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

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

[0008a] In one aspect of the present disclosure, there is provided a controlled release oral 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.

[0008b] In another aspect of the present disclosure, there is provided a stabilized oral 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.

[0008c] 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 as disclosed herein.

[0008d] In another aspect of the present disclosure, there is provided a use of a formulation or stabilized sustained release dosage form as disclosed herein in the manufacture of a medicament for administration to a human patient, wherein the medicament results in a baseline-adjusted Cmax of at least about 0.2 ng/mL and less than 110 ng/mL.

[0008e] In a further aspect of the present disclosure, there is provided a use of a formulation or stabilized sustained release dosage form as disclosed herein in the manufacture of a medicament for administration to a human patient, wherein the medicament results in a baseline-adjusted $AUC_{0\text{-}inf}$ of at least 52 ng*h/mL and less than 34500 ng*h/mL.

[0008f] In another aspect of the present disclosure, there is provided a use of a formulation or dosage form according as disclosed herein in the manufacture of a medicament for vitamin D supplementation in a patient.

[0008g] In a further aspect of the present disclosure, there is provided a use of a formulation or dosage form as disclosed herein in the manufacture of a medicament for the treatment or prophylaxis of a vitamin-D responsive disease in a patient.

[0008h] In another aspect of the present disclosure, there is provided a formulation or stabilized sustained release dosage form as disclosed herein for use in vitamin D supplementation in a patient.

[0008i] In a further aspect of the present disclosure, there is provided a formulation or stabilized sustained release dosage form as disclosed herein for use in treating or preventing a vitamin D-responsive disease in a patient.

[0009] The present disclosure ~~invention~~ also comprises a storage-stabilized formulation for controlled release of a vitamin D compound in the gastrointestinal tract of a subject which ingests the formulation. In one ~~aspect~~embodiment, 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 ~~invention~~ 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 embodiment, 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 ~~aspect~~embodiment, 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 embodiment~~aspect~~, 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 embodiment, 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 °C and 60% relative humidity that varies at all dissolution testing time points by 30% or less compared to the amount released at the same dissolution time points during *in vitro* dissolution conducted on fresh product.

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

[0013] In one embodiment, the ~~invention~~ present disclosure comprises a stable sustained release vitamin D formulation comprising 25-hydroxyvitamin D_2 or 25-hydroxyvitamin D_3 or combinations thereof

41. The formulation or dosage form of claim 40, wherein the t_{max} is at least 28 hours.

42. The formulation or dosage form of claim 35, wherein the t_{max} is in a range of 4 to 96 hours.

43. The formulation or dosage form of claim 42, wherein the t_{max} is in a range of 18 to 30 hours.

44. The formulation or dosage form of claim 43, wherein the t_{max} is in a range of 13 to 28 hours.

45. The formulation or dosage form of claim 44, wherein the t_{max} is about 28 hours.

46. A formulation or stabilized sustained release dosage form according to any one of the preceding claims comprising a 25-hydroxyvitamin D compound, the formulation or 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.

47. Use of ~~A method of administering~~ a formulation or stabilized sustained release dosage form according to any one of the preceding claims in the manufacture of a medicament for administration to a human patient, wherein the medicament results in ~~comprising administering an effective amount of the formulation or 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.

48. The ~~method~~ use of claim 47, wherein the medicament results in ~~comprising administering an effective amount of the formulation or dosage form to provide~~ a baseline-adjusted Cmax in a range of about 0.2 to about 24 ng/mL.

49. Use of ~~A method of administering~~ a formulation or stabilized sustained release dosage form of any one of claims 1-46 in the manufacture of a medicament for administration to a human patient, wherein the medicament results in ~~comprising administering an effective amount of the formulation or 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.

50. The ~~method~~ use of claim 49, wherein the medicament results in ~~comprising administering an effective amount of the formulation or 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.

51. Use of a formulation or dosage form according to any one of claims 1-46 in the manufacture of a medicament for ~~A method of~~ vitamin D supplementation in a patient~~comprising administering to a subject in need thereof a formulation or dosage form according to any one of claims 1-46~~.

52. Use of a formulation or dosage form according to any one of claims 1-46 in the manufacture of a medicament for the~~A method of~~ treatment or prophylaxis of a vitamin-D responsive disease in a patient ~~subject comprising administering to the subject a formulation or dosage form according to any one of claims 1-46~~.

53. The ~~method~~ use of claim 52, 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.

54. The ~~method~~ use of claim 52, 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.

55. The ~~method~~ use of claim 52, 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.

56. The ~~method~~ use of claim 55, wherein the disease is secondary hyperparathyroidism.

57. The ~~method~~ use of claim 56, wherein the ~~subject~~ patient has chronic kidney disease (CKD).

58. The ~~method~~ use of claim 57, wherein the CKD is Stage 3 or 4.

59. The ~~method~~ use of claim 58, wherein the patient is vitamin-D deficient.

60. The ~~method~~ use of any one of claims 51-59, wherein the patient is human.

61. The ~~method~~ use of claim 60, wherein the human is an adult human.

62. A formulation or stabilized sustained release dosage form according to any one of claims 1-46 for use in vitamin D supplementation in a patient.

63. A formulation or stabilized sustained release dosage form according to any one of claims 1-46 for use in treating or preventing a vitamin D-responsive disease in a patient.

64. The formulation or stabilized sustained release dosage form ~~use~~ of claim 63, 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.

65. The formulation or stabilized sustained release dosage form ~~use~~ of claim 63, 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.

66. The formulation or stabilized sustained release dosage form ~~use~~ of claim 63, 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.

67. The formulation or stabilized sustained release dosage form ~~use~~ of claim 66, wherein the disease is secondary hyperparathyroidism.

68. The formulation or stabilized sustained release dosage form ~~use~~ of claim 67, wherein the patient has chronic kidney disease (CKD).

69. The formulation or stabilized sustained release dosage form ~~use~~ of claim 68, wherein the CKD is Stage 3 or 4.

70. The formulation or stabilized sustained release dosage form ~~use~~ of claim 69, wherein the patient is vitamin-D deficient.

71. The formulation or stabilized sustained release dosage form ~~use~~ of any of claims 62-70, wherein the patient is human.

72. The formulation or stabilized sustained release dosage form ~~use~~ of claim 71, wherein the human is an adult human.