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Rapid dissolving high potency danazol powders produced by spray freezing into liquid process

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Abstract

The objective of this study was to investigate the use of organic solvents in the spray freezing into liquid (SFL) particle engineering process to make rapid dissolving high potency danazol powders and to examine their particle size, surface area and dissolution rate. The maximum drug potency produced was 91% for SFL micronized danazol/PVP K-15. XRD indicated that danazol in the high potency SFL powders was amorphous. SEM micrographs revealed that the SFL danazol/PVP K-15 nanostructured aggregates had a porous morphology and were composed of many smooth primary nanoparticles with a diameter of about 100 nm. Surface areas of SFL danazol/PVP K-15 high potency powders were in the range of 28–115 m^2/g. The SFL powders exhibited significantly enhanced dissolution rates. The rate of dissolution of micronized bulk danazol was slow; only 30% of the danazol was dissolved in 2 min. However, 95% of danazol was dissolved in only 2 min for the SFL high potency powders. The SFL process offers a highly effective approach to produce high potency danazol nanoparticles contained in larger structured aggregates with rapid dissolution rates, and is especially applicable to delivery systems containing poorly water soluble drugs.

Keywords: Spray-freezing into liquid; Dissolution; Poorly water soluble drug; Nanoparticle; High potency; Amorphous

1. Introduction

It is estimated that about 40% of compounds being developed by the pharmaceutical industry are poorly water soluble (Lipinski, 2002; Radtke, 2001). A limiting factor in the oral bioavailability of poorly water soluble compounds is an inadequate dissolution rate. Increasing the dissolution rate of poorly water soluble active pharmaceutical ingredients (APIs) has become a major challenge in pharmaceutical formulation development. A promising approach is to use a particle engineering technology to overcome poor wetting and low dissolution rate of an API. Techniques that have been commonly used include mechanical milling, spray drying, solid dispersion, supercritical CO_2 precipitation techniques like RESS and PCA/SAS/SEDS (Leuner and Dressman, 2000; Merisko-Liversidge et al., 2003; Rogers et al., 2001; Tom and Debenedetti, 1991), and solvent evaporation techniques including evaporative precipitation into aqueous solution (EPAS) (Chen et al., 2002). These particle formation techniques have been used to micronize poorly water soluble API alone or in the presence of a polymer and/or surfactant(s). As a

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result, the decreased particle size and increased surface area lead to greatly enhanced dissolution rates (Leuner and Dressman, 2000; Merisko-Liversidge et al., 2003; Muller et al., 2001; Rogers et al., 2001).

Pharmaceutical powders produced by the current particle engineering technologies; however, often have very low drug potency or drug/surfactant ratio. It is difficult to stabilize small particles due to the thermodynamic driving force to lower the interfacial area. Therefore, the final product often contains large amounts of stabilizing excipients resulting in very low drug potency. For example, the API/surfactant(s) ratio in a solid dispersion must be below about 1:2 to keep the drug molecularly dispersed, otherwise, it may form small crystals that lower the dissolution rates (Leuner and Dressman, 2000). The application of supercritical CO_2 rapid expansion techniques was limited by the low solubility of API in the CO_2. The high percentages of surfactants were often used to enhance solubility of API in the CO_2 and to stabilize the system as well (Rogers et al., 2001; Tom and Debenedetti, 1991). Typically, API/surfactant ratios ranging from 1:40 to 3:1 are used in the current particle formation techniques (Delneuville et al., 1998; Kerc et al., 1999; Nair et al., 2002; Rasenack and Muller, 2002; Tantishaiyakul et al., 1996). However, solid oral dosage forms often require high potency or high API/surfactant ratios in order to achieve a therapeutic effect with tolerability to the API and minimal side effects from the excipients. However, it is highly challenging in current particle engineering technologies to achieve high dissolution rates for poorly water soluble APIs with high potency because only a small amount of stabilizing excipient(s) can be used in the process.

The spray freezing into liquid (SFL) particle engineering process was developed to improve the wetting and enhance the dissolution rate of poorly water soluble APIs (Hu et al., 2002; Rogers et al., 2002, 2003; Yu et al., 2002). In the SFL particle engineering process, a feed solution containing poorly water soluble API and excipient(s) is atomized directly into a cryogenic liquid to produce frozen particles. The frozen particles are then collected and lyophilized to obtain dry powders. The intense atomization in conjunction with rapid freezing rates have led to nanostructured aggregates composed of amorphous API nanoparticles with high surface areas and enhanced wettability. Recently, a study (Hu et al., 2002) showed that carbamazepine/PVP K-15/poloxamer 407 powders prepared by SFL exhibited significantly enhanced dissolution rates (>92% dissolved in 10 min in the purified water). In contrast, only 5% of bulk carbamazepine was dissolved in 20 min. The SFL powders wetted and dissolved instantaneously upon contact with the dissolution media because of an amorphous structure, high surface area and increased wettability. However, these SFL formulations had relatively low drug potency, typically 33%.

The objective of this study was to extend the SFL process to produce rapid dissolving high potency powders with high surface areas and dissolution rates. The potencies ranged from 50 to 90% in contrast with the typically obtained 33% in previous studies (Hu et al., 2002, 2003; Rogers et al., 2002). In order to achieve these high potencies, high concentrations of APIs were dissolved in pure or mixed organic solvents to prepare the feed solutions. The hypothesis of this study was that only small amounts of surfactant or polymer are sufficient to form SFL nanostructured aggregates with amorphous API, high surface areas, and enhanced wettability; properties which enhance dissolution rates. Danazol was used as a model API in this study. The dissolution rate was determined as a function of the danazol potency.

2. Materials and methods

2.1. Materials

Danazol USP was obtained as micronized powder from Spectrum Quality Products Inc. (Gardena, CA). Polyvinylpyrrolidone (PVP) K-15, sodium lauryl sulfate (SLS), tris(hydroxymethyl)aminomethane (Tris), and hydrochloric acid (HCl) were purchased from Spectrum Quality Products Inc. (Gardena, CA). Acetonitrile and methylene chloride were obtained from EM Industries Inc. (Gibbstown, NJ). Purified water was obtained from an ultra-pure water system (Milli-QUV plus, Millipore S.A., Molsheim Cedex, France).

2.2. High potency danazol/PVP K-15 powders by SFL

Danazol and PVP K-15 were dissolved in acetonitrile or acetonitrile/methylene chloride mixtures and

Table 1
SFL danazol/PVP K-15 concentrations in the feed solution to produce powders with differing danazol potency

Danazol/PVP K-15 ratio (w/w)	Danazol (g)	PVP K-15 (g)	Acetonitrile (ml)	Methylenechloride (ml)	Potency (%)	Percentage danazol loading in feed solution (w/w)
1:2	0.2	0.4	70	–	33	0.36
1:1	0.2	0.2	70	–	50	0.36
2:1	0.4	0.2	70	–	66	0.72
3:1	0.6	0.2	65	5	75	1.03
10:1	1	0.1	55	15	91	1.63

processed using the SFL technique (Hu et al., 2002, 2003; Rogers et al., 2002). The formulations of SFL feed solutions are listed in Table 1. The SFL feed solution was placed into the solution cell. A constant pressure (2000 PSI) from the ISCO syringe pump provided a flow rate of 50 ml/min for the SFL feed solution. The atomizing nozzle was composed of polyetheretherketone (PEEK) tubing with an inner diameter of 127 μm. The SFL feed solutions were sprayed through the nozzle and atomized into small droplets directly into the liquid N_2 phase. Frozen particles formed instantaneously and were collected and dried by a VirTis Advantage Tray Lyophilizer (The VirTis Company, Inc. Gardiner, NY). The SFL powders and control samples were stored in glass vials over desiccant in a vacuum desiccator at room temperature before characterization measurements. The micronized bulk danazol was used as a control.

2.3. Powder X-ray diffraction

Powder X-ray diffraction (XRD) 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 (Philip Analytical Inc., Natick, MA). The sample powders were placed in a glass sample holder. Samples were scanned from 5° to 45° (2θ) at a rate 0.05°/s. For comparative purposes, the three highest values for relative line intensity and their corresponding line position 2θ were compared for the micronized bulk danazol (Cullity, 2001).

2.4. Scanning electron microscopy (SEM)

A HITACHI S-4500 field emission scanning electron microscope (Hitachi Instruments Inc., Irvine, CA) was used to examine the surface morphology of each sample powder. The sample was fixed to a SEM stage with double-sided adhesive tape and gold sputter coated.

2.5. Surface area measurement

A Nova 3000 surface area analyzer (Quantachrome Corporation, Boynton Beach, FL) was used to determine 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 (Brunauer et al., 1938).

2.6. Contact angle measurement

Compacts of sample powders were prepared at a 500 kg compression force using a Carver Laboratory Press (Model M, ISI Inc., Round Rock, TX) with flat-faced 6 mm diameter punches. A droplet of SLS/Tris dissolution media (SLS 0.75%/Tris 1.21%, 3 μl) was placed onto the surface of the compact and observed using a low power microscope. The contact angle (Brown et al., 1998) 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).

2.7. Solubility study

The equilibrium solubility of danazol in purified water, THF/water co-solvent (33% w/w), acetonitrile, methylene chloride, and in the SLS/Tris dissolution media was measured. An excess of danazol was added into each of three glass vials ($n = 3$) containing 15 ml of the solvent or dissolution media. The sealed vials were equilibrated in a horizontal shaker at 37 °C for 72 h. The known amount of sample was filtered through a 0.45 μm syringe filter, diluted with acetonitrile and analyzed by HPLC.

2.8. Dissolution studies

The amount of danazol dissolved, as a function of time, was determined using USP Apparatus 2 (paddles) at 50 rpm (Vankel 7000, Vankel Technology Group, Cary, NC). All dissolution tests ($n = 3$) were conducted at sink conditions. SFL danazol/PVP K-15 powders with different danazol potencies or micronized bulk danazol containing approximately 12 mg danazol were added to 900 ml of SLS/Tris dissolution media (SLS 0.75%/Tris 1.21%) at 37 °C. A 5 ml aliquot was taken at each time point and filtered through a 0.45 μm filter then diluted with acetonitrile, filtered through a 0.45 μm filter again, and analyzed by HPLC (Hu et al., 2002; Rogers et al., 2003).

A separate experiment was conducted to confirm the absence of particles smaller than the pore size of the filter membrane in the dissolution filtrate. Dissolution samples were taken as described above and filtered through the 0.45 μm filter. The particle size distribution of the filtrate was measured by dynamic light scattering (DLS) using a Brookhaven Zetaplus (Brookhaven Instruments Corporation, New York, NY).

2.9. HPLC analysis

Each sample was filtered through 0.45 μm Acrodisc GHP syringe filter (Pall Corporation, Ann Arbor, MI) and analyzed at 288 nm using a Shimadzu LC-10 chromatograph (Shimazu Corporation, Kyoto, Japan). An Alltech 150 mm × 4.6 mm Intersil 5 μm ODS-2 reverse-phase column (Alltech Associates, Inc., Deerfield, IL) was used for the HPLC analysis. The danazol peak eluted at 5 min when running mobile phase (acetonitrile/water at 7/3 ratio, v/v) at 1 ml/min. A standard was injected after each six unknown samples through HPLC batch run. System suitability requirements were met (correlation coefficient (r^2) ≥ 0.998, precision of five replicate injection $\leq$2.0% RSD, theoretical plates $>$ 500 plates/column and peak asymmetry $\leq$1.5).

2.10. Stressed cycle stability study

SFL danazol/PVP K-15 (3:1) powders were sealed in 20 ml glass vials containing desiccant and placed in a temperature controlled oven. The temperature cycle was to increase temperature from −5 to 40 °C over 30 min, hold at 40 °C for 2.5 h and then decrease temperature from 40 to −5 °C over 30 min. The cycle was repeated 6 times per day. The duration of the stability study was one month.

2.11. Statistical analysis

The data were compared using a Student's *t*-test of the two samples assuming equal variances to evaluate the differences. The significance level ($\alpha = 0.05$) was based on the 95% probability value ($P < 0.05$).

3. Results and discussion

3.1. Solubility and potency

Recently, the SFL process was extended to use organic solvents for the feed solutions (Hu et al., 2003). The main advantage of the use of organic solvents was to significantly increase the solubility of hydrophobic API. In this study, organic solvents were used in the feed solutions to make high potency danazol powders. Firstly, the equilibrium solubility of danazol in each solvent was measured. The equilibrium solubilities of danazol in purified water, THF/water co-solvent (33%, w/w), acetonitrile, methylene chloride, and SLS/Tris dissolution media were 0.97 μg/ml, 0.71, 21.36, 92.18, and 0.15 mg/ml, respectively. High potency danazol/PVP K-15 powders were produced by the SFL process using acetonitrile or acetonitrile/methylene chloride mixture. The potency of the SFL danazol/PVP K-15 powders ranged from 33 to 91% (Table 1). The sample with 91% (w/w) potency was prepared from an acetonitrile/methylene chloride mixture. The solubility of danazol was higher in this mixed solvent than in pure acetonitrile. The results below demonstrate that a relatively small amount of PVP K-15 was needed to form SFL nanostructured aggregates with amorphous structure, high surface area, and enhanced wettability. These properties of the SFL powders led to rapid dissolution rates as described by the Noyes–Whitney equation (Horter and Dressman, 2001).

3.2. Influence of high potency on danazol

3.2.1. Crystallinity

Crystallinity greatly impacts the solubility and dissolution rate of poorly water soluble APIs (22).

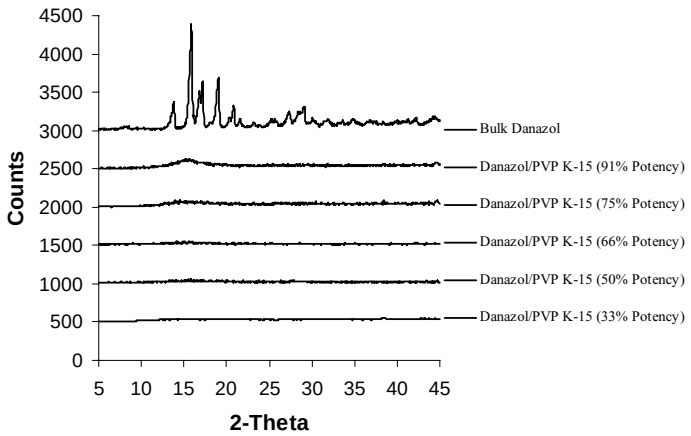

Fig. 1. Effect of potency on the crystallinity of danazol in SFL danazol/PVP K-15 powder as determined by X-ray diffraction.

Micronized bulk danazol (Fig. 1) had a similar X-ray diffraction pattern to that reported by Liversidge and Cundy (Liversidge and Cundy, 1995). The peak intensities indicated a high degree of crystallinity. The X-ray pattern of the SFL danazol/PVP K-15 powders with 33% danazol potency exhibited the opposite behavior. The characteristic diffraction peaks of danazol (Cullity, 2001) at 15.8, 17.2 and 19.0 (2θ) degrees were not evident in SFL danazol/PVP K-15 powder indicating that the danazol was in an amorphous state. Similarly, a lack of crystallinity was also found for the SFL danazol/PVP K-15 powders with higher potencies (50–91%). XRD indicated that bulk micronized danazol was in the crystalline form, but danazol in high potency SFL danazol/PVP K-15 powders was amorphous. This is because rapid freezing rates achieved by atomizing the feed solution directly into liquid nitrogen trapped the danazol in an amorphous state without allowing time for crystallization. The high chemical potential of the amorphous form relative to the crystalline state is a factor that may be expected to lead to faster dissolution rates. Several studies demonstrated that amorphous APIs dramatically enhanced bioavailability of poorly water soluble APIs (Hancock and Zografi, 1997; Hancock and Parks, 1999). Therefore, the amorphous SFL danazol powders might have better bioavailability compared to control.

3.2.2. Surface area and surface morphology

Another important factor that influences the dissolution rate is the available surface area of the API. The surface areas of the high potency powders are listed in Table 3. The surface areas of the SFL danazol/PVP K-15 powders ranged from 115.52 to 28.50 m^2/g. All surface areas of SFL danazol/PVP K-15 powders were increased markedly over the micronized bulk danazol (0.52 m^2/g). To further investigate the effect of high potency on the morphology of SFL danazol powders, the powders were examined by SEM. The SEM micrograph of bulk danazol (Fig. 2J) revealed a large crystalline plate with a fractured edge. In Fig. 2A, the SEM micrograph indicated that the SFL danazol/PVP K-15 particles with 33% potency were porous aggregates with a geometric diameter of about 700 nm. A higher magnification SEM micrograph (Fig. 2B) revealed the aggregates were composed of many nanoparticles with a geometric diameter of about 50 nm. The surface of all nanoparticles was very smooth. The SEM micrographs of the SFL danazol/PVP K-15 with 50% potency revealed (Fig. 2C) that there was a small porous aggregate with a geometric diameter of about 1.5 μm. Higher magnification showed that the aggregate was also composed of many smooth nanoparticles with a geometric diameter of about 100 nm (Fig. 2D). Both the SFL danazol/PVP K-15 particles with 66% potency (Fig. 2E and F) and 75% (Fig. 2G and H) potency had a porous morphology with a geometric diameter ranging from 1.5 μm to 750 nm. SEM micrographs showed that these particles were also comprised of many small subunits. The SFL particles (Fig. 2I) with 91% potency had a different surface morphology. They were microparticles about 3 μm in diameter, which

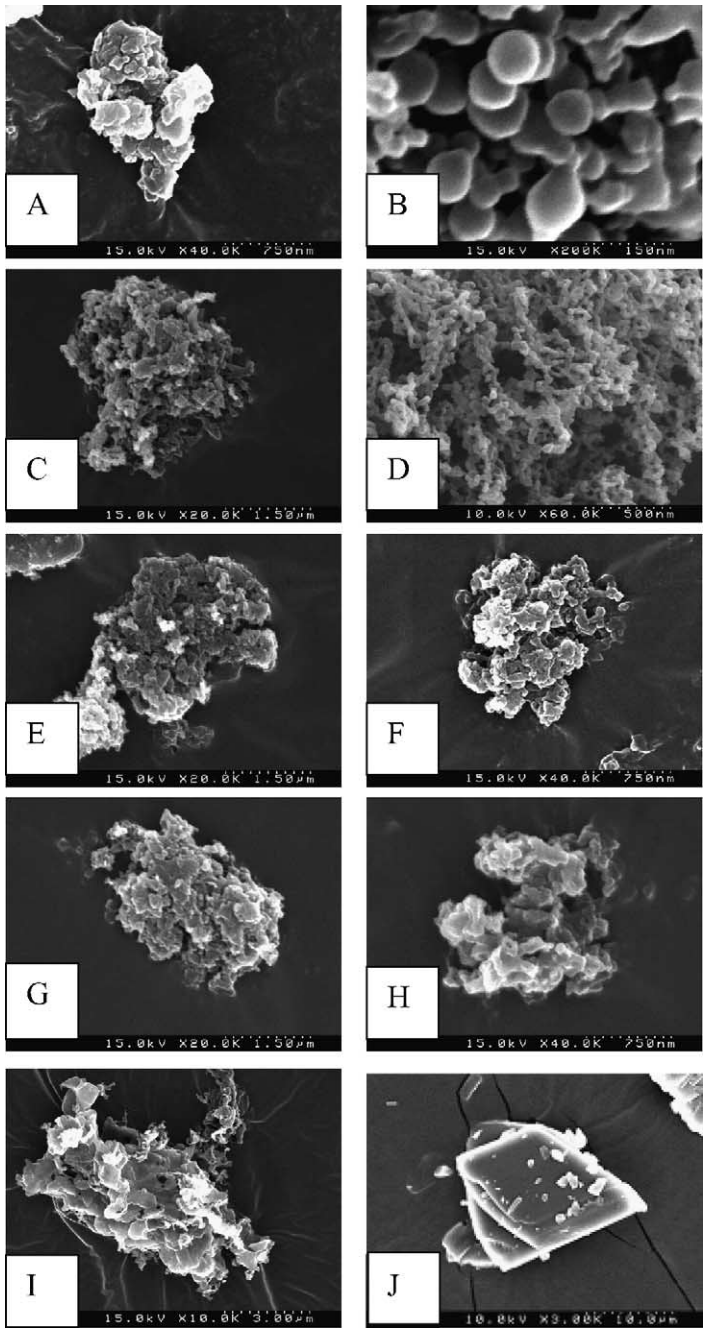

Fig. 2. SEM micrographs of SFL danazol/PVP K-15 (33% potency) (Fig. 2A and B), SFL danazol/PVP K-15 (50% potency) (Fig. 2C and D), SFL danazol/PVP K-15 (66% potency) (Fig. 2E and F), SFL danazol/PVP K-15 (75% potency) (Fig. 2G and H), SFL danazol/PVP K-15 (91% potency) (Fig. 2I), and bulk micronized danazol (Fig. 2J).

Table 2
Effect of potency on surface area and contact angle of SFL danazol/PVP K-15

Samples	Surface area (m^2/g)	Contact angle (°)
Danazol/PVP K15 (33% potency)	117.50	22 (0.4)
Danazol/PVP K15 (50% potency)	115.52	22 (0.5)
Danazol/PVP K15 (66% potency)	79.88	24 (0.4)
Danazol/PVP K15 (75% potency)	68.88	27 (1.0)
Danazol/PVP K15 (91% potency)	28.50	35 (2.0)
Bulk danazol	0.52	57 (2.2)

were larger and less porous compared to the SFL particles with lower potency.

The dissolution rate is directly proportional to the wetted surface area f the API, which in turn increases with decreasing particle size. SEM micrographs revealed that SFL danazol/PVP K-15 nanostructured aggregates had a porous morphology and were composed of many nanoparticles with a geometric diameter of about 50–100 nm. Surface areas of SFL danazol/PVP K-15 high potency powders were in the range of 28–117 m^2/g (Table 2). Several factors contributed to the large surface area and the high porosity of nanostructured aggregates produced by the SFL process (Hu et al., 2002; Rogers et al., 2001; Rogers et al., 2002). A high degree of atomization was achieved in the SFL process leading to the formation of high-surface area microdroplets. The freezing rate of the acetonitrile solution was very rapid. The formation of nuclei and their growth rate depends on the freezing rate of solution The rapid freezing rate resulting from the small droplet size limited the propensity for particle growth. In addition, the dried particles retained the shape of the micronized droplets after lyophilization. Their porous structures were due to the channels created as the solvent(s) were removed during the sublimation process. As a result, large surface areas and porous SFL powders composed of nanostructured aggregates were obtained by the SFL process. The surface area of SFL danazol/PVP K-15 powders decreased as the danazol potency increased. Here, the higher danazol loading in the feed solution led to faster growth rates during atomization and freezing and thus larger particles with lower porosity.

3.2.3. Wettability

The effective surface area also depends on the ability of the dissolution media to wet the particle surface. The wettability of SFL powders can be determined from the contact angle at the liquid/solid interface. For high contact angles, danazol is not very well wetted by the dissolution media. The contact angles for the SFL micronized powders and controls against SLS/Tris dissolution media are reported in Table 2. The mean contact angle for the SFL danazol/PVP K-15 powder was 22° (±0.5°), 24° (±0.4°), 27° (±1.0°), and 35° (±2.0°) for 50% potency, 66% potency, 75% potency, and 91% potency, respectively, which were significantly lower than that of the SFL danazol (57° ± 3.4°) ($P < 0.05$). The contact angle was an indicator of the wettability of SFL powders by the dissolution media. The significant reduction of contact angle for the high potency SFL powders compared to the controls indicated the presence of a hydrophilic solid surface (Doherty and York, 1987; Hu et al., 2002). This enrichment may be formed during the SFL process. As the danazol and PVP K-15 precipitated from the concentrated unfrozen acetonitrile, the precipitate was surrounded by hydrophilic solvent. The hydrophilic acetonitrile attracts the hydrophilic PVP K-15 molecules preferentially to the surface of the particles. In addition, the rougher surface for the SFL powders as indicated in the SEM micrographs and the higher surface areas may be expected to decrease the contact angle as observed (Hu et al., 2002). So, both preferential enrichment of the powder surface with the hydrophilic excipient and the surface roughness lower the contact angle and favor wetting of the high potency SFL powder relative to the controls. The contact angle of SFL danazol/PVP K-15 powders increased as the danazol potency increased, which was due to the decreased preferential enrichment of the powder surface with the hydrophilic excipient. Less enrichment may be expected as the danazol/PVP K-15 ratio increases.

3.2.4. Dissolution

The dissolution rate of SFL powders with different potencies is significantly greater than micronized bulk danazol (Fig. 3). The rate of dissolution of micronized bulk danazol was slow; only 30% of the danazol was dissolved in 2 min. However, the amount dissolved reached 95% in only 2 min for the SFL danazol/PVP K-15 powders (33–75% potencies). At 5 min, 99% of the danazol dissolved in the dissolution media. However, about 87% of the danazol in the SFL powder with 91% potency ratio dissolved in 2 minutes and

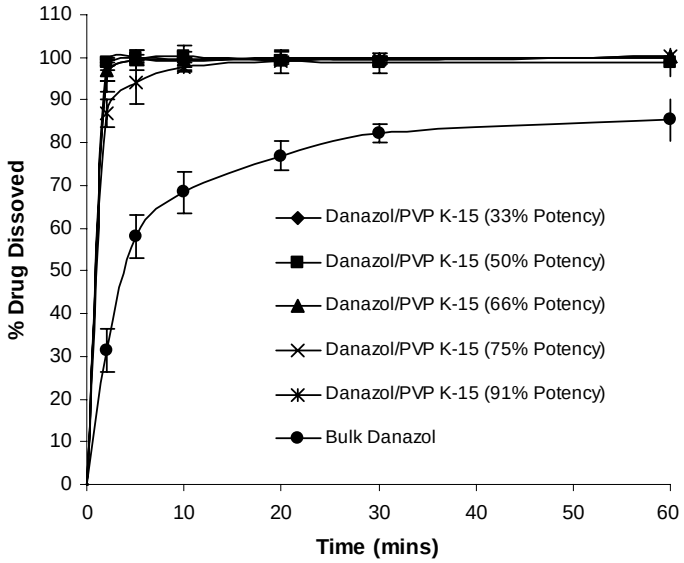

Fig. 3. Dissolution profiles (SLS 0.75%/Tris 1.21% buffer media) of SFL danazol/PVP K-15 powders with different potencies versus micronized bulk danazol.

100% danazol dissolved in 10 min. Each of the SFL powders with high potencies exhibited a significantly enhanced dissolution rates. The absence of danazol aggregates below 0.45 μm or disaggregated discrete particles passing through the 0.45 filter membrane was confirmed by DLS. The dissolution filtrate showed no particles. The SFL powders wetted and dissolved immediately upon contact with the dissolution media. The increased dissolution rate of the SFL powders may be attributed to the amorphous nature of danazol, the reduction in particle size, the enhanced surface area, and increased wettability. However, when danazol potency reached at 91%, about 87% of danazol dissolved in the first 2 min, which is lower than that of the SFL particles with lower potency. This may be caused by the lower surface area, and larger particles size.

3.3. Stability assessment

The limitation with the use of the amorphous pharmaceutical powders is the eventual conversion of the high energy, high soluble form to the lower energy crystalline form. The stress imposed in stability testing is an important factor influencing the solid-state properties of amorphous powders. A stability study was conducted for the SFL danazol/PVP K-15 high potency (3:1) at cycle stability conditions (−5 to 40 °C, six cycles per day) for one month to examine any changes in crystallinity and dissolution. Sample powders were stored in glass vials (20 ml) with aluminum-lined caps over a desiccant. The X-ray diffraction pattern of the SFL danazol/PVP K-15 (3:1) powder exhibited no change in peak intensity for danazol, suggesting that amorphous SFL powders were physically stable. The dissolution results (Fig. 4)

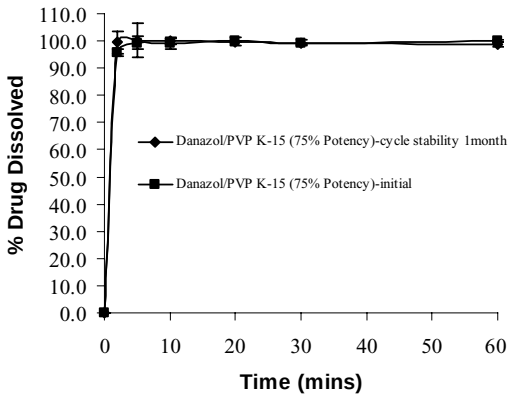

Fig. 4. Dissolution profiles (SLS 0.75%/Tris 1.21% buffer media, $n = 3$) of SFL danazol/PVP K-15 (75% potency) initial and SFL danazol/PVP K-15 after one month cycle stability.

demonstrated no significant difference in the dissolution profiles between the initial and one month samples. The dissolution rate results further confirmed the high stability of amorphous SFL powders observed by XRD. The high stability of amorphous SFL powders was partially attributed to PVP K-15 used in the SFL formulations. The inhibition of crystal growth by PVP is a well-known phenomenon (Kearney et al., 1994; Simonelli et al., 1970). The amorphous forms can be maintained with a stabilizing agent like PVP in the formulation. The inhibitory effect of PVP on crystallization may be due to the interaction of the API with PVP resulting in a reduction in the molecular mobility of the API.

4. Conclusions

Rapid dissolving SFL danazol/PVP K-15 powders with high potency (up to 91%) have been produced by SFL with an organic solvent mixture. The high potency SFL powders contained amorphous nanostructured aggregates with high surface area and excellent wettability. In only 5 min, 99% of the danazol dissolved. The production of surface areas on the order of 100 m^2/g required small amounts of surfactant stabilizer due to the rapid freezing rate, which allowed little time for particle growth. The composition of surfactant in the product could be controlled simply by the feed composition, as all of the surfactant precipitated with the API. Thus, the formulation is simpler to prepare than techniques that require separation of free surfactant from adsorbed surfactant in an aqueous suspension to achieve high potency (Chen et al., 2002). In SFL, solvent mixtures may be formulated to achieve high solubility of API in order to produce high potency powders. Furthermore, the polar solvent mixture in the continuous phase favors migration of the polar surfactant to the surface of the particles during particle formation. The coating with polar surfactant favors wetting of the high surface area during dissolution. The stability study with desiccant demonstrated that high potency amorphous SFL powders were physical stable without crystallization under a high stress cycle. The SFL process offers a highly effective approach to produce high potency nanoparticles contained in larger structured aggregates with rapid dissolution rates, and is especially applicable to delivery systems containing poorly water soluble drugs.

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