COMMUNICATION

Crystallization of Progesterone for Pulmonary Drug Delivery

DOAA RAGAB,[1,2] SOHRAB ROHANI,[1] MAGDA W. SAMAHA,[2] FERIAL M. EL-KHAWAS,[2] HODA A. EL-MARADNY[2]

[1]Department of Chemical and Biochemical Engineering, The University of Western Ontario, London, Ontario, Canada N6A 5B9

[2]Faculty of Pharmacy, Department of Industrial Pharmacy, University of Alexandria, Alexandria, Egypt

Received 13 February 2009; revised 30 June 2009; accepted 3 July 2009

Published online 18 August 2009 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/jps.21896

ABSTRACT: The purpose of this study is to investigate the suitability of the crystallization process to produce microcrystals of progesterone for respiratory drug delivery. Crystallization of progesterone was carried out from water–isopropanol (IPA) mixture. The antisolvent (water) was added at two different addition rates (10 and 100 mL/min). The mass percentage of antisolvent was varied between (50% and 75%), and the initial drug concentration was adjusted at (0.5 and 1 g/L). The effect of crystallization method (antisolvent precipitation or combined cooling and antisolvent) was also examined. These operating conditions were investigated in a 2^4 factorial design in an effort to optimize the process. Different solid-state and surface characterization techniques were applied in conjunction with measurements of powder flow properties using aerodynamic particle sizer (APS). Powder dispersibility and aerosol performance were analyzed using Anderson Cascade Impactor (ACI). Antisolvent addition rate, initial drug concentration and dynamic solvent composition are shown to have a significant effect on the aerosol characteristics of progesterone microcrystals. An increase of 38.73% in the fine particle fraction (FPF) was demonstrated for some powders produced by combined cooling and antisolvent crystallization. In conclusion, it was possible to control particle size and hence, pulmonary deposition using process parameters alone, and produce particles with a narrow particle size distribution and a mean particle size of 5 μm with nearly no particles larger than 10 μm by direct crystallization. The suitability of deep pulmonary deposition was proved by the platelet-like morphology of processed microcrystals and greater surface-to-volume ratio than spherical particles. J Pharm Sci 99:1123–1137, 2010

Keywords: respiratory drug delivery; progesterone; crystallization; microcrystals; cooling; ant-solvent; isopropanol; aerodynamic particle sizer; Anderson Cascade Impactor

INTRODUCTION

Micronized drugs are required for different pharmaceutical dosage forms. The bioavailability of poorly water-soluble drug substances like many newly developed pharmaceutically active molecules is a well-known limitation of some drugs. For class II drugs and class IV drugs, according to the biopharmaceutics classification system,[1] the dissolution rate is the limiting factor for the drug absorption rate in human body. In order to achieve a higher solubility or a higher dissolution rate of a drug, several methods are available. A common

Correspondence to: Sohrab Rohani (Telephone: 519-661-4116; Fax: 519-661-3498; E-mail: srohani@uwo.ca)

Journal of Pharmaceutical Sciences, Vol. 99, 1123–1137 (2010)

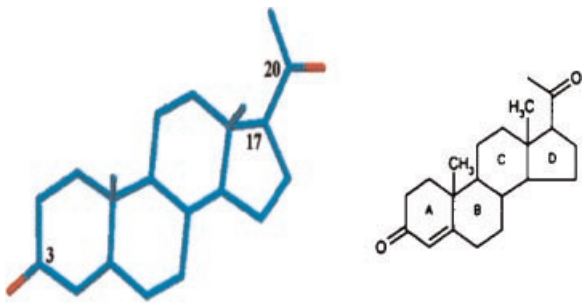
method for increasing the dissolution rate is to ensure a high specific surface area by micronization.[2,3] Furthermore, micronized drug powders are required for pulmonary drug delivery. For pulmonary drug delivery, the drug powder should have a narrow particle size distribution and a mean particle size of 5 μm with nearly no particles larger than 10 μm. Besides the particle size of the single particles, the pulmonary available fraction is determined by the aerodynamic behavior of the drug powder. For a good dry powder inhaler (DPI) formulation, drug particles with low agglomeration tendency, sufficient flow properties (expressed by Carr's index, which is the difference between the true and bulk powder density divided by the true density) and good batch-to-batch conformity are required.[4] The common way for micronization by jet-milling provides only limited opportunity for the control of important product characteristics such as size, shape, morphology, surface properties, and electrostatic charge.[5] Surfaces in mechanically micronized powders are not naturally grown as the crystal cleaves at the crystal face with the smallest attachment energy.[6] The micronization process using mills is extremely inefficient.[7] Due to the high-energy input, crystallinity is decreased[8] and chemical degradation is enhanced.[9,10] As a thermodynamically activated surface[11,12] is created, the surface properties and thus the drug substance properties are altered. The conversion of crystalline solid surfaces to partially amorphous solid surfaces leads to a physical and chemical instability of the micronized drug[13] and its reduced shelf life. Disordered structures in the material influence the processing properties and the performance in formulations.[14–17]

In spite of the development of new processes capable of generating powders for inhalation,[18] crystallization followed by drying and comminution are the established and most extensively used techniques for their manufacture. The popularity of this approach has been attributed to the relative simplicity and ease of scale-up of such methods.[19] Precipitation by antisolvent crystallization represents an attractive approach for the production of respirable particles. Precipitation is a rapid crystallization process characterized by high levels of solute supersaturation, generated by the homogeneous mixing of a solution of an API with an appropriate antisolvent. Generating a molecularly homogeneous solution composition throughout the crystallizer prior to nucleation is difficult at high supersaturation[20] resulting in disperse crystal nucleation and growth rates throughout the crystallizer.[21] Agglomeration and ageing of precipitates may broaden the particle size distribution (PSD) further.[22] Strategies to control the PSD by limiting crystal growth and agglomeration during precipitation include the use of crystal growth inhibiting polymers;[23–25] the use of controlled mixing technologies;[26,27] the application of ultrasound to accelerate diffusion and nucleation;[28,29] and the use of supercritical fluid antisolvent technologies.[18] These approaches, however, demonstrate several major deficiencies. First, the presence of polymeric stabilizing excipients in the final API-containing particles is undesirable. Second, the presence of polymeric stabilizers on the surface of the particles contributes to amorphous content,[24] although crystallization techniques are intended to avoid the generation of amorphous regions. Third, the use of growth inhibitors is highly specific for the molecule being crystallized and is also concentration dependent. All these factors result in further complications when developing an appropriate crystallization process.

Crystallization method in combination with process variables can affect both the nucleation and growth phases of crystallization.[30–32] Hence optimization of the process variables used in the crystallization of an active pharmaceutical ingredient can affect the polymorphic form, crystal size, and crystal habit (macromorphology) of the final crystal.

Progesterone is a naturally occurring chiral steroid (Scheme 1) secreted by the ovary as part of the menstrual cycle. It belongs to the broad category of substances called progestogens (or progestins) and is used in birth control pills and in menopausal hormone replacement therapies. The important pharmacological use of estrogens and progestins is as oral contraceptives.

Progesterone is poorly water-soluble drug. Oral progesterone is almost completely inactivated in



Scheme 1. Molecular structure of progesterone showing the four chiral atoms (C21-C20-C17-C13).