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RESEARCH PAPER

Stable Amorphous Danazol Nanostructured Powders with Rapid Dissolution Rates Produced by Spray Freezing into Liquid

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ABSTRACT

The objective of this study was to produce, by spray freezing into liquid (SFL) technology, high-potency, high glass transition temperature (T_g) danazol/polymer powders that remain amorphous and exhibit high dissolution rates after 6 months. Three polymers were investigated, including polyvinylpyrrolidone (PVP) K-15, poloxamer 407, and PEG 8000. The physicochemical properties of SFL powders were characterized by X-ray diffraction (XRD), scanning electron microscopy, particle size distribution, surface area analysis, moisture content, and dissolution rate. The influence of moisture content, drug potency, and excipient type on T_g of SFL powders was investigated using modulated differential scanning calorimetry (mDSC). XRD results indicated that danazol was amorphous for each added excipient. The surface area of danazol/PVP K-15 powders (89.8 m^2/g) was higher than that of danazol/PEG 8000 (12.0 m^2/g) and danazol/poloxamer 407 (5.49 m^2/g). The SFL powders with the various excipient types exhibited similar and significantly enhanced dissolution rates relative to micronized bulk danazol. As the potency of danazol in the SFL danazol/PVP K-15 powders was increased from 33% to 91%, the T_g decreased from 126°C to 104°C. The SFL powders, which were packaged in sealed 30-mL glass vials with a desiccant, were physically stable when stored at 25°C for 6 months, based on dissolution rates and mDSC and XRD measurements. SFL danazol/PVP K-15 powders with high surface areas and high glass transition temperatures remain amorphous and exhibit rapid dissolution rates after 6 months' storage.

Key Words: Spray-freezing into liquid; Dissolution; Poorly water-soluble drug; Stability; Glass transition temperature; Amorphous.

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INTRODUCTION

The spray freezing into liquid (SFL) particle engineering technology was developed to enhance the wetting and dissolution properties of poorly water-soluble active pharmaceutical ingredients (APIs).[1–4] In the SFL process, a feed solution containing poorly water-soluble API and/or excipient(s) is atomized directly into a cryogenic liquid to produce frozen particles. The frozen particles are then collected and lyophilized to obtain dry SFL 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. More recent studies demonstrated that SFL micronized powders containing danazol were amorphous as indicated by X-ray diffraction (XRD).[1,5,6] Scanning electron microscopy (SEM) micrographs indicated that SFL nanostructured aggregates were highly porous, with surface areas ranging from 11 m^2/g to 115 m^2/g. The dissolution of amorphous SFL danazol powders at 2 min was about 95%, a profound enhancement when compared with 30% for the crystalline micronized bulk danazol.[1,6]

Because the amorphous form of a pharmaceutical solid has a higher chemical potential than the thermodynamically stable crystalline form, it can exhibit enhanced dissolution rate and bioavailability. A key challenge is to stabilize the amorphous solid to prevent crystallization during storage.[5,7] The glass transition temperature (T_g) of an amorphous pharmaceutical solid can have a large influence on its physicochemical stability.[8] The molecular mobility of a high-energy amorphous API in a solid mixture with an excipient decreases when the storage temperature is reduced below its T_g. This loss in molecular mobility retards diffusion, thus reducing the potential for nucleation and growth of crystalline domains. Several studies report that the viscosity of amorphous material is more than 10^{12} cPs.[9,10] However, when the temperature rises above T_g, the increased molecular mobility of the API may lead to crystallization. It has been reported that certain amorphous pharmaceutical solids stored at 20°C to 50°C below their T_g were stable against crystallization.[11,12] For high surface area nanostructured amorphous materials, the driving force for crystallization is large, thus it is important to form a very rigid blend with a high T_g. There are several factors that influence the T_g of amorphous pharmaceutical solid mixtures. A key factor is the T_g of excipient and its compatibility with API. Miscible API-polymer blends exhibit a single T_g, which is intermediate to the T_g values of API and polymer.[13–15] In addition, the API/polymer ratio has a large effect on the T_g value of the mixture. Therefore, the choice of excipient and API/polymer ratio will greatly impact the stability of amorphous pharmaceutical solids. Moisture is another major factor that causes crystallization of API. Water can act as a plasticizer to depress the T_g and enhance crystallization.[8,16]

The first objective of this study was to investigate the influence of excipient type on the particle size, surface area, T_g, and dissolution rate of amorphous danazol powders produced by the SFL process. All the excipients led to powders with high danazol dissolution rates. Therefore, additional experiments focused on the excipient that provided the highest T_g, polyvinylpyrrolidone (PVP) K-15. The effect of drug potency (or drug/polymer ratio) and moisture on T_g was determined. The stability of danazol/PVP K-15 powders was studied after 6 months to examine whether any crystallization occurred and if the dissolution rate changed.

MATERIALS AND METHODS

Chemicals

The micronized bulk danazol was obtained from Spectrum Quality Products, Inc. (Gardena, CA). PVP K-15, PEO-*b*-PPO-*b*-PEO (Pluronic F127; poloxamer 407), polyethylene glycol 8000 (PEG 8000), sodium lauryl sulfate (SLS), and tris(hydroxymethyl)aminomethane (Tris) were purchased from Spectrum Quality Products, Inc. Acetonitrile and methylene chloride were obtained from EM Industries, Inc. (Gibbstown, NJ). Purified water was obtained from an ultrapure water system (Milli-QUV plus, Millipore S.A., Molsheim Cedex, France).

Preparation of SFL Danazol Powders

Danazol, PVP K-15, poloxamer 407, PEG 8000, or danazol/PEG 8000 (1:2) and danazol/poloxamer 407 (1:2) mixtures were dissolved in acetonitrile, and danazol/PVP K-15 (1:2, 1:1, 2:1, 3:1, 10:1) were dissolved in acetonitrile or acetonitrile/methylene chloride mixtures and processed by SFL.[1,6] A constant pressure (2000 psi) from the ISCO syringe pump provided a spray flow rate of 50 mL/min for the SFL feed solution. The atomizing nozzle consisted of polyetheretherketone tubing with an inner diameter of 127 μm and length of 15 cm. The SFL feed solutions were atomized into small droplets directly in the liquid N_2 phase. The rapidly frozen particles 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 a sodium calcium aluminosilicate hydrate desiccant in a vacuum desiccator at room temperature before. The micronized bulk danazol was used as a control.

Powder XRD

Powder XRD was conducted with $CuK\alpha_1$ radiation with a wavelength of 1.54054 Å at 40 kV and 20 mA using a Philips 1720 X-ray diffractometer (Philip Analytical, Inc., Natick, MA). The sample powders were placed in a glass sample holder and scanned from 5° to 45° (2θ) at a rate 0.05°/sec. The peak intensities for the three largest peaks were compared with those of the micronized bulk danazol.[17]

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.

Particle Size Measurement

The particle size distribution of the SFL powders and their controls were determined by laser light diffraction using a Malvern Mastersizer S (Malvern Instruments Limited, Malvern, Worcestershire, UK). D90, D50, and D10, the respective particle size at 10%, 50%, and 90% cumulative percent undersize, were determined for the SFL powers and controls.[18]

Surface Area Analysis

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 equation.[19]

Contact Angle Measurement

Compact discs 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 disc and observed using a low-power microscope. The contact angle was determined by measuring the tangent of the droplet on the surface with a Goniometer (Model No. 100-00-115, Ramè-Hart, Inc., Mountain Lakes, NJ).

Karl-Fisher Titration

Residual water content in the SFL powders was measured using an Aquatest 2010a Karl-Fisher Titrator (Photovolt Instrument, St. Louis Park, MN). Aliquots (10 mg) of sample powders were added into the titrator vessel following equilibration of the instrument. Each sample was measured in replicates of three ($n=3$).

Modulated Differential Scanning Calorimetry

The glass transition temperature was determined by modulated differential scanning calorimetry (mDSC) analysis using a TA Instruments DSC 2920 with mDSC capability. Aliquots weighing between 2 to 10 mg were placed in an aluminum pan (kit 0219-0041, Perkin-Elmer Instruments, Norwalk, CT) and crimped with an aluminum lid. The samples were heated from 25°C to 275°C to encompass the danazol melting point (225°C) at a heating rate of 10°C/min under a dry nitrogen gas purge. In the case of SFL poloxamer 407 and SFL danazol/poloxamer 407 powders, which had very low T_g, the sample was cooled to −70°C and then heated to 275°C at relatively low heating rate, 3°C/min, in order to determine T_g of the sample. All samples were initially heated to 275°C at 10°C/min to erase the effect of previous thermal history.[20–22]

Dissolution Studies

The amount of danazol dissolved, as a function of time, was determined using USP Apparatus 2 (paddles) (Vankel 7000, Vankel Technology Group, Cary, NC). All dissolution testing ($n=3$) was conducted under sink conditions. SFL micronized powders and control sample containing approximately 12 mg danazol were added to 900 mL of aqueous SLS/Tris dissolution media (SLS 0.75%/Tris 1.21%) at 37°C. The paddle speed was 50 rpm. A 5-mL aliquot was taken at each time point and analyzed by high-performance liquid chromatography (HPLC).[1]

HPLC Analysis

Each sample was filtered through 0.45-μm Acrodisc GHP syringe filter (Pall Corporation, Ann Arbor, MI), then diluted with acetonitrile and filtered through a 0.45-μm filter again. Samples were analyzed at

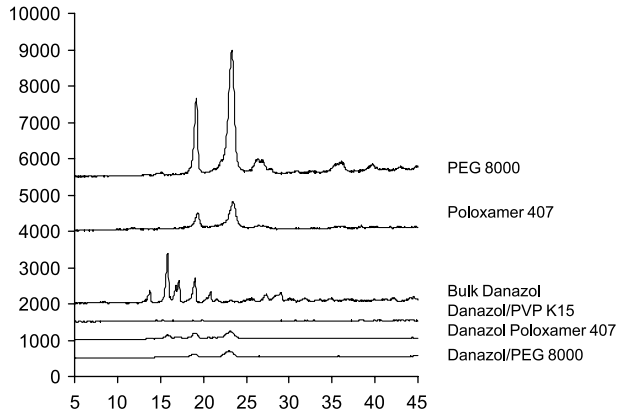

Figure 1. Effect of excipients on the crystallinity of danazol powders prepared by SFL as determined by powder XRD.

288 nm using a Shimadzu LC-10 chromatograph (Shimazu Corporation, Kyoto, Japan) and an Alltech 150-mm × 4.6-mm Intersil 5-μm ODS-2 reverse-phase column (Alltech Associates, Inc., Deerfield, IL). The danazol peak eluted at 5 min with mobile phase (acetonitrile/water at 7/3 ratio, v/v) flowing at 1 mL/min. A standard was injected after every six samples throughout the HPLC batch run. System suitability requirements were met [correlation coefficient (r^2) ≥ 0.998, precision of five replicate injection $\leq 2.0\%$ relative standard deviation (RSD), theoretical plates >500 plates/column and peak asymmetry ≤ 1.5].

Stability Study

Sample powders were stored over a desiccant in type I glass vials (30 mL) with aluminum-lined caps. The stability testing was conducted under the International Conference on Harmonization (ICH) stability conditions.[23] The SFL powders were stored at 25°C/60%RH for 6 months and characterized as a function of exposed time.

Statistical Analysis

The data were compared using a student's *t*-test of the two samples assuming equal variance to evaluate the difference. The significance level ($p=0.05$) was based on the 95% probability value ($p<0.05$).

RESULTS AND DISCUSSION

Influence of Excipient Type on SFL Powders

Crystallinity

The degree of crystallinity of danazol in the SFL powders was determined by powder XRD. Micronized bulk danazol (Fig. 1) had a similar XRD pattern to that previously reported,[24] indicating a high degree of crystallinity. However, for the SFL danazol/PVP K-15, danazol/poloxamer 407, and danazol/PEG 800 powders, the absence of characteristic peaks at 15.8, 17.2, and 19.0 (2θ) indicated an amorphous morphology for danazol.[1,24] The diffraction peaks of poloxamer 407 at 19.3 and 23.7 (2θ) and PEG 8000 at 19.5 and 23.4 (2θ) were present. XRD results showed that danazol was amorphous, regardless of excipient type used in the SFL composition. The freezing rate was fast enough to trap the danazol in an amorphous state without allowing time for crystallization. The rapid freezing rate results from atomizing the feed solution directly into liquid nitrogen.

Particle Size Distribution and Morphology

The particle size distribution for the SFL powders and controls (Table 1) were determined by laser light diffraction using a Malvern Mastersizer. The mean particle diameter (D50) of the SFL danazol/PVP K-15 powders was 1.18 μm. In contrast, D50 of the danazol/PEG 8000 and danazol/poloxamer 407 were 6.52 μm and 8.68 μm, respectively. The size reduction was significant after SFL processing compared with the starting material, micronized bulk danazol, which had a D50 of 23.42 μm. Various factors contributed to the limited particle growth during SFL process. The liquid–liquid impingement that occurs as the feed

Table 1. Effect of excipients on particle size distribution.

Samples	D10 (μm)	D50 (μm)	D90 (μm)
Micronized bulk danazol	7.42	23.42	51.7
SFL danazol/PVP K-15	0.15	1.18	22.88
SFL danazol/PEG 8000	1.08	6.52	26.46
SFL danazol/poloxamer 407	1.7	8.68	20.35

solution impacts the liquid nitrogen resulted in intense atomization into fine microdroplets. The atomized droplets were frozen very rapidly upon contact with the liquid N_2. The small droplet size and the rapid freezing rate limited the propensity for particle growth. However, the SFL danazol/PVP K-15 powders had D50 particle sizes less than those of danazol/PEG 8000 and danazol/poloxamer 407 powders.

The effect of excipients on the morphology of SFL powders was examined further by SEM. The SEM micrograph of bulk danazol (Fig. 2A) revealed a large crystalline plate with a fractured edge. In contrast, the morphology of SFL danazol/PVP K-15 (Fig. 2B) was a porous aggregate with a geometric diameter of about 700 nm. A higher magnification SEM micrograph (Fig. 2C) revealed an aggregate composed of many smooth nanoparticles with a geometric diameter of about 50 nm. The porous structures of SFL particles were due to the channels created as the solvent(s) were removed during the sublimation process. The SEM micrograph of the SFL danazol/PEG 8000 (Fig. 2D) powder revealed porous microparticles with a geometric diameter of about 6 μm. SFL danazol/poloxamer 407 particles (Fig. 2E) were larger and less porous relative

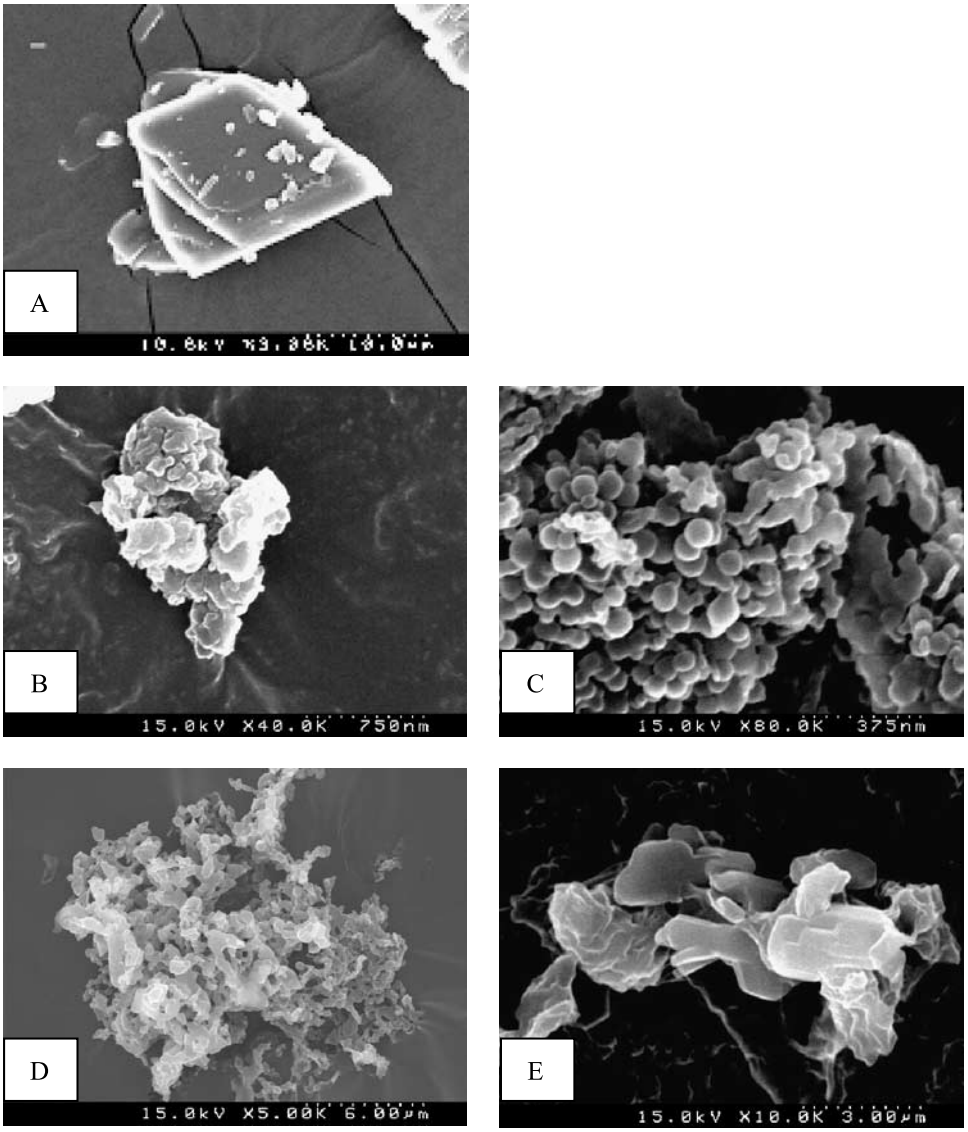

Figure 2. SEM micrographs of bulk micronized danazol (A), SFL danazol/PVP K-15 (B, C), SFL danazol/PEG 8000 (D), and SFL danazol/poloxamer 407 (E).

to the danazol/PEG 8000 and danazol/PVP K-15 particles. The SEM result confirmed the nanostructure of SFL particles observed by the particle size analysis.

Surface Area and Wettability

The surface area (Table 2) of SFL danazol/PVP K-15, danazol/PEG 8000, and danazol/poloxamer 407 were 89.8 m^2/g, 12.0 m^2/g, and 5.49 m^2/g, respectively. All surface areas of SFL powders were more than an order of magnitude greater than that of the micronized bulk danazol (0.52 m^2/g) ($p<0.05$). The large surface areas of SFL powders reflect the small particle size and porous morphology observed in the SEM micrographs. The surface areas of danazol/PEG 8000 and danazol/poloxamer 407 were lower than that of danazol/PVP K-15, which was consistent with the latter's larger particle size and less porous morphology.

The effective surface area also depends on the ability of the dissolution media to wet the particle surface. The wettability of SFL powders was determined from the contact angle at the SLS/Tris dissolution media/compact of SFL powders. The contact angles (Table 2) of SFL danazol/PVP K-15, danazol/PEG 8000, and danazol/poloxamer 407 were 22, 41, and 39 degrees, respectively. The great reduction of contact angle for SFL powders compared with the control (57 degrees) ($p<0.05$) indicated the presence of a more hydrophilic surface due to the polar excipient.[1,6] In addition, the rougher surface for the SFL powders as indicated in the SEM micrographs may be expected to decrease the contact angle as observed.[1] These data indicate that both preferential enrichment of the powder surface with the hydrophilic excipient and surface roughness lower the contact angle and favor wetting of the SFL powder relative to the control.

Dissolution Rate

The profiles presented in Fig. 3 illustrate the dissolution rates of the SFL powders and micronized bulk danazol ($n=3$). Only 58% of the micronized bulk danazol control dissolved in 5 min. However, profound improvements in the dissolution rates were found for SFL powders relative to the control (Fig. 3). For example, the amount of danazol from SFL danazol/PVP K-15 powders dissolved in 5 min was 99%. The difference in the dissolution rates of SFL powders prepared with the various polymer excipients was negligible at 5 min and inconsequential in the first 2 min. Each excipient was successful in producing extremely rapid dissolution. The increased dissolution rate of the SFL powders may be attributed to the amorphous nature of danazol, reduced particle size, and enhanced surface area. Furthermore, the hydrophilic polymer excipient aids the wettability of the large surface area.

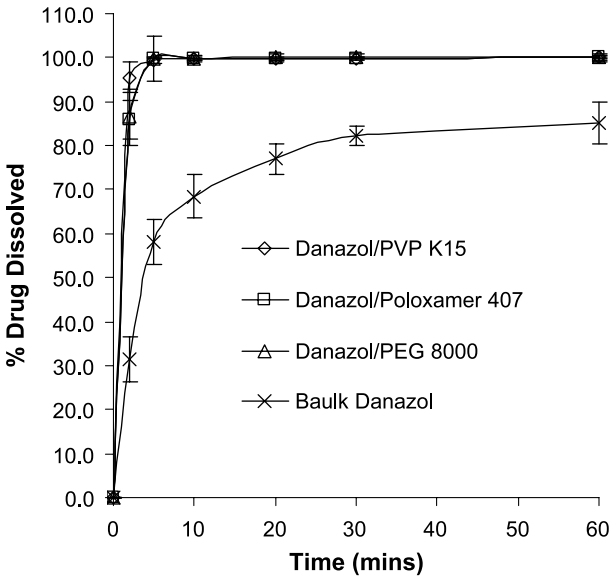

Figure 3. Dissolution profiles (SLS 0.75%/Tris 1.21% buffer media, $n=3$) of powders prepared by SFL and micronized bulk danazol.

Table 2. Effect of excipients on surface area and wettability.

Samples	Surface area (m^2/g)	Contact angle (degrees)
Micronized bulk danazol	0.5	57.0
Danazol/poloxamer 407	5.5	39.3
Danazol/PEG 8000	12.0	41.0
Danazol/PVP K-15	89.8	21.7

Influence of Moisture, Potency, and Excipient Type on T_g of SFL Powders

The T_g of the sample powders was determined by mDSC. The T_g was defined as the point on the curve with the steepest slope in the heat capacity increment during the second heating cycle.[21,22] The hypothesis of this study was that the physicochemical properties of amorphous SFL powders could be predicted and maintained by controlling the T_g of the SFL powder composition. Therefore, the influence of moisture

Table 3. Effect of excipients on the T_g of powders prepared by SFL.

Samples	T_g (°C)
SFL danazol	88.34
SFL PVP	146.13
SFL danazol/PVP K-15 (1:2)	126.87
SFL poloxamer 407	−21.21
SFL danazol/poloxamer 407 (1:2)	−5.71

content, danazol potency, and excipient type on T_g of amorphous SFL powders was investigated in the study.

T_g and Excipient Type

The mDSC results (Table 3) showed that the T_g of SFL danazol, PVP K-15, and poloxamer 407 were 88°C, 146°C, and −21°C, respectively. The T_g of SFL danazol/PVP K-15 powder was 126°C, which was much higher than that of SFL danazol/poloxamer 407 (−5°C) powder. The different excipients greatly impacted the T_g value of SFL powders. In addition, the mDSC results showed that both SFL danazol/PVP K-15 and danazol/poloxamer 407 had a single T_g intermediate compared with that of the pure components, indicating that danazol was in a miscible state with these polymers.[21,25] The two components are either thermodynamically miscible or the rapid freezing trapped the blend in a single T_g metastable state.

T_g and Danazol Potency

A more recent study demonstrated that the SFL process produced rapid-release, high-potency (33% to 91% w/w) SFL danazol powders for a danazol/PVP K-15 formulation.[6] The influence of drug potency on the SFL particle characterization has been discussed in the previous study.[6] In this study, the influence of danazol potency or likewise, the danazol/PVP K-15 ratio, on T_g of SFL powders was investigated. The mDSC results demonstrated that, as the danazol potency was increased from 33% to 91%, the T_g of SFL danazol/PVP K-15 powders decreased from 126°C to 104°C (Fig. 4), still 16°C above that of pure danazol. These results indicated a concentration-dependent T_g lying between the T_g of the danazol and PVP K-15. The Gordon-Taylor equation[26] may be used to predict the dependence of T_g on the weight fractions, w_1 and w_2, in a mixture

$$T_{g12} = \frac{w_1 T_{g1} + K w_2 T_{g2}}{w_1 + K w_2} \quad (1)$$

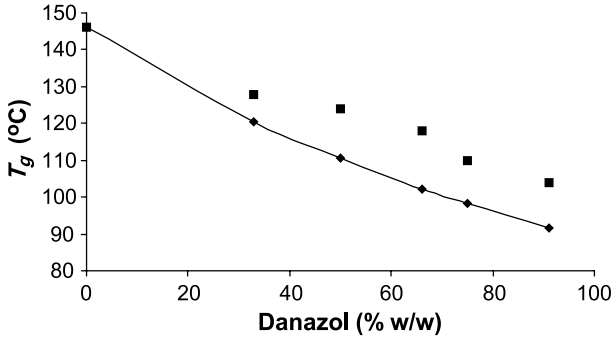

Figure 4. Effect of danazol potency on the T_g of SFL danazol/PVP K-15 powders. The solid line represents the predicted values from Gordon-Taylor equation. The symbols represent the measured T_g values.

where the subscripts 1 and 2=the API and polymer, respectively. The constant K, which is a measure of interaction between the API and polymer, can be estimated using the Simha-Boyer equation,[27]

$$K = \frac{\rho_1 T_{g1}}{\rho_2 T_{g2}} \quad (2)$$

where ρ_1 and ρ_2=the true densities of two components. Figure 4 shows that the measured T_g values of SFL danazol/PVP K-15 were higher than the T_g values predicted by the Gordon-Taylor equation, suggesting a positive deviation from ideal behavior. This positive deviation suggests that the API and polymer bind more strongly to each other than would be expected from the average of the pure component interactions. This positive deviation was present for all potencies investigated.

T_g and Water Content

The residual water associated with amorphous pharmaceutical solids can have significant effects on their T_g.[8,16,28] Water has a very low T_g of approximately −134°C.[13] Uptake of water can plasticize the

Table 4. Effect of moisture content on the T_g of SFL danazol/PVP K-15.

Moisture (% w/w)	T_g (°C)
1.48	126.87
5.21	108.68
8.13	96.58
11.38	64.00

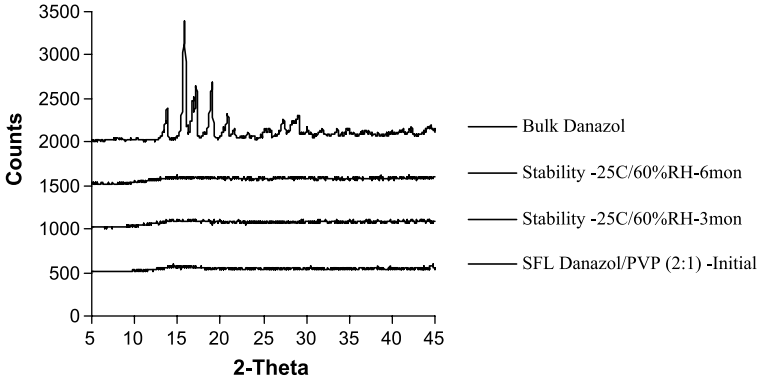

Figure 5. Powder XRD patterns of micronized bulk danazol, SFL danazol/PVP K-15 (2:1) initial, and SFL danazol/PVP K-15 6 months at 25°C/60%RH.

drug or polymer and greatly increase the free volume of the solid, leading to a decrease in T_g. The SFL danazol/PVP K-15 powders stored in the opened container were exposed to 40°C/75%RH up to 2 hr and the water content was determined as a function of exposed time. Table 4 shows that the T_g decreased from 127°C to 64°C as the moisture content increased from 1.48% to 11.38%. No crystalline peak (melting peak) of danazol was observed in the DSC results, indicating danazol in the sample was still in amorphous form. Because PVP K-15 is a hygroscopic polymer, there was initial moisture content for SFL danazol/PVP K-15 sample, as a result of absorption of water vapor from the surrounding atmosphere during the packing step and as a result of water vapor in the atmosphere in the lyophilization process. This large reduction in T_g indicates that these amorphous pharmaceutical solids should be stored with a desiccant.

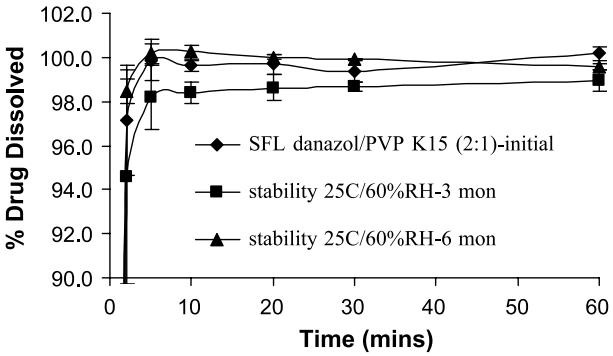

Figure 6. Dissolution profiles (SLS 0.75%/Tris 1.21% buffer media, $n=3$) of SFL danazol/PVP K-15 (2:1) initial and SFL danazol/PVP K-15 6 months at 25°C/60%RH.

Stability of SFL Powders

The current ICH guideline recommends long-term stability testing to be conducted at 25°C/60%RH (ICH Guideline Q1A). A stability study was conducted for the SFL danazol/PVP K-15 at these conditions for 6 months. Sample powders were stored over a desiccant in glass vials (30 mL) with aluminum-lined caps. The XRD, DSC, and in vitro dissolution rates for the amorphous pharmaceutical solids were used to check their stability. The XRD (Fig. 5) of SFL danazol/PVP K-15 powders exhibited no change in peak intensity for danazol, suggesting that the danazol crystallinity was unchanged for 6 months. In addition, the DCS results showed there were no endotherms at 225°C, which was the melting point of danazol. Furthermore, the T_g of the 6-month sample was 117.41°C, which was similar to the T_g of initial SFL danazol/PVP K-15 powders (118.76°C). If the danazol crystallized, the mixture T_g would not have stayed constant. Thus, the DSC results indicated that danazol was amorphous after 6 months' storage. Figure 6 demonstrates that the difference in the dissolution profiles between the initial and 6-month samples was insignificant. The profiles were compared in terms of the similarity factor f_2, according to the method reported by Shah et al.[29] The results of the XRD patterns, DSC, and dissolution rates indicate excellent stability for the amorphous SFL danazol/PVP K-15 powders at 25°C/60%RH for 6 months.

CONCLUSION

For the three polymeric excipients, the SFL process produced rapidly dissolving amorphous danazol

powders with small particle size, high surface area, and enhanced wettability. A single T_g peak was observed for each SFL 6-month stability sample, indicating a stable miscible blend. The danazol/PVP K-15 powders had the highest T_g values and were thus used for long-term stability studies. The T_g of the SFL danazol/PVP K-15 powders remained high, decreasing from 126°C to 104°C as the danazol potency increased from 33% to 91%. The danazol/PVP K-15 powders stored with the desiccant at 25°C did not crystallize even after 6 months, as demonstrated with XRD and mDSC measurements, and the dissolution rate remained high. The ability to stabilize nanostructured high surface area API powders in high T_g formulations offers great promise for the development of poorly water-soluble drugs by significantly enhancing dissolution rates.

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