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Solid lipid dispersion of calcitriol with enhanced dissolution and stability

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ABSTRACT

Solid dispersion of calcitriol with lipophilic surfactants and triglycerides was developed by melt-mixing method to modify the release and enhance stability of the drug. The solid dispersions were characterized by differential scanning calorimetry (DSC), hot stage polarized optical microscopy (HSPM), infrared spectroscopy (FTIR) and stability studies. The solid dispersion significantly enhanced the stability of calcitriol, which could be attributed to the high antioxidant activity of the solid lipid dispersion. The rapid dissolution rate from the solid dispersion was attributed to the amorphous or solid solution state of drug with improved specific surface area and wettability than the drug crystals. Therefore, solid dispersion of calcitriol with D-a-tocopheryl polyethylene glycol 1000 succinate (TPGS) offers a good approach to modify the release and enhance stability of calcitriol. The influence of lipophilic solid dispersion on drug bioavailability needs further investigation.

1. Introduction

Calcitriol is the biologically active form of cholecalciferol in the intestine, proved to be 4–13 fold active as cholecalciferol in stimulating intestinal calcium transport [1] and play an important role in the regulation of calcium metabolism [2]. Moreover, calcitriol has been proved effective in treatment of osteoporosis, glucocorticoid-induced osteoporosis, secondary hyperparathyroidism and psoriasis [2–5]. In addition, it showed remarkable effect on cancers such as prostatic carcinoma, osteosarcoma, leukemia, etc [6–8].

However, even with the demonstrated excellent efficacy, calcitriol plays a limited pharmaceutical role mainly because of its exceptionally low aqueous solubility and extreme susceptibility to light, heat and oxygen [9], which induced a big challenge for developing calcitriol into a stable and therapeutically effective dosage form. The conventional calcitriol oral products, Rocaltrol® soft capsule and Rocaltrol® oral

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solution, have complicate manufacturing processes with low industrial applicability and the liquid formulations showed severe inherent stability issue.

The current trend in calcitriol research is concentrated on the development of potential delivery system to increase its stability against oxygen. Libertyville [10] designed low oxygen content compositions of calcitriol, i.e. a unit dose system comprising 1α,25-dihydroxycholecalciferol in a sealed vessel. Paul [11] and Paulhaguet [12] added antioxidants such as tocopherol and BHT respectively to enhance the stability of calcitriol. By far, there were few reports on solid formulation of calcitriol.

Solid dispersion is one of the most effective approaches to improve dissolution rate and hence bioavailability of poorly water-soluble drugs at solid state [13]. Out of the many polymers, biocompatible lipid materials are widely used as carriers for solid dispersion systems because of their ability to solubilize hydrophobic drug molecules, as well as the ability to stabilize solid dispersion by drug–carrier interactions and/or antiplasticizing effects of the carrier. It is known solid dispersions are thermodynamically unstable with the high energy input during preparation [14]. The representative lipid materials include surface-active carriers like TPGS (D-a-tocopheryl polyethylene glycol 1000 succinate), and Janssens [14] observed the improved dissolution of solid dispersion made of itraconazole and TPGS. In addition, Yoo [15] reported excellent miscibility and stability of TPGS and polymers as carriers of solid dispersions.

Recently, melting method has gained popularity for preparing solid dispersion due to many advantages, such as free of solvents, simple procedure and uniform product quality [16]. For this method, the melting temperature must be high enough to ensure that the drug is completely melted and transformed to amorphous state. But at high temperature, both drug and polymer carrier faces the risk of thermal degradation, especially for heat sensitive drugs [17]. Therefore, lowering the process temperature of melting method is a big challenge for pharmaceutical scientists.

It was found that the melting point of solid lipid would decrease upon adding of medium chain triglycerides (MCT). Jenning reported that the melting point of glyceryl behenate (85 °C) was depressed in a concentration dependent manner with the addition of Miglyol to carrier [18]. As excellent and stable solvents for water-insoluble drugs, MCT are compatible with other cosolvents, lipids and surfactants [19] and therefore, were used in the commercial product of calcitriol i.e. Rocaltrol®.

In addition, silicon dioxide can be used as liquisolid carriers to overcome the stickiness and tackiness problems of lipid carriers for further investigation such as tableting [20,21].

The abilities of solid dispersion to incorporate drug for immediate release and enhancing drug bioavailability make it an interesting drug delivery system for oral administration. However, few literature have assessed the application of solid dispersion for delivery of calcitriol.

Therefore, the objective of this research was to develop solid dispersion by using MCT and TPGS as lipid carriers and SiO_2 as solidifier, in order to improve the solubility of calcitriol in aqueous media and enhance the stability of calcitriol. Furthermore, a complete characterization of the solid dispersion properties and of the drug/carrier interactions was conducted by using differential scanning calorimetry (DSC), hot stage polarized optical microscopy (HSPM), Fourier transform infrared spectroscopy (FTIR). Also, the stability and dissolution behavior of calcitriol in solid dispersion were evaluated.

2. Materials and methods

2.1. Materials

Calcitriol was supplied by Guangzhou Eastbang Pharm. Sci. & Tech. Co., Ltd (Guangdong, China). D-a-Tocopheryl polyethylene glycol 1000 succinate (TPGS) was obtained from Aladdin Reagent Factory (Shanghai, China). Medium chain triglycerides (MCT) were supplied by Xiya Reagent Factory (Sichuan, China). Colloidal silicon dioxide (SiO_2) was obtained from Huzhou Zhanwang Pharmaceutical Co, Ltd (Zhejiang, China). All other materials used were of analytical or HPLC grade.

2.2. Preparation of solid dispersion

Solid dispersion was prepared by melt-mixing method. Firstly, calcitriol was dissolved in MCT under ultrasonication, then TPGS premelted at 60 °C was mixed with calcitriol–MCT solution with vortexing until a homogeneous mixture was obtained. The mixture was then dispersed into SiO_2 and cooled to 5 °C immediately to form solid dispersions containing 0.0001% of drug, 29.6% of MCT, 29.6% of TPGS, and 40.8% of SiO_2.

2.3. Preparation of physical mixture

Physical mixture with the same composition of solid dispersion was also prepared. TPGS was first melted at 60 °C, and vortex-mixed with MCT to form a homogeneous mixture. The melt was then dispersed into SiO_2 and cooled to 5 °C immediately. The obtained particles were then blended with crystal calcitriol uniformly.

2.4. Stability study

The dispersion samples were placed in sealing containers and stored at 5 °C (refrigerator), or in controlled temperature cabinets at 25 °C (60% RH), 30 °C (65% RH) and 40 °C (75% RH). The physicochemical properties of these dispersions were evaluated after 0, 5, 10, 30, 60, 90 days.

2.5. Thermal analysis

Thermal behavior of the samples was examined by differential scanning calorimetry (DSC 200 F3 Maja®, NETZSCH group, Germany). Samples of 1–10 mg were placed in open aluminum pans and heated at 10 °C/min to 130 °C under a nitrogen flow rate of 30 ml/min.

2.6. Hot stage polarized optical microscopy (HSPM)

The solid dispersion samples stored over 3 months (25 °C, 60% RH) after preparation were examined in a hot-stage microscope (Polarizing Microscope Mshot MP41, combined