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.

[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. 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.

[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. 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 a pharmaceutical composition comprising 25-hydroxyvitamin D, optionally 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.

[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.

[0012b] 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.**[0012c]** 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.

[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 as defined herein, characterized by dosage form to dosage form variation in in vitro dissolution release (USP Apparatus II (Paddle with Sinker) at 75 RPM, with a medium of 0.5% 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% RSD, or less than 10% 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 as defined herein, characterized by batch-to-batch variation in in vitro dissolution release (USP Apparatus II (Paddle with Sinker) at 75 RPM, with a medium of 0.5% 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% RSD, or less than 10% 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. 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.

[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 or dosage form as defined herein for the manufacture of a medicament for treating a vitamin D responsive disease or condition.

[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.