Supercritical Fluid Crystallization of Griseofulvin: Crystal Habit Modification with a Selective Growth Inhibitor

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ABSTRACT: Poly (sebacic anhydride) (PSA) was used as a growth inhibitor to selectively modify habit of griseofulvin crystals formed via the Precipitation with a compressed-fluid antisolvent (PCA) process. PSA and griseofulvin were coprecipitated within a PCA injector, which provided efficient mixing between the solution and compressed antisolvent process streams. Griseofulvin crystal habit was modified from acicular to bipyramidal when the mass ratio of PSA/griseofulvin in the solution feed stream was $\leq$1:1. The habit modification was attributed to the preferential adsorption of PSA to the fastest growing crystal face of the acicular crystal form, which inhibited growth. Scanning electron microscopy (SEM) was used to characterize the griseofulvin and PSA particles, and gave results consistent with a selective growth inhibition mechanism. SEM micrographs showed regions on griseofulvin crystals where PSA microparticles had preferentially adsorbed. X-ray powder diffraction (XRPD) and differential scanning calorimetry (DSC) analysis of the griseofulvin crystals indicated no changes in the crystalline form after the habit modification. Powder compressibility decreased from $49 \pm 3\%$ to $28 \pm 7\%$ with the modification in crystal habit. No change in the physical stability of the processed powder was observed after being stored at 25°C/60% RH and 40°C/70% RH for 23 days. Despite the change in crystal habit, griseofulvin crystals achieved 100% dissolution within 60 min in a simulated gastric fluid. J Pharm Sci 94:2688–2702, 2005

Keywords: supercritical fluids; crystallization; crystal shape; excipients; biodegradable polymers; stability; formulation

INTRODUCTION

A majority of active pharmaceutical ingredients (API's) are administered as solid dosage forms, which are produced by the formulation and processing of powdered solids.[1,2] The success or failure of a formulation is often highly dependent upon the physical properties of the API since the physical properties affect powder flow, bulk handling, ease of compression, and physical stability.[3] Two key characteristics of crystalline solid dosage forms are crystal habit and the crystal size distribution.

Precipitation with a compressed-fluid antisolvent, or PCA, is a technique for precipitating or crystallizing solutes dissolved in liquid solvents by injecting or mixing the solvent system with a compressed or supercritical fluid antisolvent. Two benefits often associated with PCA include single step processing of particulate pharmaceuticals with controlled characteristics,[4,5] and the efficient separation (by decompression) of the antisolvent

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from both the solvent and solid products.[6] When PCA is conducted above the mixture critical point (where complete miscibility between the solvent and antisolvent is exhibited), the precipitation kinetics and resulting product quality can be determined by the rate of mixing between two initially separate fluid streams.[7,8] In order to minimize the effect of imperfect mixing on the precipitation kinetics, the characteristic times for mixing (i.e., macromixing, mesomixing, and micromixing) must be less than the characteristic times for particle nucleation and growth.[9] This requirement is being met through the design and development of injectors[10] that produce a region of high turbulent energy dissipation (i.e., high intensity mixing), and ensure that both process streams pass through the region of high intensity mixing without bypassing.[11]

A consequence of the fast mixing between the two process streams is rapid crystallization, which often results in a crystal habit that is acicular (needle-shaped) or platelike.[12] These crystal habits are a result of the very fast crystal growth rate (resulting from high supersaturation levels) that is obtained. However, acicular and platelike crystal habits are undesirable from a product manufacturing point of view because they have poor powder flow properties,[3] poor filtration characteristics,[13] tendency to cake,[12] and brittleness.[14] Brittle particles often fracture upon handling, which may result in a polydisperse particle size distribution (PSD). Polydisperse PSD's are unfavorable since they adversely affect powder mixing phenomena, provide poor content uniformity, and afford the possibility of particle segregation in mixed materials.[1] Furthermore, pharmaceutical powders with an acicular or platelike habit are typically cohesive and characterized by a high compressibility.[3] A high compressibility is indicative of a powder that is nonfree flowing,[15] which makes product tableting difficult and inefficient.[2] Overall, crystals with these habits may require additional processing steps (e.g., fluid energy milling followed by size classification) in order to achieve the required PSD for a particular formulation.

There are several processing strategies that can be used to modify crystal habit, and thus circumvent the production of unfavorable crystal habits. As described by Mullin,[12] nearly every industrial crystallization has a habit modification procedure in place in order to control the type of crystal habit produced. For example, it is well known that crystal habit may be modified by operating a crystallizer under different levels of supersaturation, crystallizing the solute from different solvents, changing the process temperature, or adding a growth inhibitor to selectively modify crystal habit. Similar to conventional crystallization, changes in the process temperature[8,16,17] and the process solvent[4,18] have resulted in changes in crystal habit during PCA. However, these changes often result in the production of a new polymorph with different physical and chemical properties, which may be unacceptable in the development of a drug formulation. There have been very few reports (if any) concerning the use additives as growth inhibitors to selectively modify crystal habit during PCA. This form of habit modification is unique since crystal habit can be modified without changing the process temperature or pressure (i.e., phase behavior), which often results in the formation of a different polymorph with different physical properties. A report published by Shekunov et al.[19] used structurally similar molecules to alter crystal structure (and hence crystal habit) during PCA. In that instance modification to the crystal structure resulted in a product with different solid state properties. A United States patent application by Hanna et al.[20] describes a method to 'coat' crystals with additives using PCA. However, as shown by the examples within the patent application, their method does not appear to modify crystal habit. We are interested in additives that act as growth inhibitors to modify crystal habit since it is possible to preserve the original crystal structure and retain the same physical and chemical properties of the API.

The present work investigates a method to selectively modify crystal habit through the use of a growth inhibitor when an API is processed using PCA. A goal of this study was to produce a crystal habit that is more suitable for product manufacturing, while retaining the same crystal structure and physical properties of the original material. The model API used in this study was griseofulvin. Griseofulvin is an oral antifungal agent with a very low aqueous solubility, which results in a slow dissolution rate coupled with an erratic and incomplete absorption profile.[21] Griseofulvin is known to crystallize in an acicular habit from methylene chloride solutions when compressed CO_2 is used as the antisolvent in PCA processing.[22,23] The hydrophobic, semicrystalline polymer poly (sebacic anhydride) (PSA) was used as the growth inhibitor. PSA was selected based upon its molecular structure, solubility in the process solvent (and lack of solubility in the