Enabling Tablet Product Development of 5-Fluorocytosine Through Integrated Crystal and Particle Engineering

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ABSTRACT: The antifungal drug, 5-fluorocytosine (FC), is marketed as a capsule (250 or 500 mg strength) instead of the preferred tablet dosage form. Through systematic characterization of solid-state properties, including mechanical properties, we identify tabletability and poor physical stability of FC as the problems that likely have prevented the successful development of a FC tablet product. We then design an FC oxalate 2:1 salt (FCOXA21), based on established relationship between crystal structure and properties, to address these deficient properties. FCOXA21 is subsequently used to develop a direct compression tablet product using predictive and material-sparing powder characterization tools, that is, ring shear cell for powder flowability and compaction simulator for powder tabletability. The initial tablet formulation, which contains 84.5% (wt %) FCOXA21, exhibits excellent tabletability but inadequate flowability. We solve the powder flowability problem through controlling the particle size of FCOXA21. A batch of FCOXA21 tablets (500 mg FC equivalent dose) is then prepared. Finally, systematic evaluation on tablet weight variation, content uniformity, friability, and dissolution using standard methods confirms the commercial manufacturability of FC tablets. Through this work, we have demonstrated the potential of integrated crystal and particle engineering in expediting the development of tablet products of challenging drugs using the economical direct compression process. J Pharm Sci 103:1126–1132, 2014
Keywords: crystal engineering; particle engineering; salt selection; compaction; tablet formulation; 5-fluorocytosine; physical stability; water sorption; dissolution

INTRODUCTION

The antifungal drug 5-fluorocytosine (FC) is a nucleoside analog with activity against Candida and Cryptococcus.[1,2] It has been marketed under the trade name "Ancobon" with a daily dosage ranges 50–150 mg/kg (3.5–10.5 g for a person with 70 kg body weight) administered in divided doses at 6-h intervals.[3] Accordingly, 875–2625 mg of FC must be taken each time for four times per day. Currently, FC is commercially available only in capsules with 250 or 500 mg strengths. To achieve the target dose, a patient has to take three to six capsules each time. This high "pill burden" creates problems in patient compliance and accurate dosing. Larger capsules may be used to reduce the number of capsules that a patient needs to take to receive the desired dose. However, large capsules are difficult to swallow, which still causes poor patient compliance. Another alternative is the tablet. The tablet is smaller than the capsule for delivering the same dose because of their higher density, which is one of the important advantages of tablet over capsule for high-dose drugs. The tablet is preferred also because of its lower manufacturing cost, ability to resist tampering, higher production throughput, and the flexibility with developing a unique product image (tablet shape, size, and color). The decision to market a less desirable capsule dosage form for FC deviates from the standard practice of the pharmaceutical industry, which signals potential problems in developing a commercially viable tablet product.

Common problems that challenge the successful development of a tablet product include deficiency in properties, such as solubility, stability, bioavailability, and mechanical properties.[4] FC has a high aqueous solubility, 15.36 ± 0.01 mg/mL at 23.5°C for its monohydrate. It is rapidly and virtually completely absorbed following oral administration.[1] Since solubility and bioavailability are not the problems that hindered the development of a tablet product of FC, problems in stability and/or mechanical properties should be considered. FC forms a monohydrate when exposed to $\geq$90% relative humidity (RH) at room temperature.[5] The monohydrate converts into an anhydrate at $\leq$30% RH.[5] This susceptibility of FC solid-state forms to environment RH challenges the development of a robust wet granulation process, which is commonly employed for manufacturing tablets of high-dose drugs. Compaction properties of FC have not been reported in the literature. Therefore, our initial efforts focus on examining tabletability of FC to determine whether or not it is another factor that hindered the development of a FC tablet product.

Once potentially deficient pharmaceutical properties of FC are identified, we attempt addressing them following the Materials Science Tetrahedron principle, which highlights the development of engineering strategies for solving a problem based on a clear understanding of the interrelationships among structure, property, and performance of materials.[6] Crystal engineering and particle engineering are two actively pursued tools for solving tablet formulation challenges of problematic drugs. Through solving the challenges hindering the development of a FC tablet product, we aim at demonstrating an efficient approach for expediting tablet product development by integrating both crystal and particle engineering with formulation efforts.

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Table 1. Compositions in a Direct Compression FC Tablet Formulation

Material	%
FCOXA21	84.5
Microcrystalline cellulose	10
Croscarmellose sodium	5
Magnesium stearate	0.5
Total	100

MATERIALS AND METHODS

Materials

5-Fluorocytosine (SINCH Pharmaceuticals, Shanghai, China), oxalic acid (OXA; Sigma–Aldrich, St. Louis, MO), microcrystalline cellulose (Avicel PH102; FMC Biopolymers, Newark, DE), magnesium stearate (Mallinckrodt Inc., St. Louis, MO), and croscarmellose sodium (Ac-di-sol; JRS Pharma, Rosenberg, Germany) were used as received. Bulk powders of the OXA salt of FC, (fluorocytosinium hemioxalate, FCOXA21), were prepared by slowly adding to a 240 mg/mL hot FC aqueous solution a 213 mg/mL OXA aqueous solution at the volume ratio of 5:2 (FC solution to OXA solution). The mixture was subsequently left on the bench undisturbed for approximately 2 h at room temperature. The precipitated salt was filtered and dried in a 50°C oven overnight. One of the filtrates was collected in a vial and allowed to slowly evaporate to form single crystals of FCOXA21. A batch of the saccharin (SAC) salt of FC, (fluorocytosinium saccharinate, FCSAC11), was prepared by suspending a mixture of suitable amounts of SAC and FC in deionized water for 1 week, harvested by filtration, and dried in a 50°C oven.

Tablet formulations containing FCOXA21 were prepared by mixing microcrystalline cellulose as a binder, croscarmellose sodium as a disintegrant, and magnesium stearate as a lubricant at the compositions shown in Table 1.

Methods

Single-Crystal X-ray Diffraction

Single-crystal X-ray diffraction was carried out on a diffractometer (Bruker AXS Inc., Madison, Wisconsin) equipped with an Apex CCD area detector for data collection at 298 K, using MoK_α radiation (graphite monochromator). Data analyses were performed using a suite of software from Bruker, including APEX, SADABS, and SAINT.[7] Crystal structure was solved and refined using Bruker SHELXTL.[8] A direct-methods solution was calculated to provide most nonhydrogen atoms from the E-map. Full matrix least-squares/difference Fourier cycles were performed for locating the remaining nonhydrogen atoms. All nonhydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were located from the difference Fourier map and allowed to ride on their parent atoms in the refinement cycles. Crystal-structure visualization was carried out using Diamond (Version 3.2i; Bonn, Germany).

Powder X-ray Diffraction

Powder X-ray diffraction (PXRD) patterns were obtained on a wide-angle diffractometer (D5005; Bruker AXS) using Cu Kα radiation (45 kV and 40 mA). Each pattern was collected with a step size of 0.02° in the 2θ range of 5°–35° and a dwell time of 0.5 s. PXRD data were plotted using Originlab (v.8; Northampton, Massachusetts).

Thermogravimetry Analysis

In a thermogravimetric analyzer (Model Q50; TA Instruments, New Castle, Delaware), approximately 3 mg of each sample was heated in an open aluminum pan from room temperature to 350°C at 10°C/min under dry nitrogen purge (75 mL/min). Thermogravimetry analysis (TGA) data were analyzed using Universal Analysis 2000 software (TA Instruments).

Hot-Stage Microscopy

Crystals were observed under a polarized light microscopy (Eclipse e200; Nikon, Tokyo, Japan) equipped with a DS-Fi1 microscope digital camera for capturing digital images. Hot-stage microscopy (HSM) experiment was performed, with a heating rate of 10°C/min, on a hot stage (Linkam Scientific Instruments, Ltd., Waterfield, UK) with a temperature controller (Linksys 32; V.2.2.0, Linkam Scientific Instruments, Ltd., Waterfield, UK).

Water Sorption Isotherm

Water sorption and desorption isotherms of powders were obtained at 25°C using an automated vapor sorption analyzer (DVS 1000; Surface Measurement Systems Ltd., Alperton, Middlesex, UK). The nitrogen flow rate was 15 mL/min. At each step of the experiment, the sample was equilibrated at a desired RH with the equilibration criteria of either rate of mass change (dm/dt) $\leq$0.0001%/min or maximum equilibration time of 2 h. The RH was changed to the next target value, at either 5% or 10% RH step size, when one of the criteria was met.

Preparation of Formulated Powders

For small batches (5–10 g), formulation ingredients were thoroughly mixed in a bottle for approximately 5 min. For larger batches (50–100 g), powder mixing was performed using a V-shaped blender (Blend Master; Patterson-Kelley, East Stroudsburg, PA) at 24 rpm for 10 min.

Powder Flowability

Powder flowability was measured using a ring shear cell tester (RST-XS; Dietmar Schulze, Wolfenbüttel, Germany), with a 10-mL cell at the preshear normal stresses of 1, 3, 6, and 9 kPa using the same set of experimental parameters as in a previous study.[9] From the shear cell measurements, flow factors were plotted against major principal stress. On this plot, higher flow factor indicates better flowability.

Powder Compaction

A material testing machine (model 1485; Zwick/Roell, Ulm, Germany) was used to perform bulk powder compaction studies at a speed of 1 mm/s. Powders of FC and its salts were grinded in a mortar using a pestle to reduce particle size. Size of initial powders was not controlled but 125–300 μm sieve cuts were used in later studies. Compaction pressure ranged from 25 to 350 MPa, using a die (round, 8 mm diameter) and flat-faced punches. Punch tips and die wall were coated with a layer of magnesium stearate suspended in ethanol (5%, w/v) using a brush and dried using a fan before each compaction run. Tablets were relaxed under ambient environment for at