PEDIATRIC DOSAGE FORMS, METHODS OF MAKING AND USING

BACKGROUND

Cross Reference to Related Applications

[0001] The benefit under 35 U.S.C. §119(e) of U.S. Provisional Patent Application Serial No. 62/725,940 filed August 31, 2018, is hereby claimed, and the disclosure thereof is hereby incorporated by reference herein.

Field of the Disclosure

[0002] The disclosure relates generally to dosage forms of vitamin D compounds, e.g. calcifediol, including forms suitable for pediatric use, and methods of making and using the same.

Brief Description of Related Technology

[0003] Vitamin D compounds have traditionally been administered in immediate release formulations. More recently, some modified release dosage forms of vitamin D compounds have been described, e.g. in wax matrix form. The present disclosure relates to vitamin D preparations, including extended release preparations and those suitable for use in pediatric patient populations. Formulations for delivery of active vitamin D, analogs thereof, and prohormones thereof have been disclosed, including some extended release dosage forms. One such formulation is marketed in the United States under the brand name RAYALDEE® (calcifediol), a product which is approved to treat secondary hyperparathyroidism in stage 3 and 4 chronic kidney disease (CKD) patients. The prescribing information for this drug provides that the sustained release formulation for RAYALDEE® is a wax based extended release formulation of 25-hydroxyvitamin D_3.

SUMMARY

[0004] The disclosure relates to a vitamin D formulation, comprising a vitamin D compound, optionally 25-hydroxyvitamin D or calcifediol, dispersed in a polymer composition. In examples, the formulation can be an extended release formulation, e.g. for oral use.

[0004a] One aspect of the disclosure herein is an extended release vitamin D formulation, comprising ~~a vitamin D compound, optionally~~ 25-hydroxyvitamin D or calcifediol, dispersed in a polymer composition which is water-insoluble and water permeable, the polymer selected from one or more in the group of ethylcellulose, low-substituted hydroxypropyl cellulose, and polyvinyl acetate.

pharmaceutically acceptable excipient. ~~Another aspect of the disclosure herein is a spheronized pellet formulation comprising 25-hydroxyvitamin D and a pharmaceutically acceptable excipient.~~ In examples, the formulation can be an extended release formulation, e.g. for oral use.

[0006a] In another aspect of the present disclosure, there is provided a spheronized pellet formulation comprising 25-hydroxyvitamin D dispersed in a mixture of,

an extended release polymer selected from one or more in the group of Eudragit RL PO, Eudragit, RS PO, ethylcellulose, and Kollidon SR,

a diluent,

an absorption enhancer is selected from one or more in the group of triglycerides, medium chain triglycerides, caprylocaproyl macrogolglycerides, and polyglycolized glycerides, and

a binder selected from one or more in the group of low-viscosity, hydrophilic cellulose ethers, PVP, carboxymethyl cellulose, starch, pregelatinized starch, acacia, tragacanth, gelatin, sodium alginate, and low-substituted hydroxypropyl cellulose

[0007] The disclosure also relates to an vitamin D formulation comprising a vitamin D compound, optionally 25-hydroxyvitamin D or calcifediol, dispersed in a fatty acid glyceride mixture. In examples, the formulation can be an extended release formulation, e.g. for oral use.

~~**[0007a]** Another aspect of the disclosure herein is an extended release vitamin D formulation, comprising a vitamin D compound dispersed in a fatty acid glyceride mixture.~~

[0008] The disclosure also relates to a nano/microparticle formulation comprising a vitamin D compound, optionally 25-hydroxyvitamin D or calcifediol, and a pharmaceutically acceptable excipient. Another aspect of the disclosure herein is a nano/microparticle formulation comprising 25-hydroxyvitamin D ~~and a pharmaceutically acceptable excipient~~ dispersed in an extended release polymer. In examples, the nano/microparticle formulation can provide extended release of the vitamin D compound, e.g. by using an extended release polymer as an excipient.

[0009] The disclosure also relates to a lipid microparticle formulation comprising a vitamin D compound, optionally 25-hydroxyvitamin D or calcifediol, and a pharmaceutically acceptable lipid. ~~Another aspect of the disclosure herein is a lipid microparticle formulation comprising 25-hydroxyvitamin D, optionally calcifediol, and a pharmaceutically acceptable lipid.~~ In examples, the formulation can be an extended release formulation, e.g. for oral use.

[0010] The disclosure also relates to a non-pareil seed formulation comprising a vitamin D compound, optionally 25-hydroxyvitamin D or calcifediol, and a pharmaceutically acceptable excipient. ~~Another aspect of the disclosure herein is a non-pareil seed formulation comprising 25-hydroxyvitamin D and a pharmaceutically acceptable excipient.~~ In examples, the formulation can be an extended release formulation, e.g. for oral use. In examples, the excipient can include an extended release polymer coating.

[0011] The disclosure also relates to a pharmaceutical composition comprising a vitamin D compound, optionally 25-hydroxyvitamin D or calcifediol, and a pharmaceutically acceptable excipient selected from one or more excipients in the group of an absorption enhancer, a spheronizing aid, a water insoluble polymer, and a binder. Another aspect of the disclosure herein is an extended release pharmaceutical composition comprising 25-hydroxyvitamin D~~, optionally calcifediol, and a pharmaceutically acceptable excipient selected from one or more excipients in the group of~~ dispersed in an absorption enhancer, a spheronizing aid, a water insoluble polymer, and a binder. In examples, the formulation can be an extended release formulation, e.g. for oral use.

[0012] The disclosure also relates to a spray-congealed lipid vitamin D formulation comprising a vitamin D compound, optionally 25-hydroxyvitamin D or calcifediol, an extended release agent, and a surfactant. ~~Another aspect of the disclosure herein is a spray-congealed lipid vitamin D formulation comprising 25-hydroxyvitamin D, an extended release agent, and a surfactant.~~ In examples, the formulation can be an extended release formulation, e.g. for oral use.

~~**[0012a]** Another aspect of the disclosure herein is an extended release dosage form comprising an uncoated granule, particle or pellet, said uncoated granule, particle or pellet comprising a vitamin D compound and an extended release agent.~~

[0012a~~b~~] Another aspect of the disclosure herein is an extruded, spheronized extended release vitamin D formulation, comprising a mixture of ~~about~~ 0.01 to ~~about~~ 0.1 wt.% calcifediol, ~~about~~ 40 wt.% to ~~about~~ 60 wt.% poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.2 extended release polymer, ~~about~~ 1 wt.% to ~~about~~ 5 wt.% triglycerides, ~~about~~ 30 wt.% to ~~about~~ 50 wt.% microcrystalline cellulose spheronizing aid, further optionally comprising ~~about~~ 1 wt.% to ~~about~~ 20 wt.% ethylcellulose, and further optionally comprising ~~about~~ 1 wt.% to ~~about~~ 10 wt.% additional binder, optionally low-substituted hydroxypropyl cellulose or methylcellulose, wherein the formulation is free of hydrocarbon waxes and hydrocarbon oils.

[0012b~~c~~] Another aspect of the disclosure herein is an extruded, spheronized extended release vitamin D formulation, comprising a mixture of ~~about~~ 0.01 to ~~about~~ 0.1 wt.% calcifediol, ~~about~~ 1 wt.% to ~~about~~ 10 wt.% ethylcellulose extended release polymer, ~~about~~ 20 wt.% to ~~about~~ 40 wt.% filler, optionally lactose, ~~about~~ 40 wt.% to ~~about~~ 60 wt.% microcrystalline cellulose spheronizing aid, ~~about~~ 1 wt.% to ~~about~~ 15 wt.% triglycerides, further optionally comprising ~~about~~ 1 wt.% to ~~about~~ 10 wt.% ethylcellulose, and further optionally comprising ~~about~~ 1 wt.% to ~~about~~ 15 wt.% additional binder, optionally methylcellulose or low-substituted hydroxypropyl cellulose, wherein the formulation is free of hydrocarbon waxes and hydrocarbon oils.

[0012c] In a further aspect of the present disclosure, there is provided an extruded, spheronized oral extended release vitamin D formulation, comprising a mixture of 0.01 to 0.1 wt.% calcifediol, 5 wt.% to 60 wt.% ethylcellulose extended release polymer, 5 wt.% to 40 wt.% glyceryl behenate extended release agent, and 20 wt.% to 50 wt.% spheronizing aid, optionally microcrystalline cellulose.

[0012d] In another aspect of the present disclosure, there is provided a method for improving batch to batch consistency in an in vitro release profile of the formulation or composition disclosed herein, comprising compounding the vitamin D compound with a water-insoluble polymer material and optionally one or more additional excipients.

[0013] The disclosure also relates to a pharmaceutical batch of dosage forms comprising a formulation according to the disclosure herein, and further characterized by low dosage form to dosage form variation in in vitro dissolution release. In examples, the dosage forms can be extended release dosage forms, e.g. for oral use.

[0014] The disclosure also relates to pharmaceutical batches of dosage forms comprising a formulation according to the disclosure herein, and further characterized by low

batch-to-batch variation in in vitro dissolution release. In examples, the dosage forms can be extended release dosage forms, e.g. for oral use.

[0014a] Another aspect of the disclosure herein is a pharmaceutical batch of dosage forms comprising a formulation or composition as defined herein, characterized by dosage form to dosage form variation in in vitro dissolution release (USP Apparatus II (Paddle with Sinker) at 75 revolutions per minute (RPM), with a medium of 0.5% sodium dodecyl sulfate (SDS) in 5 mM Sodium Dihydrogenphosphate Monohydrate, pH 6.8, 37 ± 0.5 °C, with a volume of 500 mL) at 2, 4, 6, 8, 10, and 12 hour time points less than 15% relative standard deviation (RSD), or less than 10% relative standard deviation (RSD), as determined by measurement of six dosage forms.

[0014b] Another aspect of the disclosure herein is pharmaceutical batches of dosage forms comprising a formulation or composition as defined herein, characterized by batch-to-batch variation in in vitro dissolution release (USP Apparatus II (Paddle with Sinker) at 75 revolutions per minute (RPM), with a medium of 0.5% sodium dodecyl sulfate (SDS) in 5 mM Sodium Dihydrogenphosphate Monohydrate, pH 6.8, 37 ± 0.5 °C, with a volume of 500 mL) at 2, 4, 6, 8, 10, and 12 hour time points less than 15% relative standard deviation (RSD), or less than 10% relative standard deviation (RSD), as determined by measurement of representative dosage forms from six batches.

[0014c] Another aspect of the disclosure herein is an oral dosage form comprising a formulation as defined herein.

[0015] The disclosure also relates to methods of making the pharmaceutical formulations and dosage forms. In embodiments, the method can be ~~Another aspect of the disclosure herein is~~ a method of making an extended release pharmaceutical formulation~~, optionally one according to any one of the formulation as defined herein~~ comprising compounding a vitamin D compound with a water-insoluble polymer, and optionally further with at least one pharmaceutically acceptable excipient selected from one or more of a diluent, an absorption enhancer, and a binder.

[0015a] In another aspect of the present disclosure, there is provided a method of making a formulation disclosed herein, comprising compounding the vitamin D compound and water-insoluble polymer, with a pharmaceutically acceptable excipient selected from one or more of a diluent, an absorption enhancer, and a binder.

[0016] Another aspect of the disclosure herein is a method for improving batch to batch consistency in an in vitro release profile of an extended release vitamin D compound formulation, the method comprising compounding the vitamin D compound with a water-insoluble polymer material and optionally one or more additional excipients.

[0017] The disclosure also relates to a method of treating a vitamin D responsive disease or condition comprising administering a formulation or dosage form according to the disclosure herein to a patient in need thereof.

[0017a] Another aspect of the disclosure herein is use of a formulation, composition or dosage form as defined herein for the manufacture of a medicament for treating a vitamin D responsive disease or condition selected from hyperparathyroidism, hyperparathyroidism secondary to CKD (e.g., individually or in a range of any of Stage 1, 2, 3, 4, or 5), hyperparathyroidism secondary to CKD in patients undergoing hemodialysis, or tertiary hyperparathyroidism, 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, autism (or autism spectrum disorder), chronic obstructive pulmonary disease, Parkinson’s disease, polycystic kidney disease (PKD), polycystic ovary syndrome, pancreatitis, nephritis, hepatitis, and/or infection, hypertension and cardiovascular disease, atherosclerosis, arteriosclerosis, coronary artery disease, cerebrovascular disease, peripheral vascular disease, myocardial infarction, myocardial ischemia, cerebral ischemia, stroke, congestive heart failure, cardiomyopathy, obesity or other weight disorders, lipid disorders (e.g. hyperlipidemia, dyslipidemia including associated diabetic dyslipidemia and mixed dyslipidemia hypoalphalipoproteinemia, hypertriglyceridemia, hypercholesterolemia, and low HDL (high density lipoprotein)), metabolic disorders (e.g. Metabolic Syndrome, Type II diabetes mellitus, Type I diabetes mellitus, hyperinsulinemia, impaired glucose tolerance, insulin resistance, diabetic complication including neuropathy, nephropathy, retinopathy, diabetic foot ulcer and cataracts), and/or thrombosis.

[0018] For the compositions and methods described herein, optional features, including but not limited to components, compositional ranges thereof, substituents, conditions, and steps, are contemplated to be selected from the various aspects, embodiments, and examples provided herein.

[0019] Further aspects and advantages will be apparent to those of ordinary skill in the art from a review of the following detailed description, taken in conjunction with the drawings. While the compositions and methods are susceptible of embodiments (or examples) in various forms, the description hereafter includes specific embodiments (or examples) with the understanding that the disclosure is illustrative, and is not intended to limit the invention to the specific embodiments (or examples) described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] For further facilitating the understanding of the present invention, four drawing figures are appended hereto.

[0021] FIG. 1 shows dissolution release profiles of calcifediol-loaded, Eudragit-based pellets according to the disclosure herein compared to dissolution release profiles of a wax-matrix based soft capsule formulation.

[0022] FIG. 2 shows dissolution release profiles of calcifediol-loaded, ethylcellulose (EC)-based pellets according to the disclosure herein compared to dissolution release profiles of a wax-matrix based soft capsule formulation.

What is claimed is:

1. An extended release vitamin D formulation, comprising ~~a vitamin D compound, optionally~~ 25-hydroxyvitamin D or calcifediol, dispersed in a polymer composition which is water-insoluble and water permeable, the polymer selected from one or more in the group of ethylcellulose, low-substituted hydroxypropyl cellulose, and polyvinyl acetate.

~~**2.** The formulation of claim 1, wherein the polymer composition comprises a polymer which is water-insoluble and water permeable.~~

~~**3.** The formulation of claim 2, wherein the polymer comprises a methacrylic acid polymer.~~

~~**4.** The formulation of claim 3, wherein the polymer comprises poly(ethyl acrylate, methyl methacrylate).~~

~~5~~2. The formulation of claim ~~2~~1, wherein the polymer comprises an ethylcellulose.

~~6~~3. The formulation of claim ~~2~~1, wherein the polymer comprises a low-substituted hydroxypropyl cellulose polymer.

~~7~~4. The formulation of claim ~~2~~1, wherein the polymer comprises a polyvinyl acetate polymer.

5. The formulation of claim 4, wherein the polyvinyl acetate polymer is further blended with polyvinyl pyrrolidone.

~~8~~6. The formulation of claim 1, wherein the vitamin D compound-containing composition is disposed ~~with~~ within a release-controlling membrane.

~~9~~7. The formulation of claim ~~8~~6, wherein the release-controlling membrane comprises a water-soluble polymer.

~~10~~8. The formulation of claim ~~8~~6, wherein the release-controlling membrane comprises a mixture of a water-insoluble polymer and a pore-former.

~~11~~9. The formulation of claim ~~10~~8, wherein the water-insoluble polymer is present in an amount exceeding the amount of pore former.

~~12~~10. The formulation of any one of the preceding claims, wherein the composition is in the form of a spheronized pellet.

~~**13.** The formulation of any one of the preceding claims, wherein the vitamin D compound is 25-hydroxyvitamin D and/or 25-hydroxyvitamin D_3.~~

~~**14.** The formulation of claim 13, wherein the vitamin D compound is 25-hydroxyvitamin D_3.~~

~~**15**~~**11.** A spheronized pellet formulation comprising 25-hydroxyvitamin D ~~and a pharmaceutically acceptable excipient~~dispersed in a mixture of,

an extended release polymer selected from one or more in the group of Eudragit RL PO, Eudragit, RS PO, ethylcellulose, and Kollidon SR,

a diluent,

an absorption enhancer is selected from one or more in the group of triglycerides, medium chain triglycerides, caprylocaproyl macrogolglycerides, and polyglycolized glycerides, and

a binder selected from one or more in the group of low-viscosity, hydrophilic cellulose ethers, PVP, carboxymethyl cellulose, starch, pregelatinized starch, acacia, tragacanth, gelatin, sodium alginate, and low-substituted hydroxypropyl cellulose.

~~**16.** The formulation according to claim 15, wherein the pharmaceutically acceptable excipient comprises an extended release polymer.~~

~~**17.** The formulation according to claim 16, wherein the extended release polymer is one or more selected from the group of Eudragit RL PO, Eudragit RS PO, ethylcellulose, and Kollidon SR.~~

~~**18.** The formulation according to any one of claims 16 to 17, further comprising at least one pharmaceutically acceptable excipient selected from one or more in the group of a diluent, an absorption enhancer, and a binder.~~

~~**19.** The formulation according to claim 18, wherein the diluent is selected from one or more in the group of lactose, saccharose, glucose, starch, microcrystalline cellulose, microfine cellulose, mannitol, sorbitol, calcium hydrogen phosphate, aluminum silicate, amorphous silica, and sodium chloride, starch, and dibasic calcium phosphate dehydrate.~~

~~**20.** The formulation according to claim 19, wherein the diluent is a pore former.~~

~~21~~12. The formulation according to claim ~~18 or 19~~11, wherein the absorption enhancer ~~is selected from one or more in the group of triglycerides, medium chain triglycerides, caprylocaproyl macrogolglycerides, and~~comprises polyglycolized glycerides.

~~22~~13. The formulation according to claim 11 or 12~~any one of claims 18 to 21~~, wherein the binder is selected from one or more in the group of low-viscosity, hydrophilic cellulose ethers~~, PVP, carboxymethyl cellulose, starch, pregelatinized starch, acacia, tragacanth, gelatin, sodium alginate, and low-substituted hydroxypropyl cellulose~~.

~~23~~14. The formulation according to any one of claims ~~18~~ 11 to ~~22~~13, wherein the ~~diluent is a~~ spheronizing aid, ~~optionally~~ is selected from one or both of ~~MCC~~microcrystalline cellulose and low-substituted hydroxypropyl cellulose.

~~24~~15. The formulation according to ~~any one of claims 18 to 22~~claim 14, wherein the ~~binder is a~~ spheronizing aid~~, optionally low-substituted hydroxypropyl~~ comprises microcrystalline cellulose.

~~25~~16. The formulation of any one of the preceding claims, ~~wherein~~ in the form of a particle, granule, or spheronized pellet which is characterized by a friability which is not more than 1.0 %, or less than 1.0%.

~~**26.** The formulation of any one of the preceding claims, wherein the 25-hydroxyvitamin D is 25-hydroxyvitamin D_3.~~

~~**27.** An extended release vitamin D formulation, comprising a vitamin D compound dispersed in a fatty acid glyceride mixture.~~

~~**28.** The formulation of claim 27, wherein the fatty acid glyceride mixture comprises glyceryl behenate.~~

~~29~~17. A nano/microparticle formulation comprising 25-hydroxyvitamin D ~~and a pharmaceutically acceptable excipient~~dispersed in an extended release polymer.

~~**30.** The nano/microparticle formulation according to claim 29, wherein the pharmaceutically acceptable excipient is an extended release polymer.~~

~~31~~18. The nano/microparticle formulation according to claim ~~29~~17, wherein the ~~excipient~~ extended release polymer comprises an insoluble polymer and a stabilizer.

~~32~~19. The nano/microparticle formulation according to claim ~~31~~18, wherein the insoluble polymer is selected from a methacrylate polymer.

~~33~~20. The nano/microparticle formulation according to claim ~~31~~ 18 or ~~32~~19, wherein the stabilizer comprises polyvinyl alcohol.

~~34~~21. The nano/microparticle formulation according to any one of claims ~~29~~ 17 to ~~33~~20, characterized by a mean particle size in a range of 100 nm to 10 microns, or 900 nm to 10 microns.

~~**35.** The formulation of any one of the preceding claims, wherein the vitamin D compound is 25-hydroxyvitamin D and/or 25-hydroxyvitamin D_3.~~

~~**36.** The formulation of claim 35, wherein the vitamin D compound is 25-hydroxyvitamin D_3.~~

~~**37.** A lipid microparticle formulation comprising 25-hydroxyvitamin D, optionally calcifediol, and a pharmaceutically acceptable lipid.~~

~~**38.** The lipid microparticle formulation according to claim 37 wherein the pharmaceutically acceptable excipient is lipid which is solid or semi-solid at room temperature.~~

~~**39.** A non-pareil seed formulation comprising 25-hydroxyvitamin D and a pharmaceutically acceptable excipient.~~

~~**40.** The formulation of claim 39, wherein the pharmaceutically acceptable excipient comprises an extended release polymer coating.~~

~~22~~41. ~~An~~ The formulation~~extended release dosage form~~ of any one of claims 1 to 21, ~~comprising~~ wherein the vitamin D compound dispersed in a polymer composition is in the form of an uncoated granule, particle or pellet~~, said uncoated granule, particle or pellet comprising a vitamin D compound and an extended release agent~~.

~~**42.** The extended release dosage form according to claim 41, wherein the vitamin D compound is selected from 25-hydroxyvitamin D.~~

~~**43.** The extended release dosage form according to claim 41 or 42, wherein the extended release agent is selected from the group consisting of a water insoluble polymeric component.~~

~~23~~44. The formulation ~~extended release dosage form~~ according to claim 22~~43~~, wherein the water insoluble polymeric component comprises a pH-independent swelling property and is permeable and/or dispersible.

2445. The formulation ~~extended release dosage form~~ according to any one of claims ~~43~~1-11 or 16-23, wherein the polymeric component is selected from an ammonioalkyl methacrylate copolymer.

2546. The formulation ~~extended release dosage form~~ according to ~~any one of claims 43 to 45~~claim 24, wherein the polymeric component comprises ethyl cellulose.

2647. The formulation ~~extended release dosage form~~ according to any one of claims ~~43 to 46~~1-11 or 16-23, wherein the polymeric component comprises a blend of PVA and PVP.

2748. The formulation ~~extended release dosage form~~ according to ~~any one of claims 43 to 47~~claim 22, further including a lipophilic compound.

2849. The formulation ~~extended release dosage form~~ according to ~~any one of claims 41 to 48~~claim 22, in the form of a spheronized pellet.

~~**50.** The extended release dosage form according to any one of claims 42 to 49, wherein the 25-hydroxyvitamin D is 25-hydroxyvitamin D_3.~~

2951. An extended release pharmaceutical composition comprising 25-hydroxyvitamin D~~, optionally calcifediol, and a pharmaceutically acceptable excipient selected from one or more excipients in the group of~~ dispersed in an absorption enhancer, a spheronizing aid, a water insoluble polymer, and a binder.

3052. The pharmaceutical composition according to claim 29~~51~~, wherein the absorption enhancer is selected from one or more in the group of triglycerides, medium chain triglycerides, caprylocaproyl macrogolglycerides, and polyglycolized glycerides.

3153. The pharmaceutical composition according to claim 29~~51 or 52~~, wherein the spheronizing aid is selected from one or more in the group of crospovidone, carrageenan, chitosan, pectinic acid, glycerides, beta cyclodextrine (β-CD), cellulose derivatives, microcrystalline cellulose, powdered cellulose, polyplasdone crospovidone, and polyethylene oxide.

3254. The pharmaceutical composition according to ~~any one of claims 51 to 53~~claim 29, wherein the water insoluble polymer is selected from one or more in the group of methacrylate polymers, poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride), poly(ethyl acrylate, methyl methacrylate), cellulosic polymers, ethyl cellulose, low-substituted hydroxypropyl cellulose, polyvinyl acetate, polyvinyl pyrrolidone, and polyvinyl acetate blended with polyvinyl pyrrolidone.

33~~55~~. The pharmaceutical composition according to ~~any one of claims 51 to 54~~claim 29, further comprising a lipid release modifier, optionally one or more mono-, di-, and tri-acylglycerols of fatty acids selected from one or more of palmitic acid, tallow acid, stearic acid, oleic acid, linoleic acid, linolenic acid, arachidic acid, behenic acid, and combinations thereof.

34~~56~~. The pharmaceutical composition according to claim 33~~55~~, wherein the lipid release modifier is selected from one or more mono-, di-, and tri-acylglycerols of fatty acids selected from one or more of palmitic acid, stearic acid, and behenic acid.

35~~57~~. The pharmaceutical composition according to claim 33~~55~~ or 34~~56~~36, wherein the lipid release modifier has an hydrophile/lipophile balance (HLB) in a range of 2 to 6.

~~**58.** A spray congealed lipid vitamin D formulation comprising 25-hydroxyvitamin D, an extended release agent, and a surfactant.~~

~~**59.** The formulation according to claim 58, wherein the extended release agent is selected from one or more in the group of paraffin, glycerol monostearate, fatty acid esters of glycerol, fatty acid esters of PEG, blends of fatty acid esters of glycerol and fatty acid esters of PEG, lauroyl macrogolglycerides, lauroyl polyoxylglycerides, blends of lauroyl macrogolglycerides and lauroyl polyoxylglycerides, Gelucire, caprylocaproyl macrogol-8-glyceride, glyceryl distearate, Precirol, glyceryl dibehenate, and Compritol 888.~~

~~**60.** The formulation according to claim 58 or 59, wherein the surfactant is selected from one or more in the group of PEG, PEG 4000, Tween and Tween 80.~~

~~**61.** The formulation according to any one of claims 58 to 60, having a water content (KF) of less than 0.30 wt.%.~~

36~~62~~. An extruded, spheronized extended release vitamin D formulation, comprising a mixture of ~~about~~ 0.01 to ~~about~~ 0.1 wt.% calcifediol, ~~about~~ 40 wt.% to ~~about~~ 60 wt.% poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.2 extended release polymer, ~~about~~ 1 wt.% to ~~about~~ 5 wt.% triglycerides, ~~about~~ 30 wt.% to ~~about~~ 50 wt.% microcrystalline cellulose spheronizing aid, further optionally comprising ~~about~~ 1 wt.% to ~~about~~ 20 wt.% ethylcellulose, and further optionally comprising ~~about~~ 1 wt.% to ~~about~~ 10 wt.% additional binder, optionally low-substituted hydroxypropyl cellulose or methylcellulose, wherein the formulation is free of hydrocarbon waxes and hydrocarbon oils.

37~~63~~. An extruded, spheronized extended release vitamin D formulation, comprising a mixture of ~~about~~ 0.01 to ~~about~~ 0.1 wt.% calcifediol, ~~about~~ 1 wt.% to ~~about~~ 10 wt.%

ethylcellulose extended release polymer, ~~about~~ 20 wt.% to ~~about~~ 40 wt.% filler, optionally lactose, ~~about~~ 40 wt.% to ~~about~~ 60 wt.% microcrystalline cellulose spheronizing aid, ~~about~~ 1 wt.% to ~~about~~ 15 wt.% triglycerides, further optionally comprising ~~about~~ 1 wt.% to ~~about~~ 10 wt.% ethylcellulose, and further optionally comprising ~~about~~ 1 wt.% to ~~about~~ 15 wt.% additional binder, optionally methylcellulose or low-substituted hydroxypropyl cellulose, wherein the formulation is free of hydrocarbon waxes and hydrocarbon oils.

38. An extruded, spheronized oral extended release vitamin D formulation, comprising a mixture of 0.01 to 0.1 wt.% calcifediol, 5 wt.% to 60 wt.% ethylcellulose extended release polymer, 5 wt.% to 40 wt.% glyceryl behenate extended release agent, and 20 wt.% to 50 wt.% spheronizing aid, optionally microcrystalline cellulose.

39. The formulation of claim 38, further comprising a hydroxypropylmethyl cellulose binder.

40. The formulation of claim 38 or 39, wherein the spheronizing aid comprises microcrystallinecellulose.

41. The formulation of any one of claims 38 to 40, wherein the amount of ethylcellulose extended release polymer is in a range of 1 wt.% to 20 wt.%.

42. The formulation of any one of claims 38 to 41, herein the amount of glyceryl behenate extended release agent is in a range of 5 wt% to 25 wt.%.

43. The formulation or composition according to any one of the preceding claims, wherein the 25-hydroxyvitamin D is 25-hydroxyvitamin D_3.

44~~64~~. The formulation or composition of any one of ~~the preceding~~ claims 1-16 or 22-44, having a particle size in a range of ~~about~~ 500 nm to ~~about~~ 2.8 mm.

45~~65~~. The formulation or composition of claim 44~~64~~, having a particle size in a range of ~~about~~ 250 microns to ~~about~~ 2.8 mm.

46~~66~~. The formulation or composition of claim 45~~65~~, having a particle size in a range of ~~about~~ 250 microns to ~~about~~ 2 mm.

47~~67~~. The formulation or composition of any one of the preceding claims, characterized by an in vitro dissolution release profile (USP Apparatus II (Paddle with Sinker) at 75 revolutions per minute (RPM), with a medium of 0.5% sodium dodecyl sulfate (SDS) in 5 mM Sodium Dihydrogenphosphate Monohydrate, pH 6.8, 37 ± 0.5 °C, with a volume of 500 mL) of:

less than 20% at 2 hours;
35% to 45% at 4 hours;
55% to 80% at 6 hours;
65% to 85% at 8 hours;
85% to ~~at least~~ 100% at 10 hours; and
90% to ~~at least~~ 100% at 12 hours.

48~~68~~. The formulation or composition of any one of the preceding claims, characterized by an in vitro dissolution release profile (USP Apparatus II (Paddle with Sinker) at 75 revolutions per minute (RPM), with a medium of 0.5% sodium dodecyl sulfate (SDS) in 5 mM Sodium Dihydrogenphosphate Monohydrate, pH 6.8, 37 ± 0.5 °C, with a volume of 500 mL) of:

14% to 18% at 2 hours;
36% to 45% at 4 hours;
55% to 69% at 6 hours;
74% to 88% at 8 hours;
89% to ~~at least~~ 100% at 10 hours; and
97% to ~~at least~~ 100% at 12 hours.

49~~69~~. The formulation or composition of any one of the preceding claims ~~or a dosage form comprising a formulation of any one of the preceding claims~~, wherein the formulation or or composition ~~dosage form~~ is free of hydrocarbon waxes, including paraffin.

50~~70~~. The formulation or composition of any one of the preceding claims ~~or a dosage form comprising a formulation of any one of the preceding claims~~, wherein the formulation or or composition ~~dosage form~~ is free of hydrocarbon oils, including mineral oil.

51~~71~~. A pharmaceutical batch of dosage forms comprising a formulation or composition according to any one of the preceding claims, characterized by dosage form to dosage form variation in in vitro dissolution release (USP Apparatus II (Paddle with Sinker) at 75 revolutions per minute (RPM), with a medium of 0.5% sodium dodecyl sulfate (SDS) in 5 mM Sodium Dihydrogenphosphate Monohydrate, pH 6.8, 37 ± 0.5 °C, with a volume of 500 mL) at 2, 4, 6, 8, 10, and 12 hour time points less than 15% relative standard deviation (RSD), or less than 10% relative standard deviation (RSD), as determined by measurement of six dosage forms.

52~~72~~. Pharmaceutical batches of dosage forms comprising a formulation or composition according to any one of the preceding claims, characterized by batch-to-batch variation in in vitro dissolution release (USP Apparatus II (Paddle with Sinker) at 75 revolutions per minute (RPM), with a medium of 0.5% sodium dodecyl sulfate (SDS) in 5

mM Sodium Dihydrogenphosphate Monohydrate, pH 6.8, 37 ± 0.5 °C, with a volume of 500 mL) at 2, 4, 6, 8, 10, and 12 hour time points less than 15% relative standard deviation (RSD), or less than 10% relative standard deviation (RSD), as determined by measurement of representative dosage forms from six batches.

5373. An oral dosage form comprising a formulation according to any one of the preceding claims.

5474. The oral dosage form of claim 5373, comprising a formulation according to any one of the previous claims disposed in a capsule shell, optionally a hydroxy propyl methylcellulose (HPMC) shell or hard gelatin shell.

5575. The oral dosage form of claim 5373, comprising a formulation according to any one of the previous claims disposed in a sachet.

5676. Use of a formulation, composition or dosage form according to any one of claims 1 to 75 55 for the manufacture of a medicament for treating a vitamin D responsive disease or condition selected from hyperparathyroidism, hyperparathyroidism secondary to CKD (e.g., individually or in a range of any of Stage 1, 2, 3, 4, or 5), hyperparathyroidism secondary to CKD in patients undergoing hemodialysis, or tertiary hyperparathyroidism, 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, autism (or autism spectrum disorder), chronic obstructive pulmonary disease, Parkinson’s disease, polycystic kidney disease (PKD), polycystic ovary syndrome, pancreatitis, nephritis, hepatitis, and/or infection, hypertension and cardiovascular disease, atherosclerosis, arteriosclerosis, coronary artery disease, cerebrovascular disease, peripheral vascular disease, myocardial infarction, myocardial ischemia, cerebral ischemia, stroke, congestive heart failure, cardiomyopathy, obesity or other weight disorders, lipid disorders (e.g. hyperlipidemia, dyslipidemia including associated diabetic dyslipidemia and mixed dyslipidemia hypoalphalipoproteinemia, hypertriglyceridemia, hypercholesterolemia, and low HDL (high density lipoprotein)), metabolic disorders (e.g. Metabolic Syndrome, Type II diabetes mellitus, Type I diabetes mellitus, hyperinsulinemia, impaired glucose tolerance, insulin resistance, diabetic complication including neuropathy, nephropathy, retinopathy, diabetic foot ulcer and cataracts), and/or thrombosis.

5777. The use according to claim 5676, wherein the medicament is for treating a pediatric patient.

5878. The use according to claim 5676, wherein the medicament is for treating a geriatric patient.

5979. The use according to any one of claims 56 to 5876 to 78, wherein the medicament is for administration by a method including sprinkling the formulation onto a substrate prior to orally ingesting the formulation and substrate.

6080. The use according to any one of claims 58 to 5876 to 78, wherein the medicament is for administration by a method including dispersing the formulation into a suspension base prior to orally ingesting the formulation and suspension base.

6181. The use according to any one of claims 56 to 6076 to 80, wherein the medicament is treating a patient having hyperparathyroidism secondary to Chronic Kidney Disease.

6282. A method for improving batch to batch consistency in an in vitro release profile of an the extended release vitamin D compound formulation or composition of any one of claims 1-16 or 22-50, comprising compounding the vitamin D compound with a water-insoluble polymer material and optionally one or more additional excipients.

6383. The method of claim 6282, wherein the compounding comprises wet granulation.

6484. The method of claim 6383, wherein the compounding comprises extrusion spheronization.

6585. The method of any one of claims 62 to 6482 to 84, wherein the water-insoluble polymer comprises one or more polymers selected from the group of a methacrylic acid polymer and ethylcellulose.

6686. The method of any one of claims 62 to 6582 to 85, wherein the one or more additional excipients comprise one or more selected from the group of a diluent, an absorption enhancer, and a binder.

6787. A method of making a an extended release pharmaceutical formulation, optionally one according to any one of the preceding formulation claimsclaim 1, comprising compounding a the vitamin D compound with aand water-insoluble polymer, and optionally

~~further~~ with ~~at least one~~a pharmaceutically acceptable excipient selected from one or more of a diluent, an absorption enhancer, and a binder.

6888. The method of claim 6787, wherein the water-insoluble polymer material comprises ~~one or more polymers selected from the group of a methacrylic acid polymer and~~ ethylcellulose.

6989. The method of any one of claims 67 to 6887 ~~to 88~~, comprising compounding the vitamin D compound and water-insoluble polymer with a diluent which is selected from one or more in the group of lactose, saccharose, glucose, starch, microcrystalline cellulose, microfine cellulose, mannitol, sorbitol, calcium hydrogen phosphate, aluminum silicate, amorphous silica, and sodium chloride, starch, and dibasic calcium phosphate dihydrate.

7090. The method of any one of claims 67 to 6987 ~~to 89~~ comprising compounding the vitamin D compound and water-insoluble polymer with a diluent which is a pore former.

7191. The method of any one of claims 67 to 7087 ~~to 90~~, comprising compounding the vitamin D compound and water-insoluble polymer with an absorption enhancer which is selected from one or more in the group of triglycerides, medium chain triglycerides, caprylocaproyl macrogolglycerides, and polyglycolized glycerides.

7292. The method of any one of claims 67 to 7187 ~~to 91~~, comprising compounding the vitamin D compound and water-insoluble polymer with a binder which is selected from one or more in the group of low-viscosity, hydrophilic cellulose ethers, PVP, carboxymethyl cellulose, starch, pregelatinized starch, acacia, tragacanth, gelatin, sodium alginate, microcrystalline cellulose, and low-substituted hydroxypropyl cellulose.

7393. The method of claim 7292, wherein the binder is a spheronizing aid, optionally ~~MCC~~microcrystalline cellulose.

7494. The method of any one of claims 67 to 7385 ~~to 93~~, wherein the compounding comprises wet granulation.

7595. The method of any one of claims 67 to 7485 ~~to 94~~, wherein the compounding comprises extrusion and spheronization.

7696. The method of any one of claims 67 to 7582 ~~to 95~~, further comprising omitting hydrocarbon waxes from the formulation, optionally paraffin.

7797. The method of any one of claims 67 to 7682 ~~to 96~~, further comprising omitting hydrocarbon oils from the formulation, optionally mineral oil.

78~~98~~. The method of any one of claims 75 to 77~~85 to 97~~, wherein the extrusion and spheronization provides a spheronized pellet and the spheronized pellet is a spheronized matrix pellet.

79~~99~~. The method of any one of claims 68 to 78~~83 to 98~~, comprising creating a liquid mixture of the vitamin D compound, a solubilized binder, and an absorption enhancer, and applying the liquid mixture to a dry composition comprising the water-insoluble polymer material, with mixing.