Improvement of Dissolution Rates of Poorly Water Soluble APIs Using Novel Spray Freezing into Liquid Technology

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Purpose. To develop and demonstrate a novel particle engineering technology, spray freezing into liquid (SFL), to enhance the dissolution rates of poorly water-soluble active pharmaceutical ingredients (APIs).

Methods. Model APIs, danazol or carbamazepine with or without excipients, were dissolved in a tetrahydrofuran/water cosolvent system and atomized through a nozzle beneath the surface of liquid nitrogen to produce small frozen droplets, which were subsequently lyophilized. The physicochemical properties of the SFL powders and controls were characterized by X-ray diffraction, scanning electron microscopy (SEM), particle size distribution, surface area analysis, contact angle measurement, and dissolution.

Results. The X-ray diffraction pattern indicated that SFL powders containing either danazol or carbamazepine were amorphous. SEM micrographs indicated that SFL particles were highly porous. The mean particle diameter of SFL carbamazepine/SLS powder was about 7 μm. The surface area of SFL danazol/poloxamer 407 powder was 11.04 m^2/g. The dissolution of SFL danazol/poloxamer 407 powder at 10 min was about 99%. The SFL powders were free flowing and had good physical and chemical stability after being stored at 25°C/60%RH for 2 months.

Conclusions. The novel SFL technology was demonstrated to produce nanostructured amorphous highly porous particles of poorly water soluble APIs with significantly enhanced wetting and dissolution rates.

KEY WORDS: danazol; carbamazepine; spray freezing into liquid; dissolution; stability.

INTRODUCTION

Many potentially bioactive molecules have been rejected during the early stages of development because they are poorly water soluble and difficult to wet. Active pharmaceutical ingredients (APIs) with poor aqueous solubility often demonstrate low bioavailability when administrated orally due to the dissolution rate-limiting absorption in the gastrointestinal (GI) tract. Of particular interest is the poorly water soluble, highly permeable APIs discussed in the Biopharmaceutics Classification System (BCS Class II) (1), such as danazol and carbamazepine. The irregular and delayed absorption of danazol and carbamazepine has been attributed to slow dissolution rates (2,3). The physicochemical properties of the APIs play a significant role in controlling their dissolution from a dosage form. According to the Noyes-Whitney equation, the aqueous solubility of an API is a factor determining dissolution rate. Other factors include the particle size distribution, degree of crystallinity, as well as the presence of surfactants and other additives. Other physical properties such as wettability, density, and viscosity contribute to particle flocculation, flotation, and agglomeration, which further influence dissolution rates.

Increasing the dissolution rate of poorly water soluble APIs is a significant challenge to pharmaceutical scientists. Technologies that have been commonly used to improve the dissolution rate of poorly water soluble APIs include mechanical milling, spray drying, precipitation, and freeze-drying. Spray drying is a widely used technology (4). However, because the spray drying process uses elevated temperatures, it is not always appropriate for use with thermolabile compounds. The process precipitation with a compressed fluid antisolvent (PCA), also referred to as SEDS or SAS, has been used to produce particles containing poorly water-soluble API and water-soluble excipients (5). In some cases this process can be limited by the lack of solvent systems compatible with compressed carbon dioxide that dissolve both hydrophilic and hydrophobic substances simultaneously. Although lyophilization or freeze-drying (6) is a promising technique for producing pharmaceutical powders, the freezing rate in some cases is too slow so that the solvent crystallizes as it is frozen.

The objective of this study was to develop and demonstrate the use of the novel spray freezing into liquid (SFL) particle engineering technology to enhance the dissolution rate of two poorly water soluble APIs, danazol and carbamazepine, and to determine the physicochemical stability of SFL powders.

SFL is a novel cryogenic atomization technology in which either an aqueous or an aqueous-organic cosolvent solution containing an API and pharmaceutical excipient(s) is atomized directly into a compressed liquid, such as compressed fluid CO_2, helium, propane, ethane, or the cryogenic liquids nitrogen, argon, or hydrofluoroethers. SFL technology was created by the adaptation of several atomization processes. SFL is derived in part from the PCA process, which utilizes liquid-liquid impingement between an organic or organic/aqueous feed solution through a nozzle that is submerged into compressed CO_2 fluid. As the two liquids collide, the high Reynolds and Webber numbers lead to intense atomization into micronized droplets. In PCA the solvent(s) must be miscible with compressed fluid CO_2 to produce dry particles from the microdroplets. The low solubility of water in CO_2 limits markedly the use of solvents containing water, which are often needed to dissolve hydrophilic excipients. Other limitations include the need for elevated pressures and the recovery of product from a high-pressure vessel. With the novel SFL technology, the solvents are frozen during the spray and are not required to be miscible with the cryogenic liquid in contrast to PCA. Liquid nitrogen is utilized as the cryogenic fluid in this study instead of CO_2 because of the ultra-rapid freez-

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ing rates resulting from its low boiling point of –196°C. The feed solution is atomized below the liquid surface in a dewar flask at atmospheric pressure. The suspended frozen powder can then be separated from the cryogenic continuous phase by sieve filtration or other means.

In spray freezing into vapor over liquid (SFV/L) (7–11), the feed solution is atomized through a nozzle positioned at a distance above the boiling refrigerant. The droplets may begin to solidify while passing through the vapor gap and then freeze completely as contact is made with the boiling refrigerant liquid. Spray-freezing into halocarbon vapor over liquid has been performed by Briggs and Maxwell and Adams *et al.* (7,8). The resulting particles ranged in diameter from 0.84 mm to 1.68 mm (7). Halocarbon refrigerants present problems. Chlorofluorocarbons are deleterious to the ozone layer, and the replacement hydrofluoroalkane refrigerants are expensive (12). In addition, both chlorofluorocarbons and hydrofluoroalkane are suitable solvents for lipophilic compounds, so API extraction into the halocarbon cryogen can result in low product yield (13).

Gombotz *et al.* and Gusman and Johnson developed spray freezing into nitrogen vapor over liquid technologies for the purpose of capturing frozen API particles following atomization (14,15). As the atomized droplets pass through the vapor gap above the liquid nitrogen, they may collide and coalesce. The solutes may precipitate and grow in the unfrozen liquid droplets as they cool and/or coalesce. The particle morphology is not quenched until the droplets are fully solidified on contact with the liquid nitrogen phase below the vapor. Each of these factors may broaden the particle size distribution.

In the novel SFL technology, the solution is sprayed below the surface of the cryogenic liquid phase to avoid particle growth in the vapor gap described above for the conventional SFV/L process. The liquid-liquid impingement that occurs as the feed solution impacts the cryogenic media results in intense atomization into fine microdroplets that freeze instantaneously. A schematic representation of the SFL apparatus is shown in Fig. 1. A pressurized syringe pump is used to propel the feed solution from the solution vessel through an insulated nozzle that is submerged beneath the surface of the cryogenic liquid. Nitrogen is the cryogen of choice because it is inexpensive, environmentally friendly, inert, and may be used at atmospheric pressure, unlike CO_2. Because of the ultra-rapid freezing rates achieved by atomizing the feed solution directly into liquid nitrogen, a cryogenic suspension containing the dispersed frozen microparticles is produced. The SFL micronized powder can then be separated from the liquid nitrogen by using a fine sieve to collect the powder. The frozen powder is then dried, in this study by lyophilization, to produce the dry SFL micronized powder.

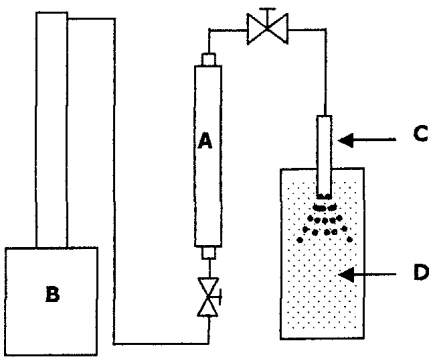

Fig. 1. Schematic diagram of the SFL apparatus illustrating the solution cell (A), high pressure pump (B), atomizing nozzle (C), and the cryogenic liquid cell (D).

The SFL process offers a variety of advantages relative to traditional technologies mentioned above. Because of intense atomization, the formation of high-surface area droplets and the low intrinsic temperature of liquid nitrogen, ultra-rapid freezing rates are achieved. As a result of the ultra-rapid freezing rates, the time for phase separation of solutes within the feed solution is minimized. Therefore, the API molecules may be dispersed homogeneously throughout the solidified excipient matrix of the frozen microparticle. After lyophilization, the dried microparticle retains the shape of the microdroplet, but is highly porous due to the channels created as the solvent(s) are removed. The API is molecularly dispersed within a homogeneous excipient matrix that composes the porous microparticle.

Aqueous media should immediately wet and dissolve the SFL microparticles due to the high surface area of the porous microparticles. The dissolution media will fill the pore channels and dissolve the API and hydrophilic excipients, which are utilized to enhance the aqueous dissolution of a lipophilic API.

MATERIALS AND METHODS

Chemicals

Danazol USP and carbamazepine USP were obtained as micronized powders. A polyoxyethylene-*b*-polyoxypropylene-*b*-polyoxyethylene triblock copolymer (Pluronic F127; Poloxamer 407), polyvinylpyrrolidone (PVP) K-15, sodium lauryl sulfate (SLS) NF, sodium taurocholate, lecithin NF, potassium chloride NF, and sodium hydroxide NF were purchased from Spectrum Quality Products Inc. (Gardena, CA, USA). Tetrahydrofuran (THF), methanol, acetonitrile, and acetic acid were obtained from EM Industries Inc. (Gibbstown, NJ, USA). Purified water was obtained from an ultrapure water system (Milli-QUV plus, Millipore S. A., Molsheim Cedex, France).

SFL Processing

SFL feed solutions were prepared according to the following procedure. Danazol or carbamazepine was dissolved in THF. Poloxamer 407, PVP K-15, and/or SLS were dissolved in water. The aqueous and organic solutions were then mixed to obtain danazol/excipient blend and carbamazepine/excipient blend SFL feed solutions.

A schematic diagram of the SFL apparatus is shown in Fig. 1. The SFL feed solution was placed into the solution cell (A). A constant pressure of 4000 PSI from the ISCO syringe pump (B) (Model 100 DX, ISCO Inc., Lincoln, NE, USA) provided a flow rate of 11 mL/min for the SFL feed solution. The solution cell was connected to an insulated nozzle (C), which was positioned to atomize the SFL feed solution beneath the surface of the cryogenic liquid (D). In these experiments liquid N_2 was used as cryogenic liquid. The atomizing nozzle used was composed of polyetheretherketone tubing

with an inner diameter of 63.5 μm. The SFL feed solutions were then sprayed through the nozzle and atomized directly into the liquid N_2 phase. Frozen particles formed instantaneously. The frozen particles were collected and lyophilized in a Labconco freeze dryer (Freeze dryer 5, Labconco Corporation, Kansas City, MO, USA) for 48 h.

To investigate the influence of the ultra rapid freezing rate in conjunction with atomization in the SFL technology, a lyophilized mixture formed directly by conventional lyophilization process was used as a control (LM control). The lyophilized mixture was made of an API and excipients frozen at −78°C and lyophilized for 48 h. The compositions of the lyophilized mixtures were identical to the SFL powders. The influence of the excipients on the physicochemical properties of the SFL powders was further studied by comparison with a physical mixture of API and excipients (PM control). The physical mixtures were of the same composition as the SFL API powders. The micronized APIs were also used as a control. The SFL powders and control samples were stored in glass vials over desiccant in a vacuum desiccator at room temperature before the characterization measurement.

Powder X-Ray Diffraction

Powder X-ray diffraction (XRD) was conducted using $CuK\alpha_1$ radiation with a wavelength of 1.54054 Å at 40 kV and 20 mA from a Philips 1720 X-ray diffractometer (Philips Analytical, Natick, MA, USA). 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 API samples (16).

Scanning Electron Microscopy (SEM)

A HITACHI S-4500 field emission SEM (Hitachi Instruments Inc., Irvine, CA, USA) 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 Distribution

The particle size distribution of the sample powders was determined using the method based on a time-of-flight measurement (Aero-Disperser®, Amherst Process Instrument, Amherst, MA, USA). The mean particle diameter and span index were determined for the SFL powers and controls.

Surface Area Measurement

A Nova 3000 surface area analyzer (Quantachrome Corporation, Boynton Beach, FL, USA) 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 (17).

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, USA) with flat-faced 6 mm diameter punches. A droplet of purified water or fed state simulated intestinal fluid (FeSSIF) media (3 μl) was placed onto the surface of 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, USA).

Dissolution Studies

The amount of API dissolved, as a function of time, was determined using USP Apparatus 2 method (Vankel 7000, Vankel Technology Group, Cary, NC, USA). All dissolution studies were conducted at sink conditions. The FeSSIF media was prepared according to Dressman *et al.* (18). SFL danazol/poloxamer 407 powders or control samples containing approximately 3 mg danazol were added to 900 mL of FeSSIF media (37°C). The paddle speed was 50 rpm. 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 (19,20). Purified water (900 mL) was used for the carbamazepine as the dissolution media and the same operating parameters discussed for danazol. Dissolution profile for SFL carbamazepine/excipients powders were studied as well as their controls.

Stability Study

Stability studies were conducted at 25°C/60%RH. Sample powders were stored in the capped glass vials (20 mL) 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 variances to evaluate the differences. The significance level ($\alpha = 0.05$) was based on the 95%probability value ($p < 0.05$).

RESULTS AND DISCUSSION

Crystallinity

The crystallinity greatly impacts the solubility and dissolution rate of poorly water-soluble APIs (21). The chemical potential of a metastable high-energy amorphous state can be markedly larger than that of an equilibrium crystal. This higher chemical potential can lead to a substantially greater local solubility of the API near the interface and thus a faster mass transfer rate into the dissolution media. Therefore, the crystallinity of an API may be reduced to enhance the dissolution rate. Powder XRD patterns of SFL powders and control samples are presented in Figs. 2 and 3. Micronized bulk danazol had a similar X-ray diffraction pattern to that reported by Liversidge and Cundy (22). The high peak intensities of bulk danazol indicated a high degree of crystallinity. The physical mixture and lyophilized mixture showed the characteristic diffraction peaks (16) of danazol at 15.8, 17.2, and 19.0 (2θ). The X-ray pattern of the SFL danazol/poloxamer 407 powder exhibited a significant reduction in peak intensity for danazol. The diffraction peaks of danazol were not evident whereas those of poloxamer 407 at 19.3 and 23.4 (2θ) were present. This absence of peaks indicated that danazol contained in SFL danazol/poloxamer 407 powder was in an amorphous state. Similarly, lack of crystallinity was also

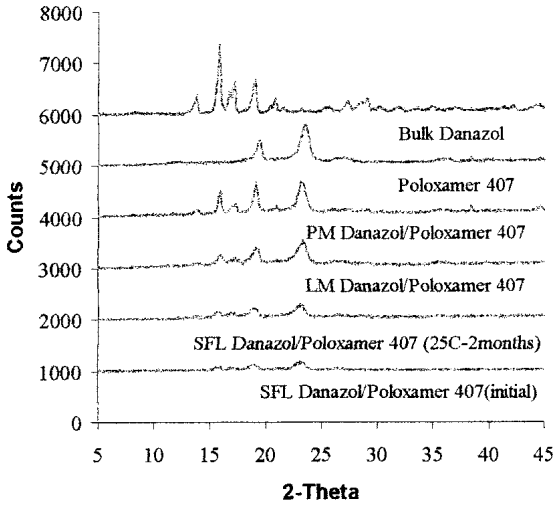

Fig. 2. Powder X-ray diffraction patterns of micronized danazol, PM danazol/poloxamer 407, LM danazol/poloxamer 407, and SFL danazol/poloxamer 407.

found for the SFL carbamazepine/SLS powder (Fig. 3). The absence of characteristic peaks of carbamazepine (23) at 15.3, 25.0, and 27.6 (2θ) indicated an amorphous state. The controls (either physical mixture or lyophilized mixture) exhibited crystalline diffraction peaks of carbamazepine. For both danazol and carbamazepine the powders produced by SFL technique exhibited very little crystallinity, in contrast with the significant crystallinity for powders made by the conventional lyophilization process. Apparently, the freezing rates in the SFL technique were fast enough to trap the API in an amorphous state without allowing time for crystallization. Ultra-rapid freezing may be expected from the high surface area of the atomized droplets and the rapid heat transfer from the droplets to the liquid nitrogen.

Particle Size Distribution and Morphology

The particle size of an API is another important parameter controlling the dissolution rate. Decreasing the particle size increases the surface area, which enhances the dissolution rate (24). The particle size distribution for the SFL powders and controls (Table I) were determined in an Aero-Disperser® based on time-of-flight measurements. The mean particle diameter of the SFL danazol/poloxamer 407 powder was 7.10 μm. In contrast, the mean particle diameters of the danazol and lyophilized mixture were 18.27 and 18.86 μm, respectively. Similar results were found for the SFL carbamazepine/SLS powder. The mean particle diameter of the SFL carbamazepine/SLS powder was 7.11 μm, which was smaller than that of the controls. The span index is used to describe the polydispersity in a given particle size distribution and is defined as (D90-D10)/D50, where D10, D50, and D90 are the respective particle sizes at 10, 50, and 90% cumulative percentage undersize (25). The span index of carbamazepine was 2.94, indicating high polydispersity. For the SFL powder the polydispersity was decreased markedly down to 1.31. The conventional lyophilization process reduced the mean particle diameter only slightly compared to the micronized APIs. However, for both danazol and carbamazepine, the SFL technique produced nanostructured particles with narrow particle size distributions. Various factors contributed to the limited particle growth during SFL processing. The atomized droplets were immediately frozen upon the rapid freezing rate, and the rapid freezing rates limited the time for particle growth. Also, the surfactant in the unfrozen domains in the sprayed droplets inhibits particle coalescence and crystal growth.

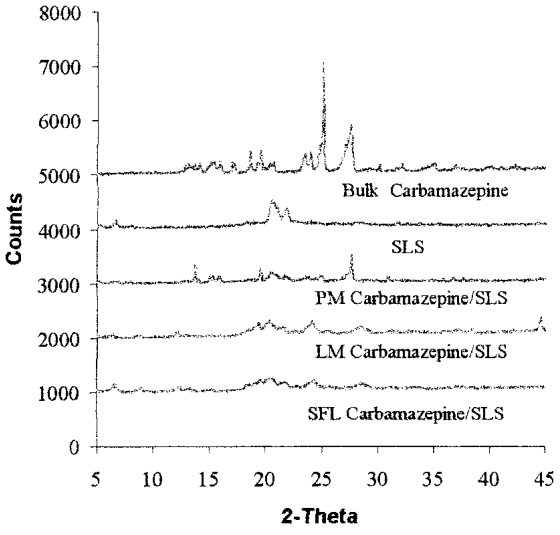

Fig. 3. Powder X-ray diffraction patterns of micronized carbamazepine, PM carbamazepine/SLS, LM carbamazepine/SLS, and SFL carbamazepine/SLS.

To further investigate the effect of the SFL technique on the morphology of APIs, sample powders were examined by SEM. The SEM micrograph of the micronized bulk danazol (Fig. 4a) illustrates large crystalline particles. The SEM micrograph of the lyophilized control particles (Fig. 4b) indicates a smooth surface when compared with the bulk danazol. In contrast, the SFL danazol/poloxamer 407 particles (Fig. 4c) had a highly porous morphology. The surface area of the SFL danazol/poloxamer 407 powder was 11.04 m^2/g, which was a significant increase over the lyophilized mixture (1.27 m^2/g). The high surface area confirmed the highly porous structure of SFL powders observed by SEM. Such high surface area indicated that the SFL powder particles were highly porous, similar to the SFV/L produced protein particles reported by Maa *et al.* (4) and Costantino *et al.* (26). Similar results for SFL carbamazepine/excipients powders were observed in the SEM analysis and surface area measurement. For example, the SEM micrograph of the SFL carbamazepine/SLS sample demonstrates a fine powder consisting of porous microparticles. Powder made by the conventional lyophilization process was larger and less porous relative to the SFL powder. The surface area of SFL carbamazepine/SLS powder was 12.81 m^2/g, which was greater than that of the lyophilized mixture (2.33 m^2/g).

Table I. Effect of Composition and Process on the Particle Size Distribution

Sample	D10	D50	D90	Span index
Bulk danazol	7.14	18.27	29.56	1.23
Slowly frozen control	7.27	18.86	31.13	1.27
SFL danazol/poloxamer 407	1.54	7.10	10.20	1.22
Bulk carbamazepine	15.56	39.70	132.33	2.94
Slowly frozen control	4.58	26.71	46.74	1.58
SFL carbamazepine/SLS	1.33	7.11	10.61	1.31

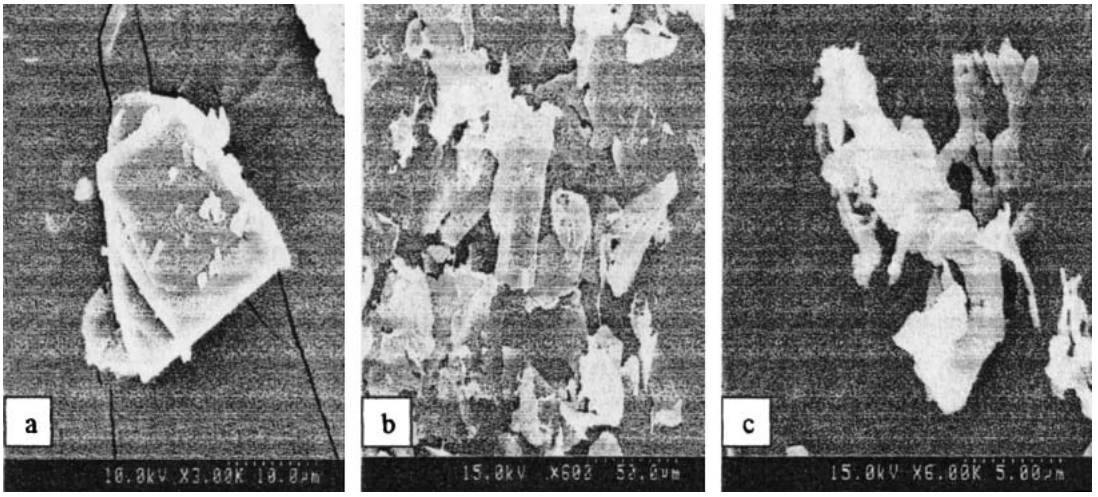

Fig. 4. SEM micrographs of micronized danazol control (Fig. 4a), LM danazol/poloxamer 407 (Fig. 4b) and SFL danazol/poloxamer 407 (Fig. 4c).

Wettability

The importance of wettability on dissolution rate—that is, the area of contact between a powder and dissolution media—has been well studied (27). To characterize wettability, the contact angle was used to determine the interfacial tension present between the compact of API powders and liquid intercontact angle values for the SFL powders, and controls are reported in Table II. The limits in the contact angle are 0° for complete wetting and 180° for no wetting (28). The mean value of contact angle for the SFL danazol/poloxamer 407 powder was only 25° against the FeSSIF media, which was significantly lower than that of the SFL danazol (55°), lyophilized mixture (34°), and physical mixture (58°) ($p < 0.05$). The mean value for SFL carbamazepine/SLS powder was 24° against purified water, which was significantly lower than for the physical mixture (52°) and SFL carbamazepine ($p < 0.05$). The significant reduction of contact angle θ for the SFL powders compared with the controls indicated the presence of a hydrophilic solid surface. Specifically, the contact angle is described by the equation: $\cos \theta = f_1 \cos \theta_1 + f_2 \cos \theta_2$ (29), where f_1 and f_2 are the bulk volume fractions of the API and excipient. The contact angle of SFL powders was well below that of the physical mixture, indicating that the solid surface of the SFL powder was enriched in the hydrophilic excipient.

Table II. Effect of Composition and Process on the Contact Angle of Danazol and Carbamazepine Powders

Samples	Contact angle degrees (FeSSIF media)
PM danazol/poloxamer 407	58
LM danazol/poloxamer 407	34
SFL danazol	55
SFL danazol/poloxamer 407	25
	Contact angle degrees (purified water)
PM carbamazepine/SLS	52
LM carbamazepine/SLS	29
SFL carbamazepine	45
SFL carbamazepine/SLS	24

This enrichment may be formed during the SFL process. As the API and excipient precipitated from the concentrated unfrozen aqueous phase, and the precipitate was surrounded by hydrophilic solvent. The hydrophilic solvent attracts the hydrophilic excipient molecules preferentially to the surface of the particles. The lower contact angle of the SFL powders compared with the lyophilized mixture may be due to the surface roughness. The rougher surface for the SFL powders relative to the lyophilized mixture as depicted in the SEMs and the higher surface areas may be expected to decrease the contact angle as observed. 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 SFL micronized powder relative to the controls.

Dissolution

The profiles presented in Figs. 5 and 6 illustrate the dissolution of the SFL powders and controls for danazol and carbamazepine, respectively. The FeSSIF media used for the danazol dissolution studies reportedly simulates *in vivo* gas-

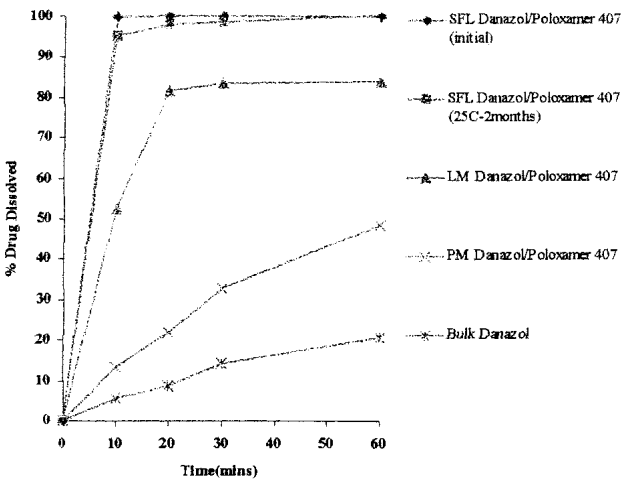

Fig. 5. Dissolution profiles of micronized danazol, PM danazol/poloxamer 407, LM danazol/poloxamer 407, and SFL danazol/poloxamer 407.

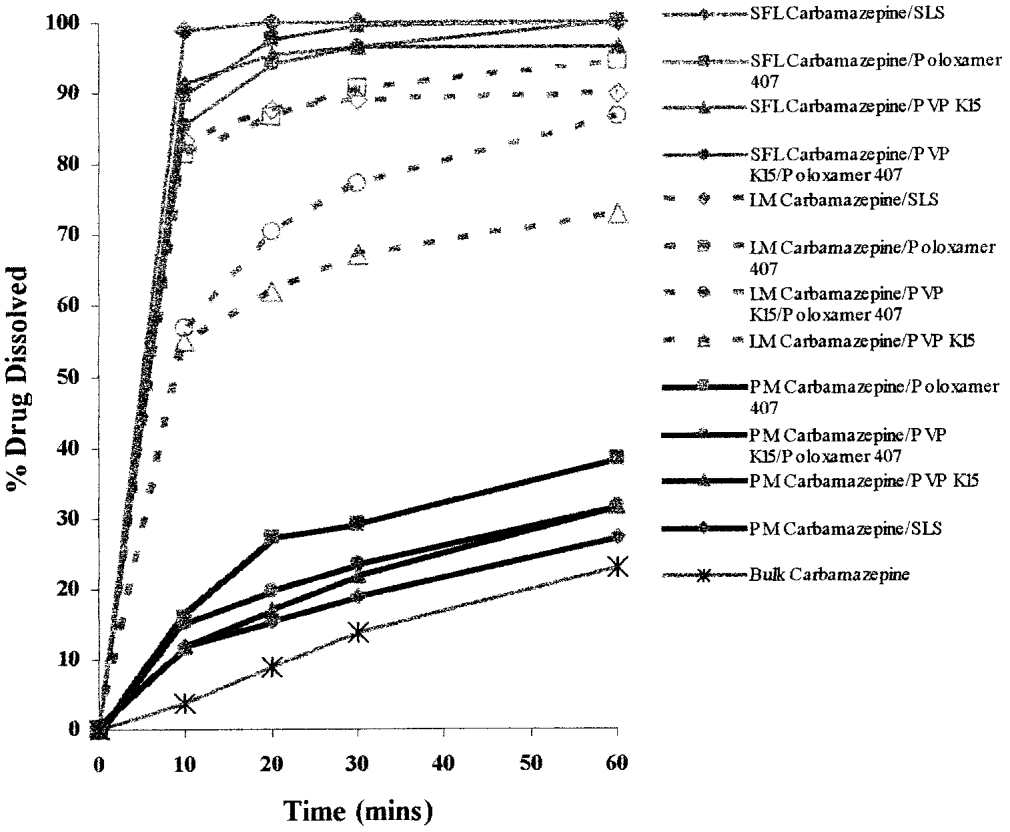

Fig. 6. Dissolution profiles of SFL carbamazepine/SLS, SFL carbamazepine/poloxamer 407, SFL carbamazepine/PVP K15, SFL carbamazepine/poloxamer 407/PVP K15, and their respective controls.

trointestinal fluid; low levels of surfactants are recommended to be included in the dissolution media to give a better correlation between *in vitro* and *in vivo* data (18). The rate of dissolution of micronized bulk danazol (Fig. 5) was slow; only 21% of the danazol dissolved in 60 min. The dissolution of the physical mixture was also quite slow, only about 48% in 60 min. The conventional lyophilization process increased the dissolution rate considerably, with 80% danazol dissolved in 60 min. However, the amount dissolved reached 99% in only 10 min for the SFL danazol/poloxamer 407 formulation. Major improvements in the dissolution rates were also found for SFL carbamazepine/excipient powders relative to the controls (Fig. 6). For example, the dissolved carbamazepine from SFL carbamazepine/SLS powder in 10 min was 98%, a profound enhancement when compared with 4% for the micronized bulk carbamazepine. The difference in the dissolution rate of SFL carbamazepine powders prepared by various excipients was negligible in 60 min and only slightly different in 20 min. Each of the excipients was successful in producing extremely rapid dissolution.

The increased dissolution rate of the SFL powders is due in part to the amorphous nature of the API, the reduction in particle size, the increase in porosity and resulting enhanced surface area, and intimate dispersion of the drug and hydrophilic excipient. The excipient may increase the local equilibrium concentration of the API in the boundary layer about the particles. The rapid freezing rate resulting from the intense atomization led to porous nanostructured particles with high amorphous API fraction and large surface area. This morphology is quite different from the low porosity, low surface area semicrystalline cakes produced by the conventional lyophilization process. At the same time, the enhanced wettability or better contact between the surface of the solid and the liquid increased the dissolution of the SFL powder. Also, the porous channels of the API/excipient matrix created in the SFL process allowed the dissolution media to easily penetrate into the particles and facilitate dissolution.

Stability

A stability study was conducted for the SFL danazol/poloxamer 407 at 25°C/60%RH for 2 months to examine any changes in crystallinity or other properties of the SFL powders. The X-ray diffraction pattern (Fig. 2) of SFL danazol/poloxamer 407 powder exhibited no change in peak intensity of danazol, but a slightly increased peak intensity of poloxamer 407. Despite the high humidity, the danazol crystallinity was unchanged over 2 months. The dissolution results (Fig. 5) demonstrated that there was only a 5% difference in the dissolution profiles between the initial and 2-month samples, which was calculated by the similarity factor f_2 for the dissolution profile comparison using the method reported by Shah (30). The slightly decreased initial release of danazol may be due to the change in crystallinity of poloxamer 407.

CONCLUSIONS

The novel SFL technology was demonstrated to produce free-flowing powder of nanostructured particles containing danazol or carbamazepine. The SFL powders exhibited sig-

nificantly enhanced dissolution rates compared to the powders formed by the conventional lyophilization process. In addition, an amorphous structure, high surface area and increased wettability of the flowable SFL powders are predominant characteristics, so the novel SFL technology is an effective particle engineering process for pharmaceutical development and manufacturing to improve dissolution rates of poorly water soluble APIs for oral delivery systems.

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