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Preparation, Characterization, and Scale-up of Ketoconazole with Enhanced Dissolution and Bioavailability

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ABSTRACT Many new molecular entities targeted for pharmaceutical applications face serious development challenges because of poor water solubility. Although particle engineering technologies such as controlled precipitation have been shown to enhance aqueous dissolution and bioavailability of poorly water soluble active pharmaceutical ingredients, the data available are the results of laboratory-scale experiments. These technologies must be evaluated at larger scale to ensure that the property enhancement is scalable and that the modified drugs can be processed on conventional equipment.

In experiments using ketoconazole as the model drug, the controlled precipitation process was shown to produce kg-scale modified drug powder with enhanced dissolution comparable to that of lab-scale powder. Ketoconazole was demonstrated to be stable throughout the controlled precipitation process, with a residual methanol level below the ICH limit. The modified crystalline powder can be formulated, and then compressed using conventional high-speed tableting equipment, and the resulting tablets showed bioavailability more than double that of commercial tablets. When appropriately protected from moisture, both the modified powder and tablets prepared from the modified powder showed no change in dissolution performance for at least 6 months following storage at accelerated conditions and for at least 18 months following storage at room temperature.

KEYWORDS Solubility, Particle engineering, Precipitation, Ketoconazole, Solubilization, Dissolution, Bioavailability, Scale-up, Tablets, Powder, Residual solvents

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INTRODUCTION

Many new molecular entities (NME) targeted for pharmaceutical applications face serious development challenges because of poor water solubility. Even if the potential efficacy of an NME is very high, in vivo performance will be low if the orally administered drug cannot dissolve in the gastrointestinal tract. One way to address this problem is to increase the surface area of the drug by reducing particle size. Commercial processes that reduce particle size include mechanical milling, freeze-drying, spray-drying, solid dispersion,

and recrystallization (Dressman & Reppas, 2000; Pace et al., 1999; Rogers et al., 2001; Serajuddin, 1999; Tom & Debenedetti, 1991). However, these particle reduction processes have limitations that affect drug particle stability and powder flow, among other properties. In addition, reduction of particle size down to the desirable nanoparticle range is difficult using these processes (Merisko-Liversidge et al., 2003; Rogers et al., 2001; York, 1999).

Recent studies and reviews have shown that particle engineering technologies increase the surface area of poorly water soluble active pharmaceutical ingredients (API) by reducing particle size to the nanoparticle range, thereby enhancing aqueous dissolution and bioavailability (Brigger et al., 2002; Cavalli et al., 2001; Cherian et al., 2000; Connors & Elder, 2004; Delie, 1998; Dressman & Reppas, 2000; Hoffart et al., 2002; Hu et al., 2004; Merisko-Liversidge et al., 2003; Muller & Peters, 1998; Pace et al., 1999; Rambali et al., 2003; Rogers et al., 2001; Rojanapanthu et al., 2003; Santhi et al., 1999; Serajuddin, 1999; Subramaniam et al., 1997; Tom & Debenedetti, 1991; York, 1999). Processes include mechanical micronization techniques, supercritical fluid processes, cryogenic spraying, solvent evaporation, and controlled precipitation. This study focuses on controlled precipitation, in which the drug is dissolved in a suitable solvent then precipitated into an aqueous solution in the presence of crystal growth inhibitors to form drug nanoparticles (Connors & Elder, 2004; Rogers et al., 2004; Elder et al., 2006). Particles prepared by controlled precipitation have the advantage of a narrower particle size distribution as compared to particle size reduction technologies, such as wet-milling. The process is fast and continuous, and levels of residual solvents are low. The excipients used are pharmaceutically acceptable.

Although controlled precipitation and other particle engineering technologies have been shown to be effective at a laboratory scale, the pharmaceutical industry lacks published data demonstrating that they can be scaled up to make large quantities of modified drug for production and that the kg-scale modified drug can be formulated into final dosage forms using conventional high-speed equipment.

The objectives of this study were to determine if

- Controlled precipitation particle engineering technology can be scaled up to produce kilogram quantities of modified API.
- Modified API produced at kilogram quantities has enhanced dissolution and bioavailability that are significantly better than the commercial API.
- Modified API produced at kilogram quantities can be formulated to produce tablets using conventional high-speed tableting equipment.

The model drug was ketoconazole, an azole antifungal drug with an aqueous solubility of 0.017 mg/mL at 25°C. Absorption is pH-dependent with bioavailability decreasing at higher pH and 75% rapid absorption at low pH. Initial half-life is 2 hr; terminal half-life is 8 hr.

MATERIALS AND METHODS

Materials

Ketoconazole USP was obtained from Spectrum Chemical Manufacturing Corporation (Gardena, CA) and is referred to as "as-received" ketoconazole in this paper. Commercial ketoconazole tablets were obtained from Janssen Pharmaceutica (Janssen-Ortho, Lot # 93P0241E, Titusville, NJ). Polyvinylpyrrolidone (PVP K30, Aldrich Chemical Company, Inc., Milwaukee, WI) and polyvinylalcohol (PVA 13–23k, Aldrich Chemical Company, Inc., Milwaukee, WI) were used as crystal growth inhibitors to stabilize the ketoconazole particles. Other materials included microcrystalline cellulose (NF, Avicel PH-102, FMC BioPolymer, Newark, DE), lactose monohydrate (NF, modified spray-dried, Fast-Flo 316, Foremost Farms, Rothschild, WI), crospovidone (BASF Aktiengesellschaft, Ludwigshafen, Germany), croscarmellose sodium (NF, Ac-Di-Sol, FMC Corporation, Philadelphia, PA), colloidal silicon dioxide (Cabot, Tuscola, IL), magnesium stearate (NF, impalpable powder, Mallinckrodt Baker Inc., Paris, KY), and methanol (Fisher Scientific, Hanover Park, IL).

Controlled Precipitation Process

Figure 1 illustrates the controlled precipitation process. Ingredients for both laboratory- and kg-scale experiments were as-received ketoconazole (53%), PVP K30 (27%), and PVA 13–23k (20%). Lab-scale (100–540 g) controlled precipitation experiments were carried out in batch mode with mixing zone temperatures equilibrated at 3, 25, and 50°C. The organic feed

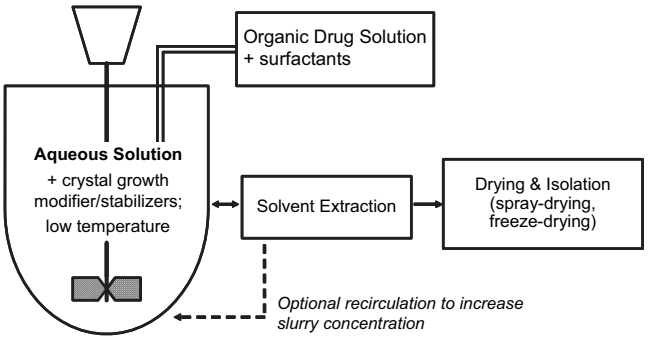

FIGURE 1 **Process diagram for controlled precipitation. Used with permission (Elder, 2006).**

was prepared by dissolving ketoconazole in methanol (4 to 5% solution). The crystal growth inhibitors were dissolved in the aqueous phase. The organic:aqueous phase ratio was 1:5 (w/w). The organic and aqueous feeds were introduced into the mixing zone to produce stabilized API particles. For the kg-scale process, 2 kg of stabilized ketoconazole particles was produced via continuous controlled precipitation with the mixing zone temperature equilibrated at 3°C.

Following batch-mode, lab-scale controlled precipitation; methanol in the slurries was reduced to less than 1% (w/w) using a semicontinuous vacuum distillation process. For less than 500 g lab-scale batches the solvent-stripped slurries were then collected and subsequently frozen in a dry-ice/acetone bath. The frozen slurries were then lyophilized using a VirTis BT4KEL manifold lyophilizer (VirTis Company, Gardiner, NY). The dry particles were removed from the lyophilizer after 24–48 hr with resulting yields of 86–95%. For the 540 g lab-scale batch, the solvent-stripped slurry was isolated by spray-drying as described below for the scale-up batches. This initial isolation trial resulted in a 78% yield.

Following continuous kg-scale controlled precipitation, methanol in the slurry was stripped using a pilot-scale vacuum distiller. The solvent-stripped slurry was then collected and spray-dried using a Mobile Minor Spray Dryer (Niro A/S, Soeborg, Denmark) with a 0.8 m inner diameter (I.D.) chamber. The inlet and outlet temperatures were maintained at 145 and 65°C, respectively, and the aqueous slurry was atomized through a two-fluid nozzle at a feed rate of 45 mL/min. The dry particles were harvested from the collection chamber located beneath the cyclone portion of the spray dryer. Overall process yield for this first kg-scale trial was 73%. Ketoconazole particles produced using controlled precipitation technology are referred to in this paper as modified ketoconazole powder.

Preparation of Physical Blend Control Powder

The as-received ketoconazole and excipient powders were blended together for approximately 2 min in a glass vial, which was at least three times the volume of the powder, using the same drug-to-excipient ratios as for the controlled precipitation process described above. The powders were blended in a WAB Turbula System Schatz mixer (Willy A. Bachofen AG Maschinenfabrik, Basel, Switzerland) for 1 min. The Turbula mixer was then stopped, and the powders were tapped and hand-shaken for 1 min. This procedure was repeated once more to ensure that the powders were uniformly blended. Ketoconazole powder produced by this mixing process is referred to in this paper as physical blend control powder.

Powder Characterization

Potency Assay

Determination of the amount of ketoconazole per mg of kg-scale modified ketoconazole powder was performed using a diode array 8425A spectrophotometer (Hewlett-Packard, Palo Alto, CA) at 223 nm. A 12-mg aliquot of powder was dissolved in 25 mL of internal standard solution. The internal standard solution was prepared by dissolving 0.35 g of benzophenone in 1 L of acetonitrile. The absorbance detection of each sample was measured in triplicate.

Residual Solvent Analysis

Calibration standards were prepared by weighing approximately 50–60 mg of solvent into a 25 mL volumetric flask partly filled with *N,N*-dimethyl formamide (DMF). DMF was then added to make a total volume of 25 mL. The solvent stock solution was diluted 1–25 mL with DMF. Samples of kg-scale modified ketoconazole powder were prepared by weighing approximately 100 mg of sample and dissolving each in 1.0 mL of DMF. Aliquots of 1.0 μL each of the standards and samples were injected into a 60 m × 0.32 mm × 1.0 μm film (14% cyanopropylphenyl) methyl silicone column (DB-1701, J&W Scientific, Division

of Agilent Technologies, Palo Alto, CA). An Agilent 6890A GC chromatograph equipped with ChemStation data collection software and a 7683 Series autosampler (injector type: split, 200°C) was used to analyze the standards and samples. The flame ionization detector was set at 275°C. The oven was programmed to hold at 50°C for 1 min, then ramp at 25°C/min to 225°C, and hold for 2 min. Helium was used as the carrier gas (20 psig, 32 cm/s, split ratio: 20:1).

Crystallinity (X-ray Diffraction)

The as-received ketoconazole was mixed with 50% (w/w) alumina powder. The lab-scale modified ketoconazole powder and physical blend control powder were each blended with 10% alumina powder. The alumina powder served as an internal standard. The samples were then leveled and analyzed by X-ray diffraction.

X-ray diffraction was performed using a Siemens D-500 automated diffractometer equipped with a cobalt X-ray tube and a position-sensitive detector. The incident beam was collimated using a 1.0° divergence slit, and data points were collected from 5 to 55° 2θ at a rate of 0.5°/min with a step width size of 0.02° 2θ. The XRD patterns were analyzed using Jade XRD pattern processing software (Version 6, Materials Data, Inc., Irvine, CA).

Particle Size Distribution (Coulter Counter)

Samples of as-received ketoconazole, the physical blend control, and lab-scale modified ketoconazole powder were reconstituted to form a 1% (w/w) suspension in deionized (DI) water, vortexed for 40 s, and sonicated for 3 min. Particle size distribution was measured by laser light diffraction using an LS230 Small Volume Plus Coulter Counter (Beckman Coulter Corporation, Fullerton, CA). The dispersed powder was added to the sampling chamber, which was filled with DI water under constant agitation until a polarized intensity differential scattering (PIDS) obscuration of 45–55% was achieved. The DI water was presaturated with drug to prevent a reduction in PIDS obscuration that would have indicated drug dissolution occurring in the chamber. Once the desired obscuration was attained, particle size analysis was performed using a polystyrene latex optical model.

Surface Morphology (Scanning Electron Microscopy)

A JEOL 6320 field emission scanning electron microscope (JEOL USA, Peabody, MA) operating at 5 keV, a current setting of 3, and a working distance of 16 mm were used to obtain SEM photomicrographs of as-received ketoconazole, the physical blend control, and lab-scale modified ketoconazole powder. Prior to SEM analysis, the samples were dispersed onto a carbon-tape-coated aluminum stub, and then coated with approximately 20 nm of a gold-palladium mixture.

Drug Dissolution

Dissolution testing was performed on as-received ketoconazole, the physical blend control, and lab- and kg-scale modified ketoconazole powder using the USP 27 Apparatus 2 (paddle) method (Distek Dissolution System 2100C with a TCS0200C heater/circulator, Crescent Scientific Pvt. Ltd., Goregaon-East, Mumbai, India). Powder containing approximately 10–20 mg of active was weighed and placed into 900 mL of dissolution media. An aqueous solution consisting of 0.3 or 0.5% (w/v) sodium dodecyl sulfate (SDS) was used to characterize the dissolution of ketoconazole. Paddle speed and bath temperature were set at 50 rpm and 37.0 ± 0.2°C, respectively. Five-milliliter samples were collected at 2, 5, 10, 15, 20, 25, 30, and 60 min in replicates of 6 ($n = 6$) by a Distek Dissolution Sampling System. After the 60 min samples were collected, the paddle speed was increased to 200 rpm, and final samples were taken at 120 min to confirm complete API dissolution. Sink conditions were maintained throughout the dissolution testing period.

Dissolution results were determined by high-performance liquid chromatography (HPLC). Samples for HPLC analysis were filtered through 0.45 μm Acrodisc GHP syringe filters (Pall Corporation, Ann Arbor, MI), and aliquots of 20 μL were injected into a PerkinElmer liquid chromatograph (PerkinElmer, Inc., Wellesley, MA) equipped with a Zorbax Bonus–RP Rapid Resolution reverse-phase column (4.6 × 75 mm, 3.5 μm pore size, Agilent Technologies, Palo Alto, CA) and a Zorbax Bonus–RP analytical guard column (4.6 × 12.5 mm, 5.0 μm). The reverse-phase and guard columns were maintained at 30°C. Ketoconazole was detected at an ultraviolet (UV) absorbance of 223 nm and eluted at 1.3 min when running mobile phase (45% acetonitrile/55% ammonium acetate in water (2 g/L)) at 2.0 mL/min.

One-way analysis of variance (ANOVA) was used to determine statistically significant differences between dissolution results; p values < 0.05 were considered statistically significant.

Long-Term Storage

Modified ketoconazole powder was packaged in sealed 60 mL Qorpak clear glass vials, each containing a desiccant packet (Indicating Humidity Sponge, VWR Scientific Corporation, West Chester, PA). Samples were tested for drug dissolution as described above after 6, 12, and 18 months storage at 25°C and 60% relative humidity (RH) and after 6 months at 40°C and 75% RH (U.S. Food and Drug Administration (FDA), 1998). Dissolution was selected as the performance indicating test based on preliminary screening of modified powders directly exposed to moisture. Samples evaluated in this manner showed significantly reduced dissolution at earlier time points than changes were observed in any other stability tests conducted.

Tablet Preparation

The modified ketoconazole powder or physical blend control powder was screened through a 20-mesh stainless steel sieve along with the other excipients listed in Table 1 (except magnesium stearate) and blended in a 4 qt (lab-scale) or 8 qt (kg-scale) V-shell blender (Patterson-Kelly, division of Harsco Corporation, East Stroudsburg, PA) at 25 rpm for 20 min. The magnesium stearate was screened through a 30-mesh stainless steel sieve, and then added to the blender. Mixing continued for 5 min at 25 rpm.

TABLE 1 **Formulation for tablets prepared from modified ketoconazole powder or physical blend control powder**

Ingredients	Amount (%)
Modified ketoconazole powder or physical blend control powder	42
Microcrystalline cellulose pH 102	40
Lactose	7.2
Crospovidone	5
Croscarmellose Na	5
Colloidal silicon dioxide	0.3
Magnesium stearate	0.5

Tablets were compressed on a 16-station Manesty Betapress (Thomas Engineering, Inc., Hoffman Estates, IL) instrumented with "The Director" data acquisition and analysis system (Speciality Measurements Inc., Lebanon, NJ), equipped at two operating stations with plain oval 0.7078-inch×0.4921-inch tooling, and operated at 12.2 rpm. Compression forces ranging from 3.8–9.7 kN were used to produce tablets of varying hardness. Tablets contained 200 mg modified ketoconazole.

Tablet Characterization

Physical Properties

Tablets were tested for weight, hardness, and drug dissolution. The hardness or crushing strength of 20 randomly chosen tablets from each granulation experiment was measured using a Schleuniger 8M hardness tester (Dr. Schleuniger Pharmatron AG, Manchester, NH). The weight of each tablet was measured to ensure weight variation was within acceptable USP limits (USP, 2004). Drug dissolution was performed using a method similar to that described above for powder, except tablets were added directly to the dissolution media as opposed to the weighed amount of powder.

Long-Term Storage

Tablets prepared from modified ketoconazole powder were prepared for long-term stability testing as described above for powders. Samples were tested for drug dissolution as described above for tablets after 6, 12, and 18 months storage at 25°C and 60% relative humidity (RH) and after 6 months at 40°C and 75% RH. (FDA, 1998).

In Vivo Bioavailability

A single-dose, oral, relative bioavailability study was conducted in six healthy adult beagle dogs to compare tablets containing modified ketoconazole powder, tablets containing as-received ketoconazole, and commercially available tablets. The study design was a randomized three-way crossover with a 7-day washout period between doses.

The beagles were fasted for 16 hr prior to dosing. Tablets were placed in the oropharyngeal region of the canine mouth, the head was tilted upward, and the throat massaged to promote swallowing. Water was administered from a squeeze bottle to further facilitate

swallowing. Animal pens were monitored for signs of tablet regurgitation to confirm dosing. Dogs were permitted free access to food approximately 3 hr following tablet administration.

Serial blood samples (3 mL) were collected immediately prior to dosing, then 0.5, 1, 2, 4, 8, 12, and 24 hr following dosing. Blood was drawn into heparanized tubes using a double-pointed 21 G needle in a plastic tube collection device (Vacutainer) directly from the jugular (preferred) or cephalic vein.

Sample preparation for bioanalysis included centrifugation of collection tubes at 3000 rpm for 5 min and removal of ~250 mg aliquot of plasma, which was added to a tared vial containing extraction solvent and internal standard. The vial was immediately vortexed, frozen on dry ice, and stored for up to 1 week at – 80°C until analysis by liquid chromatography/mass spectroscopy/mass spectroscopy (LC/MS/MS).

Individual plasma concentration-time profiles were analyzed by a noncompartmental method using WinNonlin (Pharsight Corp., Cary, NC) to obtain the area under the concentration time curve (AUC), plasma elimination half-life ($t^1/_2$, β), and mean residence time (MRT). Mean plasma concentration-time profiles were also fitted to a one-compartment model to obtain predicted peak plasma concentration (C_{max}) and predicted time to maximum plasma concentration (T_{max}).

RESULTS AND DISCUSSION

Powder Characterization

Potency Assay

The assayed potency of the kg-scale modified ketoconazole powder was similar to the targeted potency, showing ketoconazole to be stable throughout the controlled precipitation process (Table 2).

Residual Solvent Analysis

The residual methanol level of the kg-scale modified ketoconazole powder (Table 2) was below the ICH residual limit for methanol of 3000 ppm (FDA, 1997), showing at the kg scale that desired solvent levels can be achieved. Residual methanol levels measured in lab-scale batches were in the range of 390 ppm–670 ppm. The slightly lower residual levels observed for lab-scale batches were attributed to the lower volume-to-surface area of the lab-scale vacuum distillation apparatus, which was more efficient at removing solvent, as compared to the pilot-scale system employed for this study.

TABLE 2 Assay of kg-scale modified ketoconazole powder (kilogram scale)

Assayed Potency (%)	Targeted Potency (%)	Residual Methanol (ppm)	ICH Residual Methanol Limit (ppm)
52.9	52.6	1017	3000

Crystallinity

The X-ray diffraction analysis showed no significant differences between the as-received ketoconazole (Fig. 2a), the physical blend control (Fig. 2b), the lab-scale modified ketoconazole powder (Fig. 2c) and the kg-scale modified ketoconazole powder (Fig. 2d).

Particle Size Distribution

There was a slight decrease in mean particle size of the physical blend control as compared to the as-received ketoconazole, which is attributed to contributions from the excipients (Table 3). The particle size of the lab-scale and kg-scale modified ketoconazole powder was significantly smaller than both the as-received ketoconazole and the physical blend control. In addition, the particle size distribution was much narrower as a result of the rigid processing controls employed with the controlled precipitation technology.

Surface Morphology

SEM images of the as-received ketoconazole indicated crystalline, irregular-shaped particles approximately 10–50 μm in diameter (Fig. 3a). The SEM of the physical blend control showed irregular-shaped particles imbedded in a smooth polymer matrix (Fig. 3b). The SEM of the kg-scale modified ketoconazole powder clearly indicated the more uniform co-processed agglomerates of nanostructured particles and polymer stabilizer (Fig. 3c).

Drug Dissolution

Figure 4 shows the drug dissolution of as-received ketoconazole, the physical blend control, and lab-scale and kg-scale modified ketoconazole powder. Both the lab-scale and kg-scale modified ketoconazole powders showed significant improvement in dissolution

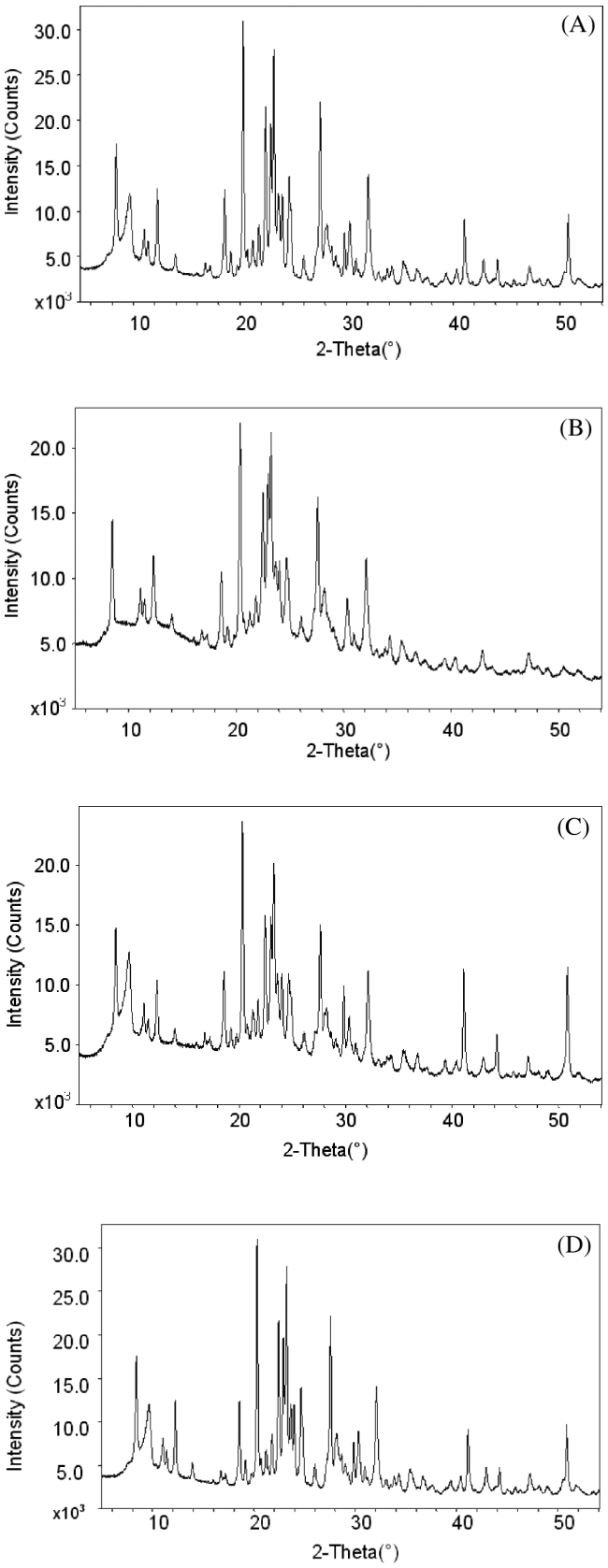

FIGURE 2 X-ray diffraction analysis of as-received ketoconazole (a), physical blend control (b), lab-scale modified ketoconazole powder (c) and kg-scale modified ketoconazole powder.

TABLE 3 Particle size distribution of as-received ketoconazole, physical blend control, lab-scale modified ketoconazole powder and kg-scale modified ketoconazole powder

Material	Mean (μm)	D10 (μm)	D50 (μm)	D90 (μm)
As-received	38.5	5.90	24.6	87.0
Physical blend	24.1	4.24	19.5	51.1
Lab-scale modified powder	1.89	0.36	1.23	3.24
kg-scale modified powder	2.12	1.20	1.92	3.16

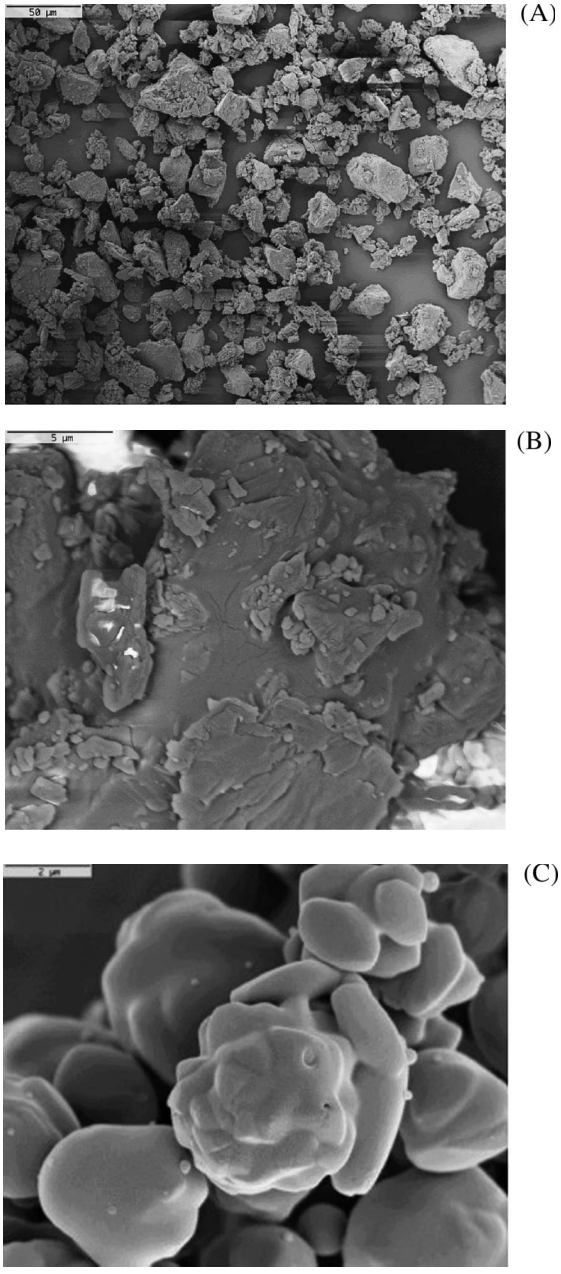

FIGURE 3 Scanning electron microscopy showing surface morphology of as-received ketoconazole (a), physical blend control (b), and kg-scale modified ketoconazole powder (c).

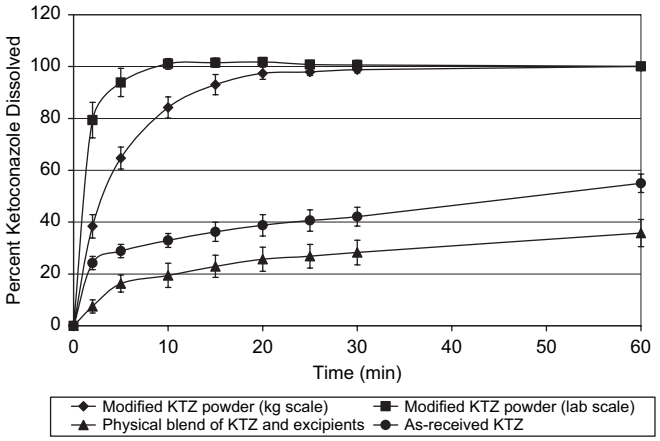

FIGURE 4 **Dissolution of as-received ketoconazole, physical blend control, and modified lab- and kg-scale ketoconazole powder (USP 27, Apparatus 2, 0.5% SDS in water, n = 6).**

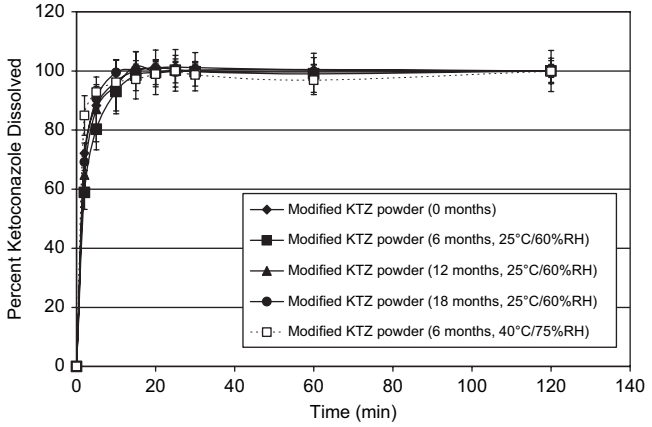

FIGURE 5 **Room temperature and accelerated stability of kg-scale modified ketoconazole powder (USP 27, Apparatus 2, 0.3% SDS, n = 6).**

rate and extent compared to the as-received ketoconazole. The physical blend showed a slightly slower dissolution compared to as-received powder as a result of the powder/excipient mixture failing to adequately disperse in the dissolution vessel.

Long-Term Storage

Figure 5 shows the results of storing kg-scale modified ketoconazole powder for 6, 12, and 18 months at 25°C and 60% RH and for 6 months at 40°C and 75% RH. When modified ketoconazole powder was protected from moisture, neither room-temperature nor accelerated conditions had a significant effect on drug dissolution.

Tablet Characterization

Physical Properties

Table 4 lists the physical properties of tablets produced from as-received ketoconazole, lab-scale and kg-scale modified ketoconazole powder, as compared to commercial ketoconazole tablets. The kg-scale tablets had better hardness than the tablets prepared from as-received ketoconazole and lab-scale modified ketoconazole and, as a result, they had improved friability. Ideally, a friability target of ≤0.1% is desired, but the obtained friability of 0.15% for the kg-scale tablets was deemed to be adequate. The disintegration time was not affected by the increased hardness of the kg-scale tablets. Compared to the commercial tablets, the three trial formulations had substantially higher tablet weight due to incorporation of stabilizing polymer during manufacturing of the modified ketoconazole and the use of a non-optimized tablet formulation for this trial. The kg-scale tablets had a higher hardness and correspondingly slower disintegration time than the commercial tablets; however, as described below, they still achieved superior in vitro (dissolution) and in vivo (bioavailability) performance.

Dissolution Testing

Drug dissolution of kg-scale tablets prepared from modified powder at time 0 (Fig. 6) was slightly slower than that of the modified powder itself at time 0 (Fig. 5), which would be expected because of the additional time required to dissolve the tablets. Figure 7 shows dissolution profiles for tablets prepared from kg-scale modified ketoconazole powder compared to commercial tablets and formulated as-received ketoconazole. The kg-scale modified ketoconazole tablets showed the fastest and complete dissolution.

Long-Term Storage

Figure 6 shows the results of storing kg-scale modified ketoconazole tablets for 6, 12, and 18 months at 25°C and 60% RH and for 6 months at 40°C and 75% RH. When tablets prepared from modified ketoconazole were protected from moisture, neither room-temperature nor accelerated conditions had a significant effect on drug dissolution.

TABLE 4 **Physical properties of tablets produced from lab-scale and kg-scale modified ketoconazole powder, ketoconazole as received and commercial ketoconazole tablets**

Property	Lab Scale	Kg-Scale	As-received	Commercial Tablets
Compression force (kN)	6.15	7.24	6.25	n/a
Average weight (mg)	900	900	900	300
Weight range (mg)	890 – 900	870 – 910	890 – 905	299 – 305
Average hardness (kp)	9.6	12	9.9	7.3
Hardness range (kp)	8.5 – 11.0	10.5 – 13.5	8.9 – 12.0	7.0 – 7.4
Friability (%)	1.24	0.15	1.06	0.76
Disintegration time (min)	13.0 – 17.0	9.5 – 14.5	10.2 – 18.7	2.5 – 3.2

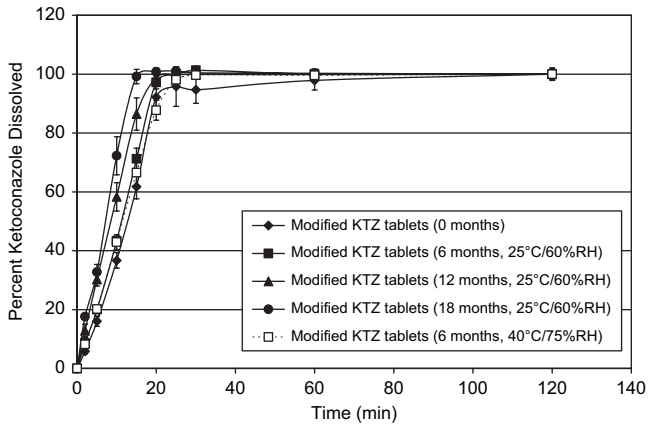

FIGURE 6 **Room temperature and accelerated stability of tablets prepared from kg-scale modified ketoconazole powder (USP 27, Apparatus 2, 0.3% SDS, n = 6).**

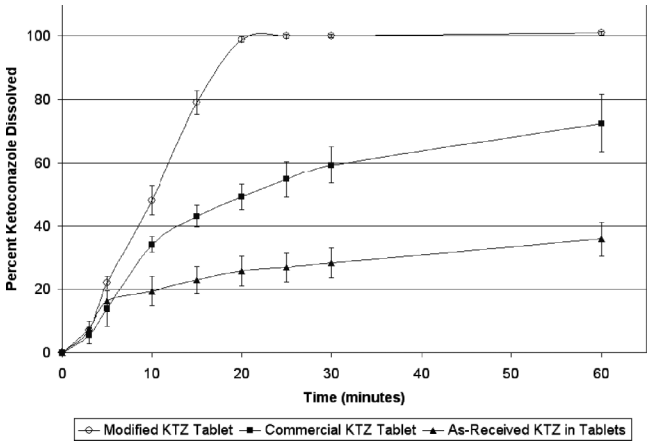

FIGURE 7 **Dissolution of tablets prepared from kg-scale modified ketoconazole powder compared to commercial tablets and formulated as-received ketoconazole.**

In Vivo Bioavailability

Figure 8 shows the mean blood level of ketoconazole in male beagle dogs, comparing tablets containing ketoconazole modified by controlled precipitation, commercial ketoconazole tablets, and tablets formulated with as-received ketoconazole. Comparisons were based on 200 mg ketoconazole per dose. The oral bioavailability, as indicated by the area under the blood level versus time curve, of the tablet containing modified ketoconazole was more than double that of the identically formulated tablet containing as-received drug or the commercial product.

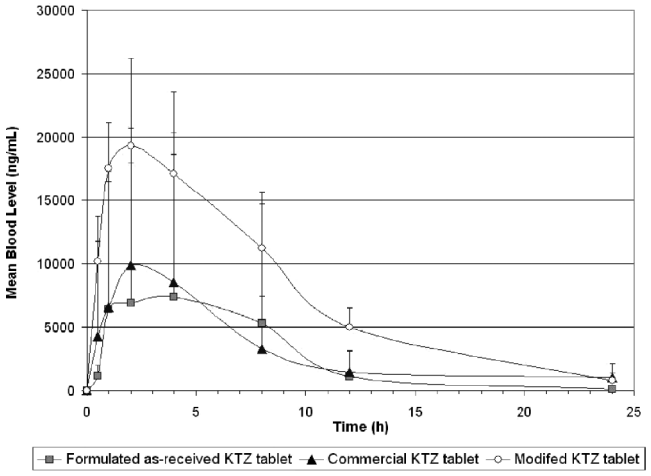

FIGURE 8 **Mean blood level of ketoconazole from tablets prepared from kg-scale modified ketoconazole powder compared to commercial tablets and formulated as-received ketoconazole. (adapted from Connors & Elder, 2004).**

Table 5 lists the pharmacokinetic parameters for tablets prepared from modified ketoconazole powder prepared at the kg-scale compared to commercial tablets and formulated as-received ketoconazole. The modified ketoconazole tablets showed higher AUC, C_{max}, and MRT. Lower variability was observed for both AUC and C_{max}. The t_{max} of modified ketoconazole and commercial ketoconazole tablets were slightly shorter than the as-received ketoconazole tablets. Based on the markedly faster rate of absorption, the modified ketoconazole tablets would be expected to have a shorter t_{max}

TABLE 5 **Pharmacokinetic data from beagle dogs comparing ketoconazole tablets prepared from kg-scale modified ketoconazole powder, commercial ketoconazole tablets and tablets formulated with as-received ketoconazole**

	T_{max} (hr)		C_{max} (ng/ml)		AUC24 (ng/ml/hr)		$t_{1/2}$ (hr)		MRT (hr)	
Tablet Formulation	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
As-received KTZ tablets	2.00	1.41	7754	12711	68515	122058	3.34	1.00	4.58	1.13
Commercial KTZ tablets	1.50	0.58	9973	10741	72642	86769	2.89	0.23	4.72	0.96
Modified KTZ tablets	1.50	0.58	18473	5063	177814	28117	4.44	2.09	6.64	1.07

compared to the commercial tablets; however, since the C_{max} achieved is approximately double the commercial tablets, the t_{max} for the modified ketoconazole tablets was equivalent. The $t_{1/2}$ was longer, but more variable, for the modified ketoconazole tablets than for the other formulations. In addition, comparison of Fig. 7 and 8 shows good in vitro–in vivo correlation.

CONCLUSIONS

The controlled precipitation process was shown to produce kg-scale ketoconazole powder with enhanced dissolution comparable to that of lab-scale powder. Ketoconazole was stable throughout the controlled precipitation process, with a residual methanol level below the ICH limit. The modified crystalline powder can be formulated, then compressed using conventional high-speed tableting equipment, and the resulting tablets showed bioavailability more than double that of commercial tablets. When appropriately protected from moisture, both the modified powder and tablets prepared from the modified powder showed no change in dissolution performance for at least 6 months following storage at accelerated conditions and for at least 18 months following storage at room temperature.

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