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Stabilizer choice for rapid dissolving high potency itraconazole particles formed by evaporative precipitation into aqueous solution

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Abstract

The objective of this study was to investigate the influence of stabilizer type on the physicochemical properties, including dissolution, of ultra-high potency powders containing itraconazole (ITZ) formed by evaporative precipitation into aqueous solution (EPAS). ITZ was dissolved in dichloromethane, which was then atomized through a heated coil at 80 °C into an aqueous solution over precise periods of time. Stabilizers were present in either the aqueous, organic or both phases. The dispersions were centrifuged and the supernatant was removed. Three hydrophilic stabilizers were investigated, including polysorbate 80, polyvinyl pyrrolidone and poloxamer 407. Rapid dissolving ultra-high potency of ITZ powders was successfully produced. Greater than 80% of ITZ was dissolved in 5 min compared to only 13% of ITZ bulk powders. The resulting stabilizer-coated drug particles had high drug-to-stabilizer ratios greater than 12, corresponding to potencies (wt drug/wt drug + wt surfactant) as high as 93%. An increase in dissolution rate was correlated with the amount of stabilizer adsorbed and the wettability. The combination of polysorbate 80 and poloxamer 407 present in the aqueous and organic phases, respectively, was superior in achieving high wetting and rapid dissolving ITZ powders. The ability to control the adsorption behavior of stabilizers by using synergistic combinations affords the opportunity to achieve high dissolution rates with higher potencies compared to previously reported values.
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Keywords: Itraconazole; Particle stabilization; Stabilizer; EPAS; Stabilizer adsorption

1. Introduction

Itraconazole (ITZ) is an orally active triazole antifungal agent with a potent broad spectrum of activity against *Candida* species and *Aspergillus* species which are the two most common human fungal pathogens

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(Jain and Sehgal, 2001). It has a molecular formula $C_{35}H_{38}Cl_2N_8O_4$ and molecular weight of 705.64. ITZ is categorized as a Class II compound by the Biopharmaceutics Classification System (BCS), and is water insoluble (solubility ~ 1 ng/mL at neutral pH) but highly permeable (Amidon et al., 1995). This compound is a weak base ($pK_a = 3.7$) and reportedly has an octanol:water partition coefficient (log *P*) of greater than 5 at pH 6 (Peeters et al., 2002). ITZ was chosen as the model drug for this study due to its low solubility and poor wetting in water, and hence low and variable bioavailability (Woestsnborghs et al., 1989). There have been many attempts to improve the bioavailability and dissolution rate of poorly water-soluble drugs like ITZ. These include reducing the particle size by mechanical means to increase surface area (Kubo et al., 1996), solubilization in surfactant systems (Martis et al., 1972; Rees and Collett, 1974), formation of water-soluble complexes (Cassella et al., 1998) and manipulation of solid state of the drug substance by inhibiting crystallization to form amorphous particles (Leuner and Dressman, 2000). Particle size reduction is a promising way to increase dissolution rates of poorly water-soluble drugs (Hu et al., 2004; Rogers et al., 2001).

Evaporative precipitation into aqueous solution (EPAS) is a particle engineering technology reported to produce submicron to micron-sized drug particles stabilized by surfactants or polymers and dispersed in an aqueous medium (Sarkari et al., 2002; Chen et al., 2002, 2004a). During processing, drug dissolved in an organic solvent is sprayed through an atomizing nozzle into an aqueous solution containing a hydrophilic stabilizer to produce an aqueous dispersion (Fig. 1). Rapid evaporation of the organic solvent at elevated temperature produces very high supersaturation and rapid precipitation of the drug in the form of suspended particles. The particles may be stabilized by a variety of stabilizers present in either or both the organic and aqueous phases. The stabilizers adsorb onto the newly formed drug particle surfaces consequently decreasing the surface energy and providing steric and/or electrostatic repulsion between particles. This process may be dictated by the thermodynamic and kinetic aspects of stabilizer adsorption: the stabilizer must adsorb on the newly created surface and attain a conformation that is conducive to steric stabilization. The primary objective of this study is to prepare rapid dissolving ultra-high potency ITZ powders by the EPAS process. We desire to have extremely high drug-to-stabilizer ratios greater than 12, corresponding to potencies (wt drug/wt drug + wt surfactant) above 90%. In a previous study, Chen et al. (2004b) reported potencies of ITZ produced by the EPAS process ranging from 40 up to only 72%. We believe that by choosing the optimal stabilizer type, and by optimizing the phase that the stabilizer is present in, that even higher potencies can be achieved for highly wettable and rapidly dissolving

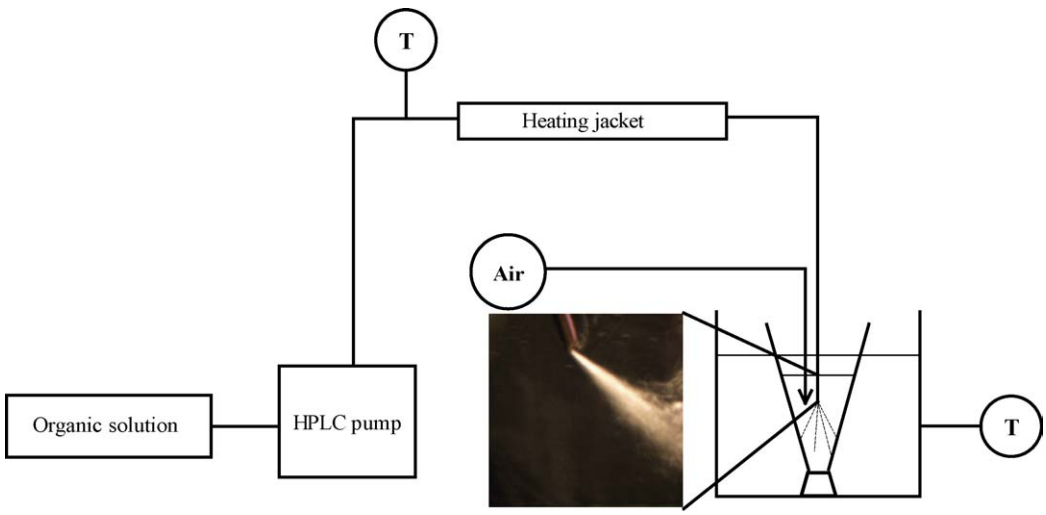

Fig. 1. Schematic representation of EPAS process and the photograph showing intense atomization of the spray.

ITZ powders. It is challenging to increase the drug-to-stabilizer ratio to values of up to 12, while at the same time maintaining high surface areas, stabilized particles with enhanced wetting and high dissolution rates. We hypothesize that the ultra-high potency ITZ powders, greater than those reported by Chen et al., with low levels of adsorbed stabilizer can be produced by an optimum choice of stabilizer(s) which can adsorb very rapidly onto the ITZ particle surfaces during the very short spray times employed in the EPAS process. The very small amount of adsorbed stabilizers was sufficient to form a hydrophilic layer on the particle surface resulting in increased particle wettability and dissolution.

2. Materials and methods

2.1. Materials

ITZ was purchased from Hawkins Inc. (Minneapolis, MN). The stabilizers including a non-ionic surfactant (polysorbate 80; MW = 1310) and a homopolymer; polyvinyl pyrrolidone (PVP K-15, MW = 15,000) were purchased from Spectrum Chemicals (Gardena, CA). The polyoxyethylene–polyoxypropylene copolymer (poloxamer 407, MW = 11,700) was purchased from BASF (Mount Olive, NJ). HPLC grade acetonitrile was obtained from EM Industries Inc. (Gibbstown, NJ) and dichloromethane was purchased from Fisher Scientific Co. (Houston, TX). Other chemicals and solvents were of analytical reagent grade. Purified water was obtained from an ultra-pure water system (Milli-QUV plus, Millipore S.A., Molsheim Cedex, France).

2.2. Particle formation using EPAS process

A schematic diagram of the EPAS apparatus is shown in Fig. 1. The EPAS process consisted of spraying a 15.0% (w/w) solution of ITZ containing 2% (w/v) stabilizer dissolved in dichloromethane via an HPLC pump (Model PU-2086, Jasco Inc., Baltimore, MD) through a 1/16 in. outer diameter (o.d.) × 0.030 in. inner diameter (i.d.) preheating coil contained within a 1-1/2 in. o.d. × 15 in. long plastic water jacket (Model 95023D, Alltech Associates Inc., Deerfield, IL) into 50 mL of 2.0% (w/w) aqueous solution of stabilizers. Water was circulated through the jacket with a temperature controller (Julabo MP, Julabo USA Inc., Allentown, PA). The temperature of the water bath and the heating jacket was maintained at 80 °C. The nozzle was made by cutting stainless steel tubing (1/16 in. o.d. × 0.030 in. i.d.) (Young et al., 2000) to form an elliptical conical orifice. The crimped end of the nozzle was filed back until the desired flow rate of 1 mL/min was achieved giving a pressure drop of about 20 MPa across the orifice. This type of nozzle produces very high pressure drops resulting in intense atomization of the organic drug solution at the tip of the nozzle. The nozzle was submerged approximately 10 cm under the surface of the aqueous solution. After atomizing for 5 min, an aqueous dispersion containing a drug-to-stabilizer ratio of 0.68 was recovered. The dispersions were centrifuged (Model J2-21, Beckman, Fullerton, CA) at 10,000 rpm for 20 min to concentrate the particles, as described previously for particles formed by EPAS (Chen et al., 2004a,b). The supernatant was decanted to remove the unbound stabilizer in order to increase the potency (wt drug/wt drug + wt surfactant) in the precipitate. The particles were frozen by submerging in liquid nitrogen and then lyophilized.

2.3. Potency test

The potency of dry powders (wt drug/wt drug + wt surfactant) was determined by dissolving a known amount of dry powder (ca. 10 mg) into 50 mL of mobile phase and then determining ITZ concentration by HPLC. Reverse-phase HPLC was conducted using a Shimadzu VP-AT series LC10 HPLC (Columbia, MD) to measure the quantity of ITZ in the prepared sample. The mobile phase consisted of acetonitrile:water (70:30, v/v) containing 0.02% diethylamine. The flow rate was 1.0 mL/min and the detector wavelength was 263 nm. ITZ was eluted from an Inertsil 5 μm ODS-2 column (4.6 mm i.d. × 150 mm; Alltech Associates Inc., Deerfield, IL) at 5 min using an injection volume of 50 μL.

2.4. Adsorption studies

To measure the amount of stabilizer adsorbed onto the particles immediately after EPAS processing, 15% (w/v) itraconazole solution containing 2% stabilizer dissolved in dichloromethane was sprayed into 50 mL aqueous solution containing 2% stabilizer

at a flow rate of 1 mL/min. After 5 min of spraying, the EPAS dispersion with a drug-to-stabilizer ratio of 0.68 (drug:organic stabilizer:aqueous stabilizer of 0.75:0.1:1), and total concentration of itraconazole of 15 mg/mL was recovered. The pressure drop was 20 MPa and the temperature of both organic and aqueous phases was 80 °C. Immediately after the dispersions were formed, aliquots of 4 mL of the dispersion were centrifuged at 10,000 rpm for 20 min for complete separation of the solids, leaving a clear supernatant at the top. After centrifugation, the supernatant and precipitate were weighed before and after drying at 40 °C to determine the amount of stabilizer adsorbed gravimetrically.

A separate set of experiments was designed to determine the equilibrium adsorption isotherm for each pure stabilizer as a function of stabilizer concentration. 2% (w/v) ITZ dissolved in dichloromethane was sprayed into 15 mL aqueous solution containing stabilizer at a flow rate of 1 mL/min. Various concentrations (from 0.1 to 3%) of stabilizers dissolved in the organic phase were used to prepare the EPAS samples in triplicate. After 5 min of spraying, the EPAS dispersion was agitated at 37 °C for 24 h, to allow adsorption to reach equilibrium. Aliquots of 4 mL of the dispersion were centrifuged at 10,000 rpm for 20 min to concentrate the solids. After centrifugation, the supernatant and precipitate were weighed before and after drying at 40 °C to determine the amount of stabilizer adsorbed gravimetrically.

Stabilizer adsorption was measured gravimetrically based on the mass balance between the supernatant and particles (Chen et al., 2004a). The composition of the small amount of supernatant left on the precipitate was assumed to be the same as that in the bulk supernatant and the amount of ITZ in the precipitate was at least 50 times more than ITZ dissolved in micelles. The amount of adsorbed stabilizer on ITZ particles is given by the following equation:

$$W_{\text{surf,ads}} = W_{\text{ppt,dry}} - W_{\text{drug,ppt}} - (W_{\text{ppt,wet}} - W_{\text{ppt,dry}}) \times \left(\frac{W_{\text{sup,dry}}}{W_{\text{sup,wet}} - W_{\text{sup,dry}}} \right)$$

where $W_{\text{sup,wet}}$ is the weight of the supernatant before drying, $W_{\text{sup,dry}}$ the weight of the supernatant after drying to remove water, $W_{\text{ppt,wet}}$ the weight of the precipitate before drying, $W_{\text{ppt,dry}}$ the weight of the precipitate after drying, $W_{\text{drug,ppt}}$ the amount of ITZ in the precipitate measured by HPLC and $W_{\text{surf,ads}}$ is the amount of adsorbed surfactant or stabilizer on ITZ.

2.5. Dissolution testing

Dissolution testing (Vankel 7000, Vankel Technology Group, Cary, NC) was conducted on isolated ITZ EPAS powders using the United States Pharmacopoeia (USP) apparatus II (paddles) at 50 rpm. Dry powder containing approximately 10 mg of ITZ was weighed out and placed into 900 mL of dissolution media that contained enzyme-free simulated gastric fluid with 0.5% sodium lauryl sulfate (pH 1.2). The dissolution media was maintained at 37 °C and degassed prior to use by sonication for 2 min. Sink conditions were maintained throughout the testing. Aliquots of the dissolution media (5 mL) were collected at 2, 5, 10, 20, 30, 60 and 120 min intervals. After 60 min, the paddle speed was increased to 200 rpm to approximate complete dissolution of ITZ at the 2 h time point. The samples were filtered using 0.45 μm filters (Gelman GHP Acrodisc 0.45 μm, VWR, West Chester, PA). To ensure that no precipitation occurred during HPLC analysis, 0.1 mL of acetonitrile was added to 4 mL of filtered samples. These were mixed using a vortex mixer for approximately 5 s and again filtered through a 0.45 μm filter into an HPLC vial for drug content analysis by reverse-phase HPLC. Dissolution profiles for ITZ EPAS powders were determined in replicates of 6.

2.6. Transmission electron microscopy (TEM)

A JEOL 2010F field emission transmission (JEOL) with energy dispersive X-ray spectroscopy (EDS) (Peabody, MA) was used to examine the primary particle size and determine the chemistry of the sample. The dry powders were redispersed in water and placed on a Cu grid, fixed on the TEM holder and inserted into the TEM column.

2.7. Contact angle

Dry powder was compressed at 1000 kg compression force using a Carver Laboratory Press (Model M, ISI Inc., Round Rock, TX) with 6 mm diameter flat-faced punches. A droplet of water (3 μL) was placed onto the surface of the compact and observed using a

low power microscope. The contact angle was determined by measuring the tangent to the curve of the droplet on the surface of the compact using a Goniometer (Model No. 100-00-115, Ramè-Hart Inc., Mountain Lakes, NJ).

2.8. Surface area

The specific surface area was determined using a Nova 3000 surface area analyzer (Quantachrome Corporation, Boynton Beach, FL) to measure N_2 sorption at 77.40 K. The surface area per unit powder mass was calculated from the fit of adsorption data to the Brunauer, Emmett and Teller (BET) equation.

2.9. Powder X-ray diffraction

Powder X-ray diffraction was conducted using Cu $K\alpha_1$ radiation with a wavelength of 1.54054 Å at 40 kV and 20 mA from a Philips 1720 X-ray diffractometer (Philips Analytical Inc., Natick, MA). The sample powders were placed in a glass sample holder. Samples were scanned from 5° to 50° (2θ) at a rate 0.05°/s. For comparative purposes, the three highest values for relative line intensity and the corresponding 2θ angle were compared.

3. Results and discussion

3.1. Adsorption studies

3.1.1. Adsorption isotherms of stabilizers onto ITZ particle surface after 24 h equilibration

The adsorption isotherm for each of the stabilizers investigated with ITZ particles produced by EPAS is shown in Fig. 2. The adsorption isotherms for poloxamer 407 and PVP followed Langmuir-behavior characterized by a steep initial slope at low concentration and a plateau, indicating the point where most of the adsorption sites on the ITZ particle surface are occupied. In the adsorption of polysorbate 80, the shape of the isotherm was more complex with changes in concavity. The adsorption increased rapidly to an initial plateau and then further gradually increased toward a second plateau. This adsorption behavior could be related to the increase of aggregate concentration typical of micelle formation. As can be seen in Fig. 2, the polysorbate 80 adsorption exhibited a strong affinity to ITZ particle surfaces as indicated by the sharp initial slope and a higher adsorption at all concentrations. Polysorbate 80 molecules would be expected to adsorb onto the hydrophobic ITZ surfaces with the PEO groups extended into water to provide steric

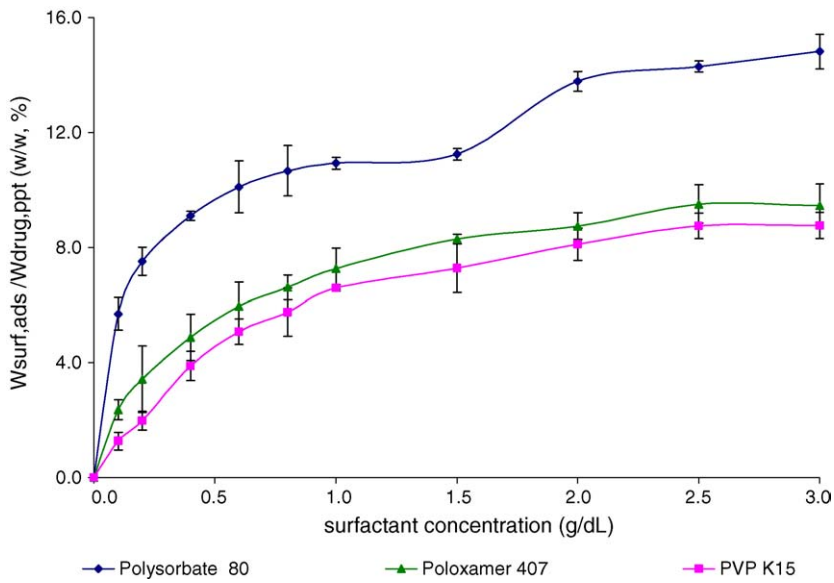

Fig. 2. The adsorption isotherms of various stabilizers onto ITZ particles.

stabilization. Luckham et al. (1995a) found that lower molecular weight ethoxylated polymers adsorb on carbon black surfaces more strongly than higher molecular weight polymers. The non-adsorbing ethylene oxide block hinders the adsorption of the higher molecular weight stabilizers. This may explain why polysorbate 80, which has shorter PEO chains, adsorbed onto the particle surfaces to a greater extent than poloxamer 407 with PEO chains about 100 segments long. In addition, polysorbate 80 with a lower HLB value (HLB = 15) would be expected to adsorb more strongly onto the hydrophobic surface than poloxamer 407 and PVP. The homopolymer PVP is very hydrophilic and has a small thermodynamic driving force for adsorption (Gennes, 1987). Sato and Kohnosu (1994) reported that the amount of PVP adsorbed onto the hydrophobic surface of TiO_2 is low in aqueous solution, which is in agreement with the results obtained by Pattanaik and Bhaumik (2000). Therefore, low adsorption of PVP found in this study was also consistent with previously reported studies.

3.1.2. Adsorption of stabilizers onto ITZ particle surface after EPAS process

The adsorption ($W_{surf,ads}/W_{drug,ppt}$) of stabilizers in each EPAS formulations was measured immediately after forming the dispersions, and the results are listed in Table 1. The results demonstrated that the combination of poloxamer 407 and polysorbate 80, present in the organic and aqueous phases, respectively, showed the highest adsorption (10.72%, w/w) after the short spray time of 5 min. The much larger adsorption for this surfactant blend produced greater wettability and hence a faster dissolution rate in contrast with much smaller adsorption values for compositions containing poloxamer 407 in both phases, where only 6.46% (w/w) stabilizer-to-drug was adsorbed. Chen et al. (2004a) found that the adsorption dynamics of the copolymer poloxamer 407 is rather slow when added alone in the aqueous phase. Chen et al. showed that adsorption of poloxamer 407 increased from 3.87 to 11.21% (w/w) surfactant-to-drug after storage at 25 °C for 72 h. This increase might be caused by slow surface rearrangement of the adsorbed polymer layer to provide space for further adsorption (Tripp and Hair, 1996). Moreover, the increase in viscosity of poloxamer 407 at high temperature could also cause the longer diffusion time. However, in the present study, we found that the combination of poloxamer 407 and polysorbate 80, present in the organic and aqueous phases, respectively, showed the highest adsorption immediately upon particle formation. Poloxamer 407 is added in the same (organic) phase as the ITZ where it precipitates from the evaporating organic droplets, and, hence, requires a relatively short time to diffuse and adsorb onto the nucleating particle surfaces. Moreover, employing a second surfactant like polysorbate 80 may facilitate orientation of poloxamer 407 at the solid–liquid interface, and enable a much shorter equilibration time to attain optimal surfactant conformation. Chen et al. required much longer equilibration times using poloxamer 407 alone, which resulted in larger particles. Polysorbate 80 is a much smaller molecule (MW: 1310) than poloxamer 407 (MW: 11,700). The small size of polysorbate 80 may be expected to lead to faster diffusion (Kim et al., 2000) to the particle surface and faster adsorption kinetics at the surface, to inhibit the otherwise rapid crystallization. In addition, the adsorption for pure polysorbate 80 was substantially larger than for the other stabilizers as was shown in Fig. 2.

Several authors have reported results of the interactions of Pluronic block copolymer with surfactant systems (Ivanova et al., 2001; Na et al., 1999). In particular, Couderc et al. (2001) reported on the synergistic behavior in mixed micelle formation of binary surfactant mixtures of poloxamer 407 and nonionic surfactant containing an EO group ($C_{12}EO_6$). Polymer–surfactant association is influenced by many factors including interactions with ions, hydrogen bonding, the hydrophobicity of the polymer and the non-polar tail of the surfactant, and the structural conformation and flexibility of the polymer. It has also

Table 1
Adsorption ($W_{surf,ads}/W_{drug,ppt}$) of stabilizers onto ITZ particle surface after EPAS process at 80 °C

Aqueous excipients	Organic excipients	$W_{surf,ads}/W_{drug,ppt}$ (%, w/w)
Polysorbate 80	Poloxamer 407	10.72 ± 0.14
PVP K-15	PVP K-15	5.38 ± 0.14
Poloxamer 407	Poloxamer 407	6.46 ± 0.36
Polysorbate 80	PVP K-15	5.86 ± 0.83
PVP K-15	Poloxamer 407	5.70 ± 0.73

Drug:organic stabilizer:aqueous stabilizer (0.75:0.1:1) (w/w/w) at final concentration of 15 mg/mL of ITZ in the aqueous EPAS dispersion.

been reported that some non-ionic surfactants may significantly increase emulsifying capacity of polymeric surfactants (Carlotti et al., 1995). Thus, the highest adsorption produced with polysorbate 80 and poloxamer 407 is consistent with the previously observed favorable interactions between these stabilizers. However, this interaction was not found in the combination of polysorbate 80 and PVP K-15 which yielded low adsorption (5.86%, w/w). It may possible that a layer of PVP K-15 which was present in the organic phase with ITZ coated the nuclei first and that polysorbate 80 could not adsorb on the polymer layer. Moreover, the small adsorption could also due to the competitive adsorption of these stabilizers onto surfaces of the ITZ particles (Noskov et al., 2002). It is constructive to further compare the different intermolecular interactions of the surface of ITZ particles with poloxamer 407 and PVP K-15. A small amount of adsorbed stabilizers was observed (5.70%, w/w) compared to the combination of poloxamer 407 and polysorbate 80. This may be attributed to the lower adsorption after 24 h for both poloxamer 407 and PVP K-15, relative to polysorbate 80. Since PVP has higher molecular weight than poloxamer 407, it will take longer to diffuse and adsorb onto the ITZ particle surfaces. The combination of PVP K-15 by itself also yielded low adsorption (5.38%, w/w).

3.2. Dissolution testing

Dissolution profiles of ITZ EPAS powders are presented in Fig. 3. The dissolution rate of all formulations is significantly greater than that compared to the bulk powder. A high dissolution rate was observed for all EPAS formulations in spite of the fact that the crystallinity of each of the EPAS powders was observed to be high, as will be discussed later in this paper. The dissolution rate was also correlated to the amount of stabilizer adsorbed. It was much higher for the formulation containing polysorbate 80 and poloxamer 407 than the other stabilizers. In 5 min, 80% of ITZ prepared by EPAS was dissolved as compared to 13% determined for the bulk powder. Results presented below (Sections 3.3 and 3.4) indicate that this observation of the highest dissolution rate is consistent with the high wettability (lowest contact angle) and very small primary particle size of ITZ produced by EPAS, respectively.

3.3. Transmission electron microscopy

TEM was used to investigate the primary particles and morphology of ITZ particles after redispersion of the dried EPAS powders in water. In Fig. 4, the TEM micrograph of ITZ with polysorbate 80 and poloxamer

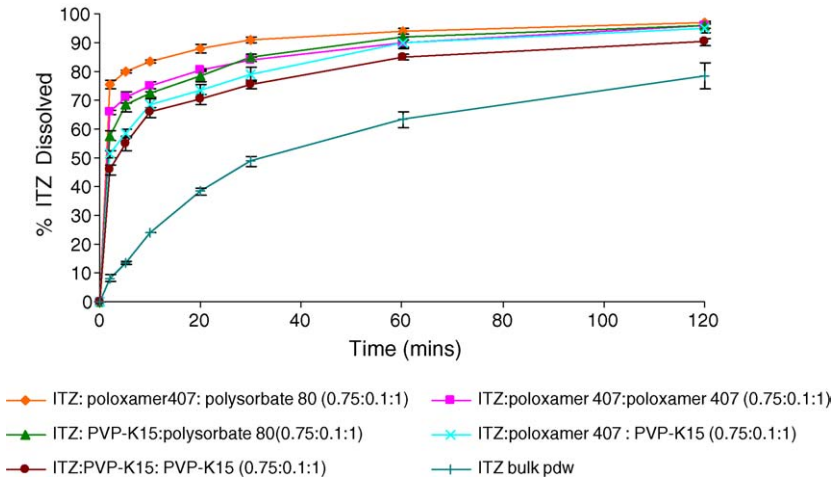

Fig. 3. Dissolution profile of itraconazole with different surfactant systems. The weight ratios shown are ITZ:organic stabilizer:aqueous stabilizer. All dispersions were centrifuged and dried by lyophilization. The final drug concentration was 15 mg/mL. The dissolution media was enzyme-free simulated gastric fluid containing 0.5% SLS (pH 1.2) and dissolution profiles were determined in replicates of 6.

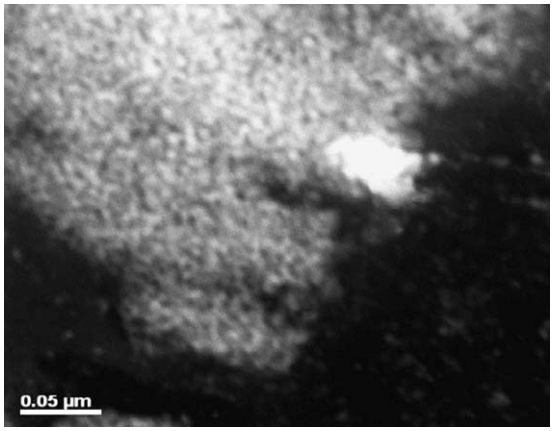

Fig. 4. TEM micrograph of of itraconazole EPAS particles with poloxamer 407 as organic stabilizer and polysorbate 80 as aqueous stabilizer. The ratio of ITZ:organic stabilizer:aqueous stabilizer was 0.75:0.1:1. The dispersion was centrifuged and dried by lyophilization. The final drug concentration was 15 mg/mL.

407 indicate aggregation of small particles after being redispersed in water. The particles were composed of small primary particles which aggregated during the drying process. This explains why the highest dissolution occurred in the formulation containing polysorbate 80 and poloxamer 407 even though the particle size of dry powders was about 7 μm measured by laser diffraction, which most probably represented aggregates being measured by laser light diffraction. Since these aggregates were not easily deaggregated into their discrete particles, laser diffraction was not used to quantitate particle size. Energy dispersive spectroscopy was used to qualitatively determine and confirm the elemental compositions of particles in this image. The EDS spectrum was obtained, the constituent elements identified and the occurrence classified into a compositional type. The EDS spectrum showed the presence of C, N, O and Cl, as shown in Fig. 5. The presence of both N and Cl atoms, which are only present in the ITZ molecule, is indicative that the large particle is ITZ which consisted of very small aggregated primary particles. It clearly showed that the bright spots of highest elemental intensity could be overlaid on the pattern of the ITZ structure. Other elements of Cu and Si were present on the film and supporting grid. The rapid evaporation of the heated organic solution in the EPAS process produces high supersaturation and rapid precipitation of ITZ in the form of a nanoparticle dispersion that is stabilized by a variety of stabilizers. The results also further confirmed the potential of EPAS

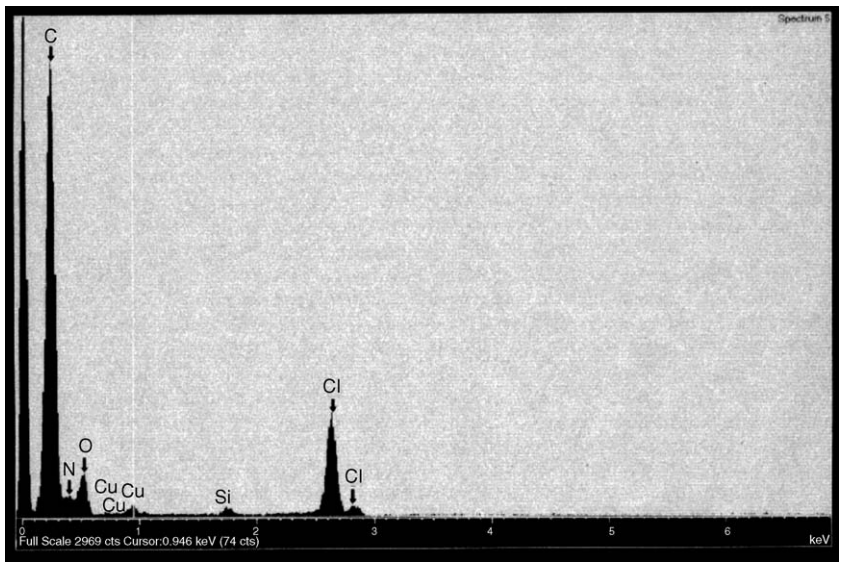

Fig. 5. EDS spectrum of itraconazole EPAS particles with poloxamer 407 as organic stabilizer and polysorbate 80 as aqueous stabilizer. The ratio of ITZ:organic stabilizer:aqueous stabilizer was 0.75:0.1:1. The dispersion was centrifuged, frozen and dried by lyophilization. The final drug concentration was 15 mg/mL. Presence of N and Cl confirms ITZ.

Table 2
Characterization of itraconazole powders

Aqueous excipients	Organic excipients	Potency of ITZ (%)	Drug:stabilizer ratio	Surface area (m^2/g)	Contact angle (°)
Bulk powder		/	/	4.22 ± 0.10	61.6 ± 0.54
Physical mixture[a]		/	/	3.09 ± 0.27	52.3 ± 0.85
Polysorbate 80	Poloxamer 407	90.5	9.5	3.25 ± 0.22	30.3 ± 0.66
PVP K-15	PVP K-15	90.3	9.3	5.77 ± 0.33	43.5 ± 0.47
Poloxamer 407	Poloxamer 407	93.8	15.1	6.31 ± 0.61	35.1 ± 0.63
Polysorbate 80	PVP K-15	93.1	13.5	3.33 ± 0.21	32.7 ± 0.79
PVP K-15	Poloxamer 407	91.4	10.6	5.87 ± 0.38	42.8 ± 0.84

Drug:organic stabilizer:aqueous stabilizer (0.75:0.1:1) (w/w/w) at final concentration of 15 mg/mL of ITZ in the aqueous EPAS dispersion. All dispersions were centrifuged and dried by lyophilization. (/) Not measured.
[a] Physical mixture consists of ITZ, polysorbate 80 and poloxamer 407 (0.75:0.1:1 w/w/w).

process in producing nanoparticles of poorly water-soluble drugs (Chen et al., 2002).

3.4. Contact angle

Surfactants or stabilizers generally improve wetting by adsorbing on the surface to cause a reduction in the solid–liquid interfacial energy. The contact angle results are shown in Table 2. Adsorbed hydrophilic stabilizer on the particle surface reduced the contact angle indicating improved wettability compared to bulk powder. It is likely that different stabilizers and their combination may display variation in wetting particle surface. The decrease in contact angle correlated with an increase in dissolution rate as reported in Table 2. For the EPAS formulation of polysorbate 80 and poloxamer 407, the contact angles were lowest due to high adsorption and wetting of particle surfaces resulting in the highest dissolution rate profile. Reduction in contact angle from 61.6° for bulk ITZ to 30.3° was achieved at a high drug potency of 90%, with a corresponding increase in drug dissolution from 14 to 80% in 5 min. This may be expected as the ITZ surface is largely hydrophobic in nature so the bulk powder does not break the interfacial tension of the dissolution media at the air/liquid boundary. The ITZ particles without stabilizers float on the surface throughout the dissolution experiment. The contact angle of the corresponding physical mixture of ITZ with polysorbate 80 and poloxamer 407 was 52.3°, indicating a much less hydrophilic surface. Therefore, increasing the accessibility for wetting by the dissolution media is an important factor to enhance the dissolution rate of ITZ. Miyazaki et al. (1981) reported that the dissolution rate enhancement of phenylbutazone was mostly due to the enhanced wetting.

3.5. Surface area

The surface areas of the dry powders were determined by BET and the results are shown in Table 2. The surface areas of ITZ EPAS formulations were higher than that of the bulk powder except for the formulations containing polysorbate 80. Polysorbate 80 is a liquid at room temperature, and consequently, it caused aggregation of the dry powder at room temperature, and subsequently low surface area as shown in Table 2. The calculated surface area for monodisperse spheres of ITZ with particle diameter about 8 μm would be $2.3\ m^2/g$. The larger surface area for the powders suggests that the particles were not uniform spheres but were aggregates composed of smaller primary particles as can be seen from the TEM results. This morphology results in high dissolution of all EPAS formulations compared to the bulk powders. The dissolution rates for the systems with higher surface areas, of the order of $5–6\ m^2/g$, were lower than for the formulation of polysorbate 80 and poloxamer 407 which had somewhat lower surface areas. The reduced wetting and dissolution can be attributed to the observation that these powder samples remained for a longer time on the top of dissolution medium before being wetted completely.

3.6. Crystallinity

X-ray diffraction was used to analyze the crystallinity of the dry powders. As shown in Fig. 6, all

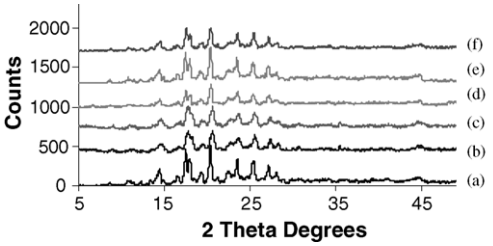

Fig. 6. X-ray diffraction patterns of ITZ formed by EPAS (a) control:bulk ITZ, (b) ITZ:PVP K-15:PVP K-15, (c) ITZ:PVP K-15:poloxamer 407, (d) ITZ:poloxamer 407:poloxamer 407, (e) ITZ:poloxamer 407:polysorbate 80 and (f) ITZ:poloxamer 407:PVP K-15. The ratios of ITZ:organic stabilizer:aqueous stabilizer were 0.75:0.1:1. All dispersions were centrifuged and dried by lyophilization. The final drug concentration was 15 mg/mL. The patterns clearly demonstrate the crystallinity of the processed ITZ.

profiles show no change in crystallinity. The crystalline peak positions were the same as for the bulk ITZ. The degree of crystallinity for these samples did not appear to correlate with dissolution results. As shown by the dissolution results, all EPAS formulations yielded very good dissolution profiles, indicating that high dissolution rates may be achieved for high surface area crystalline powders. Moreover, in terms of thermodynamics, the crystalline solids are preferable since they are more physically and thermodynamically stable compared to amorphous solids which may re-crystallize. Amorphous or disordered material is a metastable state and tends to revert back to the more stable crystalline state under unfavorable humidity and temperature conditions. Water, from the atmosphere, can be absorbed and reduce the glass transition temperature (Elamin et al., 1995) thus decreasing the energy barrier to re-crystallization (Carstensen and Van Scooik, 1990). However, the stability of amorphous materials can be enhanced by storage well below the glass transition temperature (T_g) and by using high T_g material, such as polyvinyl pyrrolidone, polyethylene glycol and various cellulose derivatives like hydroxypropyl methylcellulose, hydroxypropylcellulose, etc. (Hancock and Zografi, 1997; Saleki-Gerhardt and Zografi, 1994).

3.7. Potency of ITZ powders and drug-to-stabilizer ratio after centrifugation

The potencies of the powders after centrifugation are listed in Table 2. The potency of ITZ in the dry powders was greater than 90%, corresponding to a drug-to-stabilizer ratio greater than 9:1. The high potencies result from the removal of a large amount of non-adsorbed stabilizer in the supernatant. This concept has been successfully used to produce high potency danazol and ITZ in the EPAS studies (Chen et al., 2004a,b). Chen et al. reported the potency of itraconazole particles was increased to only 70% after 25 min of spraying followed by removal of the unbound surfactant. In the present study, we were able to increase the potency up to 90%, while maintaining high dissolution rates and small primary particle sizes. In the present study, we used high ITZ concentration in the feed solution (drug-to-organic stabilizer ratio of 7.5) with a short spray time only 5 min. These conditions allow less time for stabilizers to adsorb onto the particles and can led to the extremely high potency values up to 93% with rapid dissolution. The final drug-to-stabilizer ratios varied from 9:1 to 15:1. In general, the ratio of drug-to-stabilizer ranges from 1:10 to 1:1 when drugs are dissolved in micelles, vesicles or liposomes (Lee et al., 2001; Kushida et al., 2002). There are several advantages of the formulation with high drug-to-stabilizer ratio, such as low administration dose and less potential interactions from the excipients. Potential stability problems can result from interactions of drug substances with excipients in solid dosage forms (Mroso et al., 1982).

4. Conclusions

Rapid dissolving formulations containing ultra-high potency of ITZ powders were achieved using the EPAS process. Polysorbate 80, poloxamer 407, PVP K-15 and their combinations showed differences in the degree of improving wettability and dissolution of ITZ depending on their adsorption onto the particle surface. The adsorption of stabilizers is influenced by the HLB of the stabilizer and the hydrophobicity of the particle surface. For very lipophilic compounds, such as ITZ ($\log P > 5$), polysorbate 80, with a lower HLB value, was adsorbed more strongly than poloxamer 407 and PVP. The synergistic stabilization effect was demonstrated to be optimal for combinations of polysorbate 80 and poloxamer 407, when incorporated into the aqueous and organic phases, respectively. The stabilization observed for this mixed stabilizer system has

been explained in terms of strong adsorption for the small polysorbate 80 to compensate for the limited amount of adsorption for the copolymer poloxamer 407 after 24 h. EPAS followed by removal of free stabilizer produced high potencies up to 93% and rapid dissolution rates. The highest dissolution rates, i.e. 80% in 5 min were obtained for ITZ produced by EPAS with polysorbate 80 and poloxamer 407, as stabilizers in the aqueous and organic phases, respectively. The dissolution rates are enhanced due to the small primary particle size and by adsorbed stabilizers that raise the surface hydrophilicity, as shown by a decrease in the contact angle. The optimum choice of stabilizer(s) which adsorb rapidly onto the ITZ particle surfaces during the very short spray times employed in the EPAS process can help produce the extremely high drug-to-stabilizer ratios greater than 12, corresponding to potencies above 90%. The very small amount of adsorbed stabilizers was sufficient to form a hydrophilic layer on the particle surfaces resulting in increased particle wettability and dissolution. These results provide evidence that the selection of appropriate stabilizer(s) is an important consideration in formulation development.

This study also demonstrated the usefulness of the EPAS process as a method in controlling particle characteristics and enhancing drug dissolution. This process is a very versatile drug delivery platform and is suitable for many commonly used routes of administration, such as oral, nasal and pulmonary delivery.

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