitamin D_3.

SUMMARY OF THE INVENTION

[0016] The present invention provides methods for effectively and safely restoring blood 25-hydroxyvitamin D levels to optimal levels (defined for patients as > 30 ng/mL 25-hydroxyvitamin D) and maintaining blood 25-hydroxyvitamin D levels at such optimal levels. The method includes dosing a subject, an animal or a human patient, orally or intravenously with sufficient 25-hydroxyvitamin D_2 or 25-hydroxyvitamin D_3 or any combination of these two prohormones in a formulation that provides benefits to the recipient that were heretofore unimagined with currently available Vitamin D supplements. That is, the present invention provides effective Vitamin D supplementation that reduces the risk of transient surges (i.e., supraphysiologic levels) of blood 25-hydroxyvitamin D and related side effects.

[0017] In an embodiment of the present invention, an amount of 25-hydroxyvitamin D_2 and/or 25-hydroxyvitamin D_3 is included in a controlled release formulation and is orally administered daily to a human or animal in need of treatment. In another embodiment, an amount of 25-hydroxyvitamin D_2 and/or 25-hydroxyvitamin D_3 is included in an isotonic sterile formulation suitable for intravenous administration, and is gradually injected thrice weekly into a human or animal in need of treatment. This administration of 25-hydroxyvitamin D_2 and/or 25-hy-

droxyvitamin D_3 significantly: increases the bioavailability of the contained 25-hydroxyvitamin D_2/25-hydroxyvitamin D_3; decreases the undesirable first pass effects of the contained 25-hydroxyvitamin D_2/25-hydroxyvitamin D_3 on the duodenum; avoids producing supraphysiologic surges in blood levels of 25-hydroxyvitamin D_2 and/or 25-hydroxyvitamin D_3; increases the effectiveness of orally administered 25-hydroxyvitamin D_2/25-hydroxyvitamin D_3 in restoring blood concentrations of 25-hydroxyvitamin D to optimal levels (defined for patients as > 30 ng/mL 25-hydroxyvitamin D); increases the effectiveness of orally administered 25-hydroxyvitamin D_2/25-hydroxyvitamin D_3 in maintaining blood concentrations of 25-hydroxyvitamin D at such optimal levels; decreases disruptions in Vitamin D metabolism and related aberrations in PTH, calcium and phosphorus homeostasis; and, decreases the risk of serious side effects associated with Vitamin D supplementation, namely Vitamin D toxicity.

[0018] In one aspect, the present invention provides a stable controlled release composition comprising 25-hydroxyvitamin D_2 and/or 25-hydroxyvitamin D_3, which is formulated to allow the 25-hydroxyvitamin D to pass through the stomach, and the duodenum and jejunum of the small intestine, to the ileum. The composition effectively resists disintegration in gastric juice, and avoids substantial release of the contained 25-hydroxyvitamin D until it reaches the ileum of the small intestine, thereby minimizing absorption substantially mediated by transport to the liver in chylomicrons. The disclosed composition is gradually presented to the intralumenal and intracelulluar aspects of the ileum, reducing CYP24-mediated catabolism and provoking a sustained increase in the blood levels of 25-hydroxyvitamin D to optimal levels which can be maintained.

[0019] In another aspect, the invention provides an isotonic sterile formulation suitable for gradual intravenous administration containing 25-hydroxyvitamin D_2 and/or 25-hydroxyvitamin D_3, which allows the 25-hydroxyvitamin D to completely bypass the gastrointestinal tract, thereby eliminating first pass effects on the duodenum and jejunum, as well as absorption mediated by transport to the liver in chylomicrons.

[0020] The foregoing brief description has outlined, in general, the featured aspects of the invention and is to serve as an aid to better understanding the more complete detailed description which is to follow. In reference to such, there is to be a clear understanding that the present invention is not limited to the method or detail of manufacture, chemical composition, or application of use described herein. Any other variation of manufacture, chemical composition, use, or application should be considered apparent as an alternative embodiment of the present invention. Other advantages and a fuller appreciation of the specific adaptations, compositional variations and chemical and physical attributes of this invention will be gained upon examination of the detailed description.

[0021] Also, it is understood that the phraseology and terminology used herein are for the purpose of description and should not be regarded as limiting. The use of "including", "having" and "comprising" and variations thereof herein is meant to encompass the items listed thereafter and equivalents thereof as well as additional items and equivalents thereof.

[0022] The invention provides, inter alia, a method of treating 25-hydroxyvitamin D insufficiency and deficiency in a patient comprising orally administering to the patient a delayed, sustained release formulation comprising a first ingredient selected from the group consisting of 25-hydroxyvitamin D2, 25-hydroxyvitamin D3, or a combination of 25-hydroxyvitamin D2 and 25-hydroxyvitamin D3, or comprising gradually administering to the patient an sterile intravenous formulation comprising a first ingredient selected from the group consisting of 25-hydroxyvitamin D2, 25-hydroxyvitamin D3, or a combination of 25-hydroxyvitamin D2 and 25-hydroxyvitamin D3.

DETAILED DESCRIPTION OF THE INVENTION

[0023] The present invention relates to a method for dosing a subject, an animal or a human patient, in need of Vitamin D supplementation with sufficient 25-hydroxyvitamin D_2, 25-hydroxyvitamin D_3 or any combination of these two prohormones to effectively and safely restore blood 25-hydroxyvitamin D levels to optimal levels (defined for human subjects and patients as > 30 ng/mL 25-hydroxyvitamin D) and to maintain blood 25-hydroxyvitamin D levels at such optimal levels.

[0024] As used herein, the following definitions may be useful in aiding the skilled practitioner in understanding the invention:

[0025] As used herein, the term "substantially constant" with respect to the serum or blood level of 25-hydroxyvitamin D means that the release profile of any formulation administered as detailed hereinbelow should not include transient increases in total serum or blood levels of 25-hydroxyvitamin D_3 or 25-hydroxyvitamin D_2 of greater than approximately 3 ng/mL, after administration of a unit dose.

[0026] As used herein, the term "controlled release" and "sustained release" are used interchangeably, and refer to the release of the administered 25-hydroxyvitamin D 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 "Vitamin D toxicity" is meant to refer to the side effects suffered from excessive administration of 25-hydroxyvitamin D and excessively elevated 25-hydroxyvitamin D blood levels, including nausea, vomiting, polyuria, hypercalciuria, hypercalcemia and hyperphosphatemia.

[0028] "Supraphysiologic" in reference to intralumenal, intracelulluar and blood concentrations of 25-hydroxyvitamin D refers to a combined concentration of 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3 during a 24-hour

post-dose period which is more than 5 ng/mL greater than the generally stable levels observed over the course of the preceding 24-hour period by laboratory measurement.

[0029] "Vitamin D insufficiency and deficiency" is generally defined as having serum 25-hydroxyvitamin D levels below 30 ng/mL (National Kidney Foundation guidelines, NKF, Am. J. Kidney Dis. 42:S1-S202 (2003), incorporated herein by reference).

[0030] Unless indicated otherwise, "25-hydroxyvitamin D_2/25-hydroxyvitamin D_3" as used herein is intended to encompass 25-hydroxyvitamin D_2, 25-hydroxyvitamin D_3, or a combination thereof.

[0031] Unless indicated otherwise, "25-hydroxyvitamin D" is intended to refer to 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3 collectively. For example, an assayed blood level of 25-hydroxyvitamin D will include both 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3, if present.

[0032] It also 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. These are only examples of what is specifically intended.

[0033] The invention includes compositions comprising oral and intravenous formulations of 25-hydroxyvitamin D_2 and/or 25-hydroxyvitamin D_3 and methods of administering such formulations to treat 25-hydroxyvitamin D insufficiency and deficiency without the potential first pass effects of these prohormones on the duodenum and jejunum; without supraphysiological surges in intralumenal, 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.

[0034] The controlled release compositions intended for oral administration in accordance with the present invention are designed to contain concentrations of the 25-hydroxyvitamin D_2/25-hydroxyvitamin D_3 of 1 to 50 mcg per unit dose, 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 into the ileum of the gastrointestinal tract of humans or animals over an extended period of time. The compositions ensure a (a) substantially increased absorption of 25-hydroxyvitamin D via transport on DBP and decreased absorption via transport in chylomicrons, and (b) maintenance of substantially constant blood levels of 25-hydroxyvitamin D during the 24-hour post-dosing period. By providing a gradual, sustained and direct release of the 25-hydroxyvitamin D_2/25-hydroxyvitamin D_3 preferentially to circulating DBP (rather than to chylomicrons), blood, intralumenal and intracellular 25-hydroxyvitamin D concentration spikes, i.e., supraphysiologic levels and related unwanted catabolism are mitigated or eliminated

[0035] The compositions intended for intravenous administration in accordance with the present invention are designed to contain concentrations of the 25-hydroxyvitamin D_2/25-hydroxyvitamin D_3 of 1 to 25 mcg per unit dose, and are prepared in such a manner as to allow gradual injection, over a period of 1 to 5 minutes, to effect controlled or substantially constant release of the 25-hydroxyvitamin D_2/25-hydroxyvitamin D_3 directly to DBP in the blood. The compositions ensure complete bioavailability of the administered 25-hydroxyvitamin D, complete elimination of first pass effects on the duodenum and jejunum, decreased catabolism of 25-hydroxyvitamin D, and maintenance of substantially constant blood levels of 25-hydroxyvitamin D during the 24-hour post-dosing period. By providing a gradual, sustained and direct release of the 25-hydroxyvitamin D_2/25-hydroxyvitamin D_3 over time to circulating DBP, intralumenal, intracellular and even blood 25-hydroxyvitamin D concentration spikes, i.e., supraphysiologic levels, are mitigated or eliminated.

[0036] The compositions of the present invention comprise highly stable pharmaceutical formulations into which 25-hydroxyvitamin D_2 and/or 25-hydroxyvitamin D_3 is incorporated for convenient daily oral administration. The disclosed compositions produce gradual increases in and then sustained blood levels of 25-hydroxyvitamin D with dual unexpected benefits with continued regular administration over a prolonged period of time of unsurpassed effectiveness in restoring blood 25-hydroxyvitamin D to optimal levels, and unsurpassed safety relative to heretofore known formulations of Vitamin D or 25-hydroxyvitamin D.

[0037] The preparation of a controlled, substantially constant release form of 25-hydroxyvitamin D_2/25-hydroxyvitamin D_3 suitable for oral administration can be carried out according to many different techniques. For example, the 25-hydroxyvitamin D_2/25-hydroxyvitamin D_3 can be dispersed within a matrix, i.e. a unique mixture of rate controlling constituents and excipients in carefully selected ratios within the matrix, and encased with a coating material. Various coating techniques can be utilized to control the rate and/or the site of the release of the 25-hydroxyvitamin D_2/25-hydroxyvitamin D_3 from the pharmaceutical formulation. For example, the dissolution of the coating may be triggered by the pH of the surrounding media, and the resulting gradual dissolution of the coating over time exposes the matrix to the fluid of the intestinal environment. After the coating becomes permeable, 25-hydroxyvitamin D_2/25-hydroxyvitamin D_3 diffuses from the outer surface of the matrix. When this surface becomes exhausted or depleted of 25-hydroxyvitamin D_2/25-hydroxyvitamin D_3, the underlying stores begin to be depleted by diffusion through the disintegrating matrix

to the external solution.

[0038] In one aspect, a formulation in accordance with the present invention provides 25-hydroxyvitamin D_2 and/or 25-hydroxyvitamin D_3 within a matrix that releasably binds the ingredients in a controlled substantially constant release when exposed to the contents of the ileum.

[0039] The 25-hydroxyvitamin D_2 and/or 25-hydroxyvitamin D_3 containing matrix is suitably covered with a coating that is resistant to disintegration in gastric juices. The coated controlled release formulation of 25-hydroxyvitamin D_2/25-hydroxyvitamin D_3 is then administered orally to subjects, e.g., animals or human subjects and patients. As the formulation travels through the proximal portion of the small intestine, the enteric coating becomes progressively more permeable but, in a suitable embodiment, it provides a persisting structural framework around the 25-hydroxyvitamin D_2 and/or 25-hydroxyvitamin D_3 containing matrix. The 25-hydroxyvitamin D_2 and/or 25-hydroxyvitamin D_3 containing matrix becomes significantly exposed to intestinal fluids in the ileum through the permeable overcoating, and the 25-hydroxyvitamin D_2/25-hydroxyvitamin D_3 is then gradually released by simple diffusion and/or slow disintegration of the matrix.

[0040] Once released into the lumen of the ileum, the 25-hydroxyvitamin D_2/ 25-hydroxyvitamin D_3 is absorbed into the lymphatic system or into the portal bloodstream where it is bound to and transported by the DBP. The major portion of 25-hydroxyvitamin D_2/25-hydroxyvitamin D_3 is absorbed at a point beyond the duodenum and jejunum. These proximal portions of the small intestine can respond to high intralumenal levels of 25-hydroxyvitamin D_2/25-hydroxyvitamin D_3 and, in the process, can catabolize significant quantities of the 25-hydroxyvitamin D_2/25-hydroxyvitamin D_3. By substantially delaying 25-hydroxyvitamin D_2/25-hydroxyvitamin D_3 release until the ileum, the pharmaceutical composition described herein virtually eliminates these potential first pass effects on the proximal intestine, and reduces unwanted catabolism. Significant catabolism of administered Vitamin D prior to its absorption into the bloodstream significantly lowers its bioavailability. Elimination of first pass effects reduces the risk of Vitamin D toxicity. Substantially delayed release of 25-hydroxyvitamin D (i.e., beyond the duodenum and jejunum) markedly decreases the amount of 25-hydroxyvitamin D that is incorporated and absorbed from the small intestine via chylomicrons (since chylomicron formation and absorption occurs primarily in the jejunum) and correspondingly increases the amount of 25-hydroxyvitamin D that is absorbed directly through the intestinal wall and onto DBP circulating in lymph or portal blood.

[0041] In one embodiment of the invention, the controlled release oral formulation of 25-hydroxyvitamin D_2 and/or 25-hydroxyvitamin D_3 is prepared generally according to the following procedure. A sufficient quantity of 25-hydroxyvitamin D_2 and/or 25-hydroxyvitamin D_3 is completely dissolved in a minimal volume of USP-grade absolute ethanol (or other suitable solvent) and mixed with appropriate amounts and types of pharmaceutical-grade excipients to form a matrix which is solid or semi-solid at both room temperature and at the normal temperature of the human body. The matrix is completely or almost entirely resistant to digestion in the stomach and upper small intestine, and it gradually disintegrates in the lower small intestine.

[0042] In a suitable formulation, the matrix binds the 25-hydroxyvitamin D_2 and/or 25-hydroxyvitamin D_3 and permits a slow, relatively steady, i.e. substantially constant, release of the 25-hydroxyvitamin D_2/25-hydroxyvitamin D_3 over a period of four to eight hours or more, by simple diffusion and/or gradual disintegration, into the contents of the lumen of the lower small intestine. The formulation further has an enteric coating that partially dissolves in aqueous solutions having a pH of about 7.0 to 8.0, or simply dissolves slowly enough that significant release of 25-hydroxyvitamin D_2/25-hydroxyvitamin D_3 is delayed until after the formulation passes through the duodenum and jejunum.

[0043] As discussed above, the means for providing the controlled release of 25-hydroxyvitamin D_2 and/or 25-hydroxyvitamin D_3 may be selected from any of the known controlled release delivery systems of an active ingredient over a course of about four or more hours including the wax matrix system, and the Eudragit RS/RL system (of Rohm Pharma, GmbH, Weiterstadt, Germany).

[0044] The wax matrix system provides a lipophilic matrix. The wax matrix system may utilize, bees wax, white wax, cachalot wax or similar compositions. The active ingredient(s) are dispersed in the wax binder which slowly disintegrates in intestinal fluids to gradually release the active ingredient(s). The wax binder that is impregnated with the 25-hydroxyvitamin D_2 and/or 25-hydroxyvitamin D_3 is loaded into partially crosslinked soft gelatin capsules. The wax matrix system disperses the active ingredient(s) in a wax binder which softens at body temperature and slowly disintegrates in intestinal fluids to gradually release the active ingredient(s). The system suitably includes a mixture of waxes, with the optional addition of oils, to achieve a melting point which is higher than body temperature but lower than the melting temperature of gelatin formulations typically used to create the shells of either soft and hard gelatin capsules or other formulations used to create enteric coatings.

[0045] Specifically, in one suitable embodiment, the waxes selected for the matrix are melted and thoroughly mixed. The desired quantity of oils are added at this time, followed by sufficient mixing. The waxy mixture is then gradually cooled to a temperature just above its melting point. The desired amount of 25-hydroxyvitamin D_2 and/or 25-hydroxyvitamin D_3, dissolved in ethanol, is uniformly distributed into the molten matrix, and the matrix is loaded into soft gelatin capsules. The filled capsules are treated for appropriate periods of time with a solution

containing an aldehyde, such as acetaldehyde, to partially crosslink the gelatin in the capsule shell. The gelatin shell becomes increasingly crosslinked, over a period of several weeks and, thereby, more resistant to dissolution in the contents of stomach and upper intestine. When properly constructed, this gelatin shell will gradually dissolve after oral administration and become sufficiently porous (without fully disintegrating) by the time it reaches the ileum to allow the 25-hydroxyvitamin D_2 and/or 25-hydroxyvitamin D_3 to diffuse slowly from the wax matrix into the contents of the lower small intestine.

[0046] Examples of other lipid matrices that may be of value are glycerides, fatty acids and alcohols, and fatty acid esters.

[0047] Another suitable controlled-release oral drug delivery system is the Eudragit RL/RS system in which the active ingredient, 25-hydroxyvitamin D_2 and/or 25-hydroxyvitamin D_3, is formed into granules having a dimension of 25/30 mesh. The granules are then uniformly coated with a thin polymeric lacquer which is water insoluble but slowly water permeable. The coated granules can be mixed with optional additives such as antioxidants, stabilizers, binders, lubricants, processing aids and the like. The mixture may be compacted into a tablet which, prior to use, is hard and dry and can be further coated, or it may be poured into a capsule. After the tablet or capsule is swallowed and comes into contact with the aqueous intestinal fluids, the thin lacquer begins to swell and slowly allows permeation by intestinal fluids. As the intestinal fluid slowly permeates the lacquer coating, the contained 25-hydroxyvitamin D_2 and/or 25-hydroxyvitamin D_3 is slowly released. By the time the tablet or capsule has passed through the small intestine, about four to eight hours or more later, the 25-hydroxyvitamin D_2/25-hydroxyvitamin D_3 will have been slowly but completely released. Accordingly, the ingested tablet will release a stream of 25-hydroxyvitamin D_2 and/or 25-hydroxyvitamin D_3 as well as any other active ingredient.

[0048] The Eudragit system is comprised of high permeability lacquers (RL) and low permeability lacquers (RS). RS is a water insoluble film former based on neutral swellable methacrylic acids esters with a small proportion of trimethylammonioethyl methacrylate chlorides, the molar ratio of the quaternary ammonium groups to the neural ester group is about 1:40. RL is also a water insoluble swellable film former based on neutral methacrylic acid esters with a small portion of trimethylammonioethyl methacrylate chloride, the molar ratio of quaternary ammonium groups to neutral ester groups is about 1:20. The permeability of the coating and thus the time course of drug release can be titrated by varying the proportion of RS to RL coating material. For further details of the Eudragit RL/RS system, reference is made to technical publications available from Rohm Tech, Inc. 195 Canal Street, Maiden, Mass., 02146. See also, K. Lehmann, D. Dreher "Coating of tablets and small particles with acrylic resins by fluid bed technology", Int. J. Pharm. Tech. & Prod. Mfr. 2(r), 31-43 (1981), incorporated herein by reference.

[0049] Other examples of insoluble polymers include polyvinyl esters, polyvinyl acetals, polyacrylic acid esters, butadiene styrene copolymers and the like,

[0050] Once the coated granules are either formed into a tablet or put into a capsule, the tablet or capsule is coated with an enteric-coating material which dissolves at a pH of 7.0 to 8.0. One such pH dependent enteric-coating material is Eudragit L/S which dissolves in intestinal fluid but not in the gastric juices. Other enteric-coating materials may be used such as cellulose acetate phthalate (CAP) which is resistant to dissolution by gastric juices but readily disintegrates due to the hydrolytic effect of the intestinal esterases.

[0051] The particular choice of enteric-coating material and controlled release coating material must provide a controlled and substantially constant release over a period of 4 to 8 hours or more so that release is delayed until the formulation reaches the ileum. Moreover, the controlled release composition in accordance with the present invention, when administered once a day, suitably provides substantially constant intralumenal, intracellular and blood 25-hydroxyvitamin D levels compared to an equal dose of an immediate release composition of 25-hydroxyvitamin D_2/25-hydroxyvitamin D_3 administered once a day

[0052] In another embodiment of the invention, sterile, isotonic formulations of 25-hydroxyvitamin D_2, 25-hydroxyvitamin D_3 or combinations thereof may be prepared which are suitable for gradual intravenous administration. Such formulations are prepared by dissolving 25-hydroxyvitamin D_2 and/or 25-hydroxyvitamin D_3 in absolute ethanol, propylene glycol or other suitable solvents, and combining the resulting solutions with surfactants, salts and preservatives in appropriate volumes of water for injection. Such formulations can be administered slowly from syringes via heparin locks or by addition to larger volumes of sterile solutions (e.g., saline solution) being steadily infused over time.

[0053] The dosage forms may also contain adjuvants, such as preserving or stabilizing adjuvants. They may also contain other therapeutically valuable substances or may contain more than one of the compounds specified herein and in the claims in admixture.

[0054] Advantageously, 25-hydroxyvitamin D_2, 25-hydroxyvitamin D_3 or combinations thereof together with other therapeutic agents can be orally or intravenously administered in accordance with the above described embodiments in dosage amounts of from 1 to 100 mcg per day, with the preferred dosage amounts of from 5 to 50 mcg per day. If the compounds of the present invention are administered in combination with 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 orally administer 25-hydroxyvitamin D_2 and/or 25-hydroxyvitamin D_3 with one or more calcium salts (intended as a calcium supplement or dietary phos-

phate binder), bisphosphonates, calcimimetics, nicotinic acid, iron, phosphate binders, cholecalciferol, ergocalciferol, active Vitamin D sterols, glycemic and hypertension control agents, and various antineoplastic 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, and various antineoplastic 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.

[0055] The inclusion of a combination of 25-hydroxyvitamin D_3 and 25-hydroxyvitamin D_2 in the described delivery systems allows the resulting formulations to be useful in supporting both the Vitamin D_3 and Vitamin D_2 endocrine systems. Currently available oral Vitamin D supplements and the previously marketed oral formulation of 25-hydroxyvitamin D_3 have supported just one or the other system.

[0056] The present invention is further explained by the following examples which should not be construed by way of limiting the scope of the present invention.

EXAMPLE 1

One Embodiment of a Controlled Release Formulation for Oral Administration

[0057] Purified yellow beeswax and fractionated coconut oil are combined in a ratio of 1:1 and heated with continuous mixing to 75 degrees Celsius until a uniform mixture is obtained. The wax mixture is continuously homogenized while cooled to approximately 45 degrees Celsius. 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3, in a ratio of 1:1, are dissolved in absolute ethanol and the ethanolic solution is added, with continuous homogenization, to the molten wax mixture. The amount of ethanol added is in the range of 1 to 2 v/v%. Mixing is continued until the mixture is uniform. The uniform mixture is loaded into soft gelatin capsules. The capsules are immediately rinsed to remove any processing lubricant(s) and briefly immersed in an aqueous solution of acetaldehyde in order to crosslink the gelatin shell. The concentration of the acetaldehyde solution and the immersion time is selected to achieve crosslinking to the desired degree, as determined by near-infrared spectrophotometry. The finished capsules are washed, dried and packaged.

EXAMPLE 2

One Embodiment of a Formulation for Gradual Intravenous Administration

[0058] TWEEN Polysorbate 20 is warmed to approximately 50 to 60 °F (10 to 16 °C), and 25-hydroxyvitamin D_3, dissolved in a minimal volume of absolute ethanol, is added with continuous stirring. The resulting uniform solution of 25-hydroxyvitamin D_3, absolute ethanol and TWEEN Polysorbate 20 is transferred to a suitable volume of water for injection, which has been thoroughly sparged with nitrogen to remove all dissolved oxygen. Sodium chloride, sodium ascorbate, sodium phosphate (dibasic and monobasic), and disodium edetate are added, followed by sufficient stirring under a protective nitrogen atmosphere, to produce an isotonic homogeneous mixture containing, per 2 mL unit volume: 20 mcg of 25-hydroxyvitamin D_3; <0.01% absolute ethanol; 0.40% (w/v) TWEEN Polysorbate 20; 0.15% (w/v) sodium chloride; 1.00% (w/v) sodium ascorbate; 0.75% (w/v) sodium phosphate dibasic anhydrous; 0.18% (w/v) sodium phosphate monobasic monohydrate; and, 0.11% (w/v) disodium edetate. This mixture is sterilized by filtration and filled, with suitable protection from oxygen contamination, into amber glass ampules having an oxygen headspace of less than 1%.

EXAMPLE 3

Pharmacokinetics Testing in Dogs

[0059] Twenty male beagle dogs are divided randomly into two comparable groups and receive no supplemental Vitamin D for the next 30 days. At the end of this time, each dog in Group #1 receives a single soft gelatin capsule containing 25 mcg of 25-hydroxyvitamin D_2 prepared in a controlled release formulation similar to the one disclosed in Example 1. Each dog in the other group (Group #2) receives a single immediate-release soft gelatin capsule containing 25 mcg of 25-hydroxyvitamin D_2 dissolved in medium chain triglyceride oil. All dogs have received no food for at least 8 hours prior to dosing. Blood is drawn from each dog at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 15, 24, 36, and 72 hours after dose administration. The collected blood is analyzed for the contained levels of 25-hydroxyvitamin D, and the data are analyzed by treatment group. Dogs in Group #1 show a slower rise and a lower maximum (C_{max}) in mean blood levels of 25-hydroxyvitamin D than dogs in Group #2. However, dogs in Group #1 show a more prolonged elevation of mean blood levels of 25-hydroxyvitamin D_2 relative to dogs in Group #2, despite the fact that the C_{max} recorded in Group #1 is lower. The mean area under the curve (AUC), corrected for predose background levels (recorded at t=0), is substantially greater for Group #1 for 25-hydroxyvitamin D. These procedures demonstrate that administration of 25-hydroxyvitamin D_2 in the formulation de-

scribed in this invention to dogs results in blood levels of 25-hydroxyvitamin D which rise much more gradually and remain more stable than after dosing with the same amount of 25-hydroxyvitamin D_2 formulated for immediate release (in medium chain triglyceride oil). The greater AUC calculated for blood levels of 25-hydroxyvitamin D in Group #1 demonstrates that the bioavailability of 25-hydroxyvitamin D_2 formulated as described herein is markedly improved.

EXAMPLE 4

Pharmacokinetics Testing in Healthy Normal Volunteers

[0060] Sixteen healthy non-obese adults, aged 18 to 24 years, participate in an 11-week pharmacokinetic study in which they receive successively, and in a double-blinded fashion, two formulations of 25-hydroxyvitamin D_2. One of the formulations (Formulation #1) is a soft gelatin capsule containing 100 mcg of 25-hydroxyvitamin D_2 prepared in a controlled release formulation similar to the one disclosed in Example 1. The other formulation (Formulation #2) is an immediate-release soft gelatin capsule of identical appearance containing 100 mcg of 25-hydroxyvitamin D_2 dissolved in medium chain triglyceride oil. For 60 days prior to study start and continuing through study termination, the subjects abstain from taking other Vitamin D supplements. On Days 1, 3 and 5 of the study, all subjects provide fasting morning blood samples to establish pre-treatment baseline values. On the morning of Day 8, the subjects provide an additional fasting blood sample (t=0), are randomly assigned to one of two treatment groups. Both groups are dosed with a single test capsule prior to eating breakfast: one group receives a capsule of Formulation #1 and the other group receives a capsule of Formulation #2. Blood is drawn from each subject at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 15, 24, 36, 48, 72 and 108 hours after dose administration. On the morning of Day 70, the subjects provide additional fasting morning blood samples (t=0) and are dosed with a single capsule of the other test formulation prior to eating breakfast. Blood is again drawn from each subject at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 15, 24, 36, 48, 72 and 108 hours after dose administration. All collected blood is analyzed for the contained levels of 25-hydroxyvitamin D, and the data are analyzed by treatment formulation after correction for baseline content. Formulation #1 is found to produce a slower rise and a lower C_{max} in mean blood levels of 25-hydroxyvitamin D than Formulation #2. However, Formulation #1 also produces a more prolonged elevation of mean blood levels of 25-hydroxyvitamin D_2 relative to Formulation #2, despite the fact that the recorded C_{max} is lower. The mean AUC is substantially greater after administration of Formulation #1 for 25-hydroxyvitamin D. These procedures demonstrate that administration of 25-hydroxyvitamin D_2 in the formulation described in this invention to healthy human adults results in blood levels of 25-hydroxyvitamin D which rise much more gradually and remain more stable than after dosing with the same amount of 25-hydroxyvitamin D_2 formulated for immediate release (in medium chain triglyceride oil). The greater AUC calculated for blood levels of 25-hydroxyvitamin D after dosing with Formulation #1 demonstrates that the bioavailability of 25-hydroxyvitamin D_2 formulated as described herein is better.

EXAMPLE 5

Efficacy Study in Healthy Adult Male Volunteers With Vitamin D Insufficiency

[0061] The effectiveness of three different formulations of Vitamin D in restoring serum 25-hydroxyvitamin D to optimal levels (> 30 ng/mL) is examined in a 23-day study of healthy non-obese men diagnosed with Vitamin D insufficiency. One of the formulations (Formulation #1) is a soft gelatin capsule containing 30 mcg of 25-hydroxyvitamin D_3 prepared as illustrated in this invention. The second formulation (Formulation #2) is an immediate-release soft gelatin capsule of identical appearance containing 50,000 IU of ergocalciferol dissolved in medium chain triglyceride oil. The third formulation (Formulation #3) is an immediate-release soft gelatin capsule, also of identical appearance, containing 50,000 IU of cholecalciferol dissolved in medium chain triglyceride oil. A total of 100 healthy Caucasian and African-American men participate in this study, all of whom are aged 30 to 45 years and have serum 25-hydroxyvitamin D levels between 15 and 29 ng/mL (inclusive). All subjects abstain from taking other Vitamin D supplements for 60 days before study start and continuing through study termination, and from significant sun exposure. On Day 1 and 2 of the study, all subjects provide fasting morning blood samples to establish pre-treatment baseline values of serum 25-hydroxyvitamin D. On the morning of Day 3, the subjects provide an additional fasting blood sample (t=0), are randomly assigned to one of four treatment groups, and are dosed with a single test capsule prior to eating breakfast: the subjects in Group #1 each receive a single capsule of Formulation #1, and the subjects in Groups #2 and #3 each receive a single capsule of Formulation #2 or Formulation #3, respectively. Subjects in Group #4 receive a matching placebo capsule. Subjects in Group #1 each receive an additional capsule of Formulation #1 on the mornings of Days 4 through 22 before breakfast, but subjects in Groups #2, #3 and #4 receive no additional capsules. A fasting morning blood sample is drawn from each subject, irrespective of treatment group, on Days 4, 5, 6, 10, 17 and 23 (or 1, 2, 3, 7, 14 and 20 days after the start of dosing). All collected blood is analyzed for the contained levels of 25-hydroxyvitamin D, and the data are analyzed by treatment group after correction for baseline values. Subjects in all four treatment groups exhibit mean baseline serum 25-hydroxyvitamin D levels of approximately 16 to 18 ng/mL, based on analysis of fasting blood samples drawn on Days 1 through 3. Sub-

jects in Group #4 (control group) show no significant changes in mean serum 25-hydroxyvitamin D over the course of the study. Subjects in Group #1 show a steadily increasing mean serum 25-hydroxyvitamin D reaching at least 30 ng/mL by Day 23. In marked contrast, subjects in Group #2 exhibit marked increases in mean serum 25-hydroxyvitamin D for the first few days post-dosing, reaching a maximum of just above 25 ng/mL, and then rapidly declining thereafter. By study end, serum 25-hydroxyvitamin D is significantly lower than baseline in Group #2. Subjects in Group #3 exhibit continuing increases in mean serum 25-hydroxyvitamin D through the first 2 weeks after dosing with gradual, but progressive, decreases occurring thereafter. By study end, mean serum 25-hydroxyvitamin D is below 30 ng/mL, being only approximately 11 ng/mL higher than pre-treatment baseline. The data from this study demonstrate that administration of 600 mcg of 25-hydroxyvitamin D_3, formulated as described herein and administered at a dose of 30 mcg per day for 20 days, is substantially more effective in restoring low serum levels of 25-hydroxyvitamin D to optimal levels than immediate-release formulations of 50,000 IU of either ergocalciferol or cholecalciferol administered in single doses, as currently recommended by the NKF and other leading experts on oral Vitamin D replacement therapy.

EXAMPLE 6

Efficacy and Safety Study in End-Stage Renal Disease Patients Exhibiting Vitamin D Deficiency

[0062] The efficacy and safety of intravenous 25-hydroxyvitamin D_3 in restoring serum 25-hydroxyvitamin D to optimal levels (> 30 ng/mL) are examined in a 3-month study of patients with end-stage renal disease (ESRD) requiring regular hemodialysis and diagnosed with Vitamin D insufficiency. The formulation examined in this study is an aqueous isotonic and sterile solution containing 20 mcg of 25-hydroxyvitamin D_3 similar to the one disclosed in Example 2. A total of 50 healthy Caucasian, Asian, Hispanic and African-American subjects participate in this study, all of whom are at least 4-months on regular hemodialysis and have serum 25-hydroxyvitamin D levels below 15 ng/mL. Prior to enrolling, all subjects provide two fasting morning blood samples, separated by at least one week, to establish pre-treatment baseline values of serum calcium, plasma intact PTH, and serum 25-hydroxyvitamin D. On the morning of Day 1, the subjects are randomly assigned to one of two treatment groups, and they begin thrice weekly dosing with the test preparation, or with a matching placebo. All dosing occurs during regularly scheduled hemodialysis sessions and is accomplished by gradual injection (over a period of 1 to 5 minutes) into the blood exiting from the hemodialysis machine. Additional fasting blood samples and 24-hour urine collections are obtained from each subject at quarterly intervals for determination of serum calcium, plasma intact PTH and serum 25-hydroxyvitamin D. Throughout the study, all subjects adhere to a daily intake of approximately 1,000 to 1,500 mg of elemental calcium (from self-selected diets and calcium supplements, as needed) under the ongoing guidance of a dietician. At the conclusion of the study, the laboratory data are analyzed by treatment group and by test formulation after appropriate correction for baseline values. Both groups have comparable mean baseline values for serum 25-hydroxyvitamin D (range: 10.7 to 11.9 ng/mL), plasma intact PTH (range: 45.3 to 52.1 pg/mL) and serum calcium (range: 8.72 to 9.31 mg/dL). No significant changes in any of the laboratory mean values are observed in the placebo (control) group over the course of the study. Subjects in the treatment group receiving 25-hydroxyvitamin D_3 exhibit progressively increasing serum 25-hydroxyvitamin D levels during the first 3 months of dosing, reaching steady state levels thereafter. Mean serum calcium increases significantly from baseline in the treatment group receiving 25-hydroxyvitamin D_3, and is significantly higher than those observed in the placebo group. Episodes of hypercalcemia, defined as serum calcium above 9.5 mg/dL, are infrequently observed in both treatment groups. Data from this study demonstrate that the intravenous formulation of 25-hydroxyvitamin D_3 is effective at increasing serum 25-hydroxyvitamin D without causing unacceptable side effects related to calcium and PTH metabolism.

[0063] 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.

Claims

1. A composition for use in a method of treating 25-hydroxyvitamin D insufficiency or deficiency in a patient, the method comprising orally administering the composition to the patient, wherein the composition comprises a sustained release formulation of 25-hydroxyvitamin D2, 25-hydroxyvitamin D3, or a combination of 25-hydroxyvitamin D2 and 25-hydroxyvitamin D3, and wherein the 25-hydroxyvitamin D is administered in combination with one or more other agents selected from: one or more calcium salts, bisphosphonates, calcimimetics, nicotinic acid, iron, phosphate binders, glycemic control agents, hypertension control agents, and antineoplastic agents.

2. A sustained release oral dosage formulation of 25-hydroxyvitamin D2, 25-hydroxyvitamin D3, or a combination of 25-hydroxyvitamin D2 and 25-hydroxyvitamin D3 in combination with one or more other agents selected from: one or more calcium salts, bisphosphonates, calcimimetics, nicotinic acid, iron, phosphate binders, cholecalciferol, ergocalciferol,

active Vitamin D sterols, glycemic and hypertension control agents, and antineoplastic agents.

3. The composition for use of claim 1 or the sustained release oral dosage formulation of claim 2, wherein the sustained release formulation comprises 25-hydroxyvitamin D2, 25-hydroxyvitamin D3, or a combination of 25-hydroxyvitamin D2 and 25-hydroxyvitamin D3 in combination with one or more calcium salts.

4. The composition for use of claim 1 or the sustained release oral dosage formulation of claim 2, wherein the sustained release formulation comprises 25-hydroxyvitamin D2, 25-hydroxyvitamin D3, or a combination of 25-hydroxyvitamin D2 and 25-hydroxyvitamin D3 in combination with one or more bisphosphonates.

5. The composition for use of claim 1 or the sustained release oral dosage formulation of claim 2, wherein the sustained release formulation comprises 25-hydroxyvitamin D2, 25-hydroxyvitamin D3, or a combination of 25-hydroxyvitamin D2 and 25-hydroxyvitamin D3 in combination with nicotinic acid.

6. The composition for use of claim 1 or the sustained release oral dosage formulation of claim 2, wherein the sustained release formulation comprises 25-hydroxyvitamin D2, 25-hydroxyvitamin D3, or a combination of 25-hydroxyvitamin D2 and 25-hydroxyvitamin D3 in combination with iron.

7. The composition for use of claim 1 or the sustained release oral dosage formulation of claim 2, wherein the sustained release formulation comprises 25-hydroxyvitamin D2, 25-hydroxyvitamin D3, or a combination of 25-hydroxyvitamin D2 and 25-hydroxyvitamin D3 in combination with one or more phosphate binders.

8. The composition for use of claim 1 or the sustained release oral dosage formulation of claim 2, wherein the sustained release formulation comprises 25-hydroxyvitamin D2, 25-hydroxyvitamin D3, or a combination of 25-hydroxyvitamin D2 and 25-hydroxyvitamin D3 in combination with one or more glycemic control agents.

9. The composition for use of claim 1 or the sustained release oral dosage formulation of claim 2, wherein the sustained release formulation comprises 25-hydroxyvitamin D2, 25-hydroxyvitamin D3, or a combination of 25-hydroxyvitamin D2 and 25-hydroxyvitamin D3 in combination with one or more hypertension control agents.

10. The composition for use of claim 1 or the sustained release oral dosage formulation of claim 2, wherein the sustained release formulation comprises 25-hydroxyvitamin D2, 25-hydroxyvitamin D3, or a combination of 25-hydroxyvitamin D2 and 25-hydroxyvitamin D3 in combination with one or more antineoplastic agents.

11. A sustained release oral dosage formulation of 25-hydroxyvitamin D_2, 25-hydroxyvitamin D_3, or a combination of 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3, wherein the 25-hydroxyvitamin D2, the 25-hydroxyvitamin D3, or the combination of 25-hydroxyvitamin D2 and 25-hydroxyvitamin D3 is dispersed within a matrix and encased with a coating material.

12. The sustained release oral dosage formulation of claim 11, wherein the matrix is encased with a coating material having a melting point which is higher than body temperature but lower than the melting temperature of the coating material.

13. The sustained release oral dosage formulation of claim 11, wherein the matrix comprises a lipid.

14. The sustained release oral dosage formulation of claim 13, wherein the lipid comprises one or more glycerides, fatty acids, fatty alcohols, fatty acid esters, or combinations thereof.

15. The sustained release oral dosage formulation of claim 14, wherein the lipid comprises one or more glycerides.

16. The sustained release oral dosage formulation of claim 14, wherein the lipid comprises one or more fatty acids.

17. The sustained release oral dosage formulation of claim 14, wherein the lipid comprises one or more fatty alcohols.

18. The sustained release oral dosage formulation of claim 14, wherein the lipid comprises one or more fatty acid esters.

19. A sustained release oral dosage formulation of 25-hydroxyvitamin D_2, 25-hydroxyvitamin D_3, or a combination of 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3 wherein the 25-hydroxyvitamin D2, the 25-hydroxyvitamin D3, or the combination of 25-hydroxyvitamin D2 and 25-hydroxyvitamin D3 is dispersed within a matrix and comprises a permeable overcoating.

20. The sustained release oral dosage formulation of claim 19, wherein the 25-hydroxyvitamin D_2, the 25-hydroxyvitamin D_3, or the combination of 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3 is released

by diffusion.

21. The sustained release oral dosage formulation of claim 19, wherein the 25-hydroxyvitamin D_2, the 25-hydroxyvitamin D_3, or the combination of 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3 is released by disintegration of the matrix.

22. The sustained release oral dosage formulation of claim 19, wherein the 25-hydroxyvitamin D_2, the 25-hydroxyvitamin D_3, or the combination of 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3 is released by a combination of diffusion and disintegration of the matrix.

23. A sustained release oral dosage formulation of 25-hydroxyvitamin D_2, 25-hydroxyvitamin D_3, or a combination of 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3 wherein the 25-hydroxyvitamin D2, the 25-hydroxyvitamin D3, or the combination of 25-hydroxyvitamin D2 and 25-hydroxyvitamin D3 is dispersed within a matrix which is solid at body temperature.

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EUROPEAN SEARCH REPORT

Application Number
EP 18 15 4648

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The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
Munich	11 April 2018	Büttner, Ulf

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EUROPEAN SEARCH REPORT

Application Number
EP 18 15 4648

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EUROPEAN SEARCH REPORT

Application Number
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摘要

本發明描述了用于治療患者的 25-羥基維生素 D 不足或缺乏的方法和組合物。所述方法包括對所述患者口服給藥 25-羥基維生素 D2、25-羥基維生素 D3 或 25-羥基維生素 D2 和 25-羥基維生素 D3 的組合的緩釋劑型。該 25-羥基維生素 D 與選自下述中的一種或多種製劑聯合給藥：一種或多種鈣鹽、二膦酸鹽、擬鈣劑、烟酸、鐵、磷酸鹽結合劑、血糖控制劑、高血壓控制劑和抗腫瘤藥。