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Dissolution enhancement of Deflazacort using hollow crystals prepared by antisolvent crystallization process

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ABSTRACT

Deflazacort (DFZ), a derivate of prednisolone, is a poorly soluble drug which has been proposed to have major advantages over other corticosteroids. Poorly soluble drugs present limited bioavailability due to their low solubility and dissolution rate and several strategies have been developed in order to find ways to improve them. In general, pharmaceutical laboratories use a micronized process to reduce the particle size in order to increase the dissolution of the drugs. However, this process causes changes such as polymorphic transitions, particle agglomeration and a reduction in fluidity and wettability. These solid-state properties affect the dissolution behavior and stability performance of drugs. Crystallization techniques are widely used in the pharmaceutical industry and antisolvent crystallization has been used to obtain ultrafine particles. In this study, DFZ was investigated in terms of its antisolvent crystallization in different solvents and under various preparation conditions (methanol/water ratio, stirring and evaporation rate, etc.), in order to compare the physicochemical properties between crystallized samples and raw materials available on the Brazilian market with and without micronization. Crystalline structure, morphology, and particle size, and their correlation with the Intrinsic Dissolution Rate (IDR) and dissolution profile as relevant biopharmaceutical properties were studied. Crystallization conditions were achieved which provided crystalline samples of hollow-shaped crystals with internal channels, which increased the dissolution rate of DFZ. The antisolvent crystallization process allowed the formation of hollow crystals, which demonstrated a better dissolution profile than the raw material (crystalline and micronized), making this a promising technique as a crystallization strategy for improving the dissolution and thus the bioavailability of poorly soluble drugs.

1. Introduction

Deflazacort (DFZ) (Fig. 4A) is a poorly soluble drug derived from prednisolone and it has been proposed that it may have major advantages over other corticosteroids (Joshi and Rajeshwari, 2009). The in vitro release profiles of DFZ tablets produced by two different laboratories were shown to be significantly different, indicating that the two products are not equivalent in terms of their dissolution behavior (Sperandeo and Kassuha, 2009).

A critical problem associated with poorly soluble drugs is their low and variable bioavailability derived from their slow dissolution and erratic absorption. Various approaches have been developed with a focus on enhancing the solubility, dissolution rate, and oral bioavailability of poorly water-soluble drugs (Kawabata et al., 2011; Patil et al., 2011). In general, pharmaceutical laboratories use the micronization process to reduce the particle size in order to increase the dissolution rate of drugs (Chaumeil, 1998; Kesisoglou et al., 2007). However, this mechanical process may cause changes such as polymorphic transitions, particle agglomeration, statically charged particles and decreased fluidity and wettability (Pasquali et al., 2006), which do not necessarily improve the dissolution of drugs.

Crystallization is an important process employed to produce a wide variety of materials in the pharmaceutical industry. The control of the crystal size and shape and polymorphism is crucial as these factors can influence the physical and chemical properties of the solid including the dissolution rate and solubility (Chen et al., 2011; Garcia et al., 1999). Several crystallization techniques

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are widely used in the pharmaceutical industry and antisolvent crystallization is one of them. The basic principle is that the drug is dissolved in a solvent; the solvent solution is then mixed with an antisolvent (in which the drug is insoluble). Precipitation occurs as a consequence of the altered supersaturation level caused by mixing the solution with the antisolvent (Viçosa et al., 2012). The technique presents some advantages, involving a straightforward method which is rapid and easy to perform. This is a promising technique to prepare ultrafine drug particles which can increase the dissolution rate and improve the bioavailability (Dong et al., 2009; Wang et al., 2007). Studies have shown that antisolvent precipitation under mild conditions can be applied as a simple and useful technique to prepare poorly water-soluble drug particles with a reduction in particle size, a narrow particle size distribution and enhanced dissolution properties (Cho et al., 2010).

A literature review showed that interest in hollow crystals has been increasing in several technical areas based on their properties. Research with hollow crystals has been performed with organic (Cohen et al., 1950; Eddleston and Jones, 2010; Mallet et al., 2004; Manish et al., 2005; Martins et al., 2011) and inorganic (Dette et al., 2010a, 2010b; Dette et al., 2007; Niwa et al., 2010; Schuster et al., 2011; Wachsmuth et al., 2011; Yang et al., 2010) compounds, leading to considerable attention being focused on their properties, which include low bulk density and specific surface area. However, in the pharmaceutical area hollow crystal still are poorly explored. The antisolvent method has been used to produce hollow crystals of dexamethasone acetate monohydrate (Mallet et al., 2004); however, for anhydrous drugs the use of this technique has not been studied.

The objective of this study was to obtain hollow crystals of DFZ by antisolvent crystallization under different preparation conditions. In addition, the physicochemical characteristics of the micronized and crystalline raw materials and crystallized samples were determined and their association with the dissolution rate was investigated.

2. Materials and methods

2.1. Materials

DFZ was obtained from Taizhou Taifa Pharma Co., Ltd., China and the raw materials were purchased from Brazilian suppliers and identified as: RM1 (micronized raw material) and RM2 (crystalline raw material). The DFZ samples crystallized in methanol/water were identified as R4.

2.2. Antisolvent crystallization of DFZ

Deflazacort was used as received and sample solutions were prepared by dissolving appropriate amounts of DFZ in methanol (25 mg mL^{-1}) and heating to 65 °C. Water was used as the antisolvent and was added immediately. Solutions were left to stand (for 4 or 60 min) or stirred (for 4 min) at room temperature. The proportions of methanol:water used were: 1:1, 1:2, 1:3, 1:4, 1:5 and 1:6 (v/v). Crystallized samples were retained in a quantitative filter (pore size 28 μm), oven dried at 50 °C and weighed on an analytical balance.

2.3. Scanning electron microscopy (SEM)

The morphologies of the raw materials and crystallized samples of DFZ were determined by scanning electron microscopy (SEM). SEM images were taken using a Jeol JSM-6390LV scanning electron microscope (Jeol, USA). The samples were mounted with carbon adhesive on an aluminum holder, sputtered with gold and photographed at a voltage of 15 kV.

2.4. X-ray diffraction

X-ray diffraction (XRD) measurements were performed on a PANalytical X'pert PRO Multi-Purpose Diffractometer (PANalytical, USA), using monochromatized Cu $K\alpha_1$ radiation (λ = 1.5406 Å) operating at 45 kV and 40 mA. The samples were supported in 0.7 mm quartz capillary holders coupled to a spinner to avoid the effect known as preferred orientation of the sample.

2.5. Particle size determination

The particle size distributions were determined by optical microscopy using an Axio Imager M2m, with an AxioCam MRc5 digital camera and AxioVision v4.7 software to capture and analyze the images (Carl Zeiss, Germany) and scanning electron microscopy using a Jeol DJSM 6510LV microscope (Jeol, USA). Pictures were taken from different areas of the samples until 90 particles were considered. The micronized raw material, RM1, was observed by SEM since the particles were too small for optical microscopy.

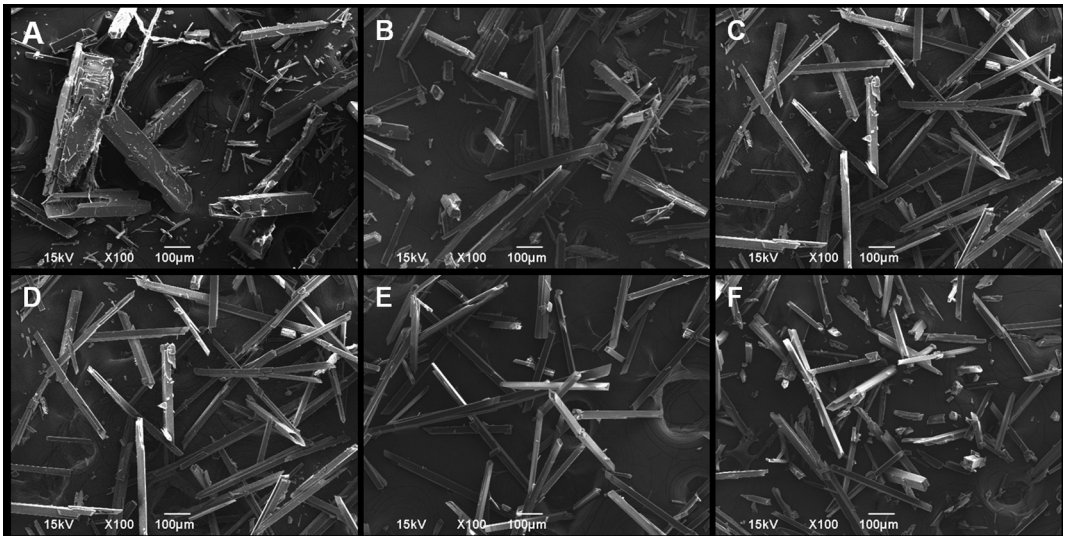

Fig. 1. Scanning electron micrographs of tubular crystals of DFZ crystallized with methanol:water (1:1, 1:2, 1:3, 1:4, 1:5 and 1:6), after 4 min, without stirring.