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] In an aspect of the present disclosure, there is provided an extended release oral spheronized pellet vitamin D formulation, comprising a vitamin D compound comprising 25-hydroxyvitamin D and/or 25-hydroxyvitamin D_3 dispersed in a polymer composition which is water-insoluble and water permeable, comprising 1 wt% to 20 wt% ethylcellulose, 30 wt% to 50 wt% of a spheronizing aid comprising microcrystalline cellulose, 1 wt% to 20 wt% of an absorption enhancer comprising medium chain (C8-C10) triglycerides, and 1 wt% to 15 wt% of a binder which is a low-viscosity cellulose ether comprising hydroxypropyl methylcellulose, wherein the formulation is free of hydrocarbon waxes, including paraffin, wherein the pellet formulation has a particle size in a range of 500 nm to 2.8 mm, and wherein the pellet is uncoated.

[0005] The disclosure also relates to a vitamin D formulation, comprising a vitamin D compound, optionally 25-hydroxyvitamin D or calcifediol, embedded in a polymer network. The polymer can be water-insoluble, and optionally swellable. In examples, the formulation can be an extended release formulation, e.g. for oral use.

[0006] The disclosure also relates to a spheronized pellet formulation comprising a vitamin D compound, optionally 25-hydroxyvitamin D or calcifediol, and a

pharmaceutically acceptable excipient. In examples, the formulation can be an extended release formulation, e.g. for oral use.

[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.

[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. 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. 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. 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. In examples, the formulation can be an extended release formulation, e.g. for oral use.

[0011a] In another aspect of the present disclosure, there is provided an oral extended release pharmaceutical composition comprising 25-hydroxyvitamin D, a spheronizing aid which is microcrystalline cellulose present in an amount of 40 wt% to 60 wt%, medium chain (C8-C10) triglycerides present in an amount of 1 wt% to 15 wt%, ethyl cellulose present in an amount of 1 wt% to 10 wt%, and a binder which is hydroxypropyl methylcellulose present in an amount of 1 wt% to 15 wt%.

[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. In examples, the formulation can be an extended release formulation, e.g. for oral use.

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

[0012b] Another aspect of the disclosure herein is an extruded, spheronized extended release vitamin D formulation, comprising a mixture of 0.01 to 0.1 wt.% calcifediol, 1 wt.% to 10 wt.% ethylcellulose extended release polymer, 20 wt.% to 40 wt.% filler, optionally lactose, 40 wt.% to 60 wt.% microcrystalline cellulose spheronizing aid, 1 wt.% to 15 wt.% triglycerides, further optionally comprising 1 wt.% to 10 wt.% ethylcellulose, and further optionally comprising 1 wt.% to 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.

[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 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 a method of making an extended release pharmaceutical formulation 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.

[0016] Another example 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.

What is claimed is:

1. An extended release oral spheronized pellet vitamin D formulation, comprising a vitamin D compound comprising 25-hydroxyvitamin D and/or 25-hydroxyvitamin D_3 dispersed in a polymer composition which is water-insoluble and water permeable, comprising 1 wt% to 20 wt% ethylcellulose, 30 wt% to 50 wt% of a spheronizing aid comprising microcrystalline cellulose, 1 wt% to 20 wt% of an absorption enhancer comprising medium chain (C8-C10) triglycerides, and 1 wt% to 15 wt% of a binder which is a low-viscosity cellulose ether comprising hydroxypropyl methylcellulose, wherein the formulation is free of hydrocarbon waxes, including paraffin, wherein the pellet formulation has a particle size in a range of 500 nm to 2.8 mm, and wherein the pellet is uncoated.

2. The formulation of claim 1, wherein the vitamin D compound is 25-hydroxyvitamin D_3.

3. An oral extended release pharmaceutical composition comprising 25-hydroxyvitamin D, a spheronizing aid which is microcrystalline cellulose present in an amount of 40 wt% to 60 wt%, medium chain (C8-C10) triglycerides present in an amount of 1 wt% to 15 wt%, ethyl cellulose present in an amount of 1 wt% to 10 wt%, and a binder which is hydroxypropyl methylcellulose present in an amount of 1 wt% to 15 wt%.

4. The pharmaceutical composition according to claim 3, further comprising a lipid release modifier, which is one or more mono-, di-, and tri-acylglycerols of behenic acid.

5. The pharmaceutical composition of claim 3, wherein the formulation is an extruded, spheronized extended release vitamin D formulation, comprising a mixture of 0.01 to 0.1 wt.% calcifediol, 20 wt.% to 40 wt.% filler, wherein the formulation is free of hydrocarbon waxes and hydrocarbon oils.

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

7. An extruded, spheronized extended release vitamin D formulation, comprising a mixture of 0.01 to 0.1 wt.% calcifediol, 1 wt.% to 10 wt.% ethylcellulose extended release polymer, 20 wt.% to 40 wt.% filler, optionally lactose, 40 wt.% to 60 wt.% microcrystalline

cellulose spheronizing aid, 1 wt.% to 15 wt.% triglycerides, further optionally comprising 1 wt.% to 10 wt.% ethylcellulose, and further optionally comprising 1 wt.% to 15 wt.% additional binder, optionally methylcellulose or low-substituted hydroxypropyl cellulose, wherein the formulation is free of hydrocarbon waxes and hydrocarbon oils.

8. 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.

9. The formulation of claim 8, further comprising a hydroxypropylmethyl cellulose binder.

10. The formulation of claim 8 or 9, wherein the spheronizing aid comprises microcrystallinecellulose.

11. The formulation of any one of claims 8 to 10, wherein the amount of ethylcellulose extended release polymer is in a range of 1 wt.% to 20 wt.%.

12. The formulation of any one of claims 8 to 11, wherein the amount of glyceryl behenate extended release agent is in a range of 5 wt% to 25 wt.%.

13. The formulation or composition of any one of claims 1-12, having a particle size in a range of 500 nm to 2.8 mm.

14. The formulation of claim 13, having a particle size in a range of 250 microns to 2.8 mm.

15. The formulation of claim 6, having a particle size in a range of 250 microns to 2 mm.

16. The formulation of any one of the preceding claims, wherein the formulation or dosage form is free of hydrocarbon oils, including mineral oil.

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

18. The oral dosage form of claim 17, comprising a formulation according to any one of the previous claims disposed inside a capsule shell, optionally a hydroxy propyl methylcellulose (HPMC) shell or a hard gelatin shell.

19. The oral dosage form of claim 17, comprising a formulation according to any one of the previous claims disposed inside a sachet.

20. Use of a formulation, composition or dosage form according to any one of claims 1 to 19 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.

21. The use according to claim 20, wherein the medicament is for treating a pediatric patient.

22. The use according to claim 20, wherein the medicament is for treating a geriatric patient.

23. The use according to any one of claims 20 to 22, wherein the medicament is for administration by a method including sprinkling the formulation onto a substrate prior to orally ingesting the formulation and substrate.

24. The use according to any one of claims 20 to 22, 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.

25. The use according to any one of claims 20 to 24, wherein the medicament is treating a patient having hyperparathyroidism secondary to Chronic Kidney Disease.