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ORIGINAL ARTICLE

Dissolution properties, solid-state transformation and polymorphic crystallization: progesterone case study

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Abstract

Progesterone is a natural steroid hormone and a poor soluble drug which presents two polymorphs (forms 1 and 2). Different methods to obtain form 2 were tested and a complete solid-state characterization of both polymorphs (forms 1 and 2) was conducted. X-ray powder diffraction, hot stage microscopy, Fourier transform infrared, dispersive Raman, ^{13}C solid-state nuclear magnetic resonance spectroscopy, thermal analysis, scanning electron microscopy techniques and intrinsic dissolution rates (IDR) were applied to investigate physical–chemical and dissolution properties of these two polymorphs. Form 2 was obtained from diluted solutions and from melting after cooling at room temperature. Form 1 was obtained from concentrated solutions and, a mixture of both polymorphs was crystallized from intermediate solutions. The crystal habit was not a distinctive characteristic of each polymorph. The effect of mechanical stress was evaluated in the metastable polymorph (form 2). We observed that grinding form 2 produced seeds of form 1 that induced the transformation of form 2 into form 1 at high temperature. The polymorphic quantification from XRD patterns of ground samples were carried out by the Rietveld method. After grinding and at room temperature conditions (~25 °C), it was observed the transformation of 17% of form 2 into form 1 in 10 days.

Keywords

Intrinsic dissolution rate, phase transformation, polymorphism, progesterone, solid-state characterization

History

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Introduction

Pharmaceutical solids can exist in more than one crystalline phases, called polymorphs, that generally present differences between them in solubility, dissolution rate, stability and bioavailability[1,2]. Polymorphs can appear during the standard manufacturing process, affecting the quality, safety and efficacy of a solid dosage form if not properly controlled[3,4].

Progesterone, pregn-4-ene-3,20-dione (Figure 1), is a natural steroid hormone that has six chiral centers[5,6]. It is secreted by the ovary as part of the menstrual cycle, is involved in pregnancy and embryogenesis of humans and another species. In humans it is used in birth control pills, in menopausal hormone replacement therapies and polycystic ovary syndromes[7]. On the other hand, in animals, it is used for artificial insemination programs. Progesterone is known to exists in two polymorphic forms: form 1 (α-form) and form 2 (β-form)[8] and its physical–chemical properties has been deeply studied[9,10]. Form 2 is considered a ''disappearing'' polymorph[6]; nevertheless, Heredia et al.[11] and Tripathi et al.[12] reported the presence of this polymorph in their experiments and established relation between its presence with improvements in dissolution characteristics. Several advantages could be obtained if the pharmaceutical and/or veterinary products would be formulated with form 2. However, to date, the Intrinsic Dissolution Rate (IDR) of progesterone polymorphs and the polymorphic stability of form 2 against grinding process have not been determined.

In this article, the IDR of both progesterone polymorphs was determined. Forms 1 and 2 were previously characterized and the solid-state transformation of form 2 into form 1 with quantification by the Rietveld method was performed. Finally, as form 2 is more soluble than form 1, solvent evaporation crystallizations were conducted in order to obtain form 2.

Materials and methods

Samples preparation and crystallization experiments

Form 1, micronized progesterone (purity > 99%) was purchased from Pharmanostra (Rio do Janeiro, Brazil) imported from China. Form 2 was obtained from the molten sample of form 1 at 140 °C by slow cooling. It guaranteed to obtain form 2 as a pure form[9].

For the polymorphic stability of form 2, ~1 g of sample was placed in a porcelain mortar and ground for different time ranges from 5 to 25 min. Recrystallizations were conducted in chloroform and in acetone by solvent evaporation at room temperature

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