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Enhanced drug dissolution using evaporative precipitation into aqueous solution

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Abstract

A new process, evaporative precipitation into aqueous solution (EPAS) has been developed to coat poorly water soluble drugs, in this case carbamazepine, with hydrophilic stabilizers to enhance dissolution rates. A heated organic solution of the drug in dichloromethane is sprayed though a fine nozzle into a heated aqueous solution. The rapid evaporation of the organic solvent produces high supersaturation and rapid precipitation of the drug in the form of a colloidal suspension that is stabilized by a variety of low molecular weight and polymeric surfactants. The stabilizer adsorbs to the drug surface and prevents particle growth and crystallization during the spray process. The suspensions are dried by spray drying or ultra-rapid freezing. The high dissolution rates are a consequence of the following advantages of the EPAS process: a small primary particle size, a hydrophilic coating on the particles that enhances wetting, and low crystallinity.

Keywords: Carbamazepine; Dissolution rates; Particle engineering; Evaporative precipitation; Surfactant

1. Introduction

Developing novel techniques to improve dissolution and bioavailability is of great importance in the development of pharmaceutical formulations, particularly those containing an active ingredient that is poorly soluble in water (Mosharraf and Nystrom, 1995; Pace et al., 1999; Pillay and Fassihi, 1999). Dissolution rates may be increased by reducing particle size to the order of a few microns or less to achieve a high surface area. They may also be improved by coating drug particles with polymeric and low molecular weight hydrophilic excipients that enhance wetting and solvation by intestinal fluids. Furthermore, it is favorable to inhibit crystallization to produce particles in amorphous high energy states (Hancock and Parks, 2000). The simultaneous application of all of these strategies would be desirable in attempting to achieve high dissolution rates; how-

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ever, few existing micronization or particle formation techniques are capable of achieving such a goal.

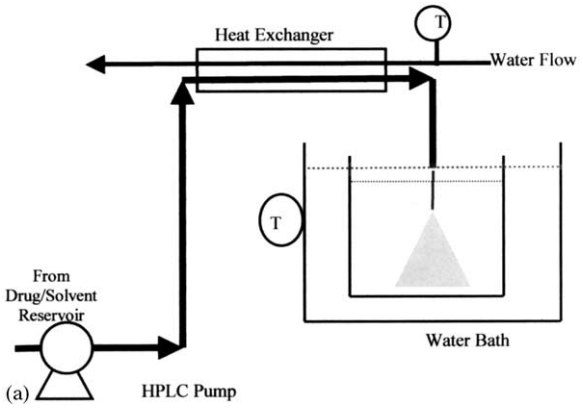
Pace et al. (1999), Rogers et al (2001) have reviewed microparticle preparations of poorly water-soluble drugs. Widely used mechanical techniques based on high shear or impaction, including microfluidization, high-pressure homogenization, ball milling, media milling, and air-jet milling can be limited by low yields due to solid losses, high polydispersities in particle size, shear-induced particle denaturation, long processing times, high energy requirements and the need for separating the product and processing agent. If the particles start in a crystalline state, they are likely to remain crystalline during particle size reduction. Solution-based phase-separation processes such as spray drying, emulsion solvent evaporation (Bodmeier and Maincent, 1988), rapid expansion from supercritical solution (RESS; Tom and Debenedetti, 1991), and precipitation with a compressed fluid antisolvent (PCA) (Dixon et al., 1993; Winters et al., 1996; Subramaniam et at, 1997; Reverchon, 1999) may be used to overcome many of the limitations of the above mechanical milling processes. These processes often require less particle handling resulting in higher yields. These continuous or semi-continuous processes may be scaled up more readily than batch mechanical processes. RESS is often limited by the low solubility of drugs in supercritical fluids even when cosolvents are utilized (Tom and Debenedetti, 1991). In PCA, the antisolvent may be a compressed liquid or a supercritical fluid, most commonly, carbon dioxide. The rapid mass transfer of organic solvent into carbon dioxide and vice-versa leads to rapid nucleation and small particle sizes. Varying the density of CO_2 and, hence, mass transfer rates offers a means to achieve control over degree of crystallinity, particle size, and morphology in PCA (Bodmeier et al., 1995).

In spray drying, RESS, and PCA, the formation of a particle containing a poorly water soluble drug and a water soluble excipient, is limited by the lack of solvent systems that will dissolve both hydrophilic and hydrophobic substances appreciably. The low solubility of water in carbon dioxide and similar compressed fluids limits its use as a solvent or cosolvent in RESS and PCA. In an attempt to process hydrophilic drugs, the PCA process has been recently modified for spraying water, ethanol, and CO_2 based solutions (Palakodaty et al., 1998; Nesta et al., 2000).

The objective of this study is to develop a novel solution-based spray process to produce amorphous micron and submicron sized particles of a poorly water-soluble drug coated with a hydrophilic stabilizer to enhance dissolution rates. The new process, evaporative precipitation into aqueous solutions (EPAS), utilizes rapid phase separation to nucleate and grow nano- and microparticles of water-insoluble drug substances. During EPAS, the active pharmaceutical ingredient (API) is first dissolved in a low boiling liquid organic solvent, in this case dichloromethane. This solution is pumped through a tube where it is heated under pressure to a temperature above the solvent's boiling point and then sprayed through a fine atomizing nozzle into a heated aqueous solution, as shown in Fig. 1a. A stabilizing surfactant is added to the organic solution, the aqueous solution, or both to optimize the particle formation and stabilization. We chose to study nonionic and ionic stabilizers consisting of homopolymers, block copolymers, and low molecular weight surfactants to explore various types of electrostatic and steric stabilization mechanisms. The nozzle is immersed into the aqueous solution to ensure that the nucleating drug particles contact the hydrophilic stabilizing surfactant rapidly; thus, inhibiting crystallization and growth of the drug particles. The stable aqueous drug suspension is dried by a variety of techniques including ultra-rapid freezing in conjunction with lyophilization, or spray drying. The dried powders are analyzed by various techniques including dissolution rate testing, X-ray diffraction to measure crystallinity, scanning electron microscopy (SEM), and aerodynamic particle sizing. The dissolution rates are discussed as a function of the final particle size, crystallinity, and morphology, and the molecular interactions between the drug and stabilizing surfactant.

Carbamazepine (CBZ), an antiepileptic drug, was chosen as the model drug for this study

because its low water solubility (11 μg/ml) leads to low and variable bioavailability (Lovrecich et al., 1994). CBZ consists of an azepine ring with fused benzene rings on either side and an amide group attached to the N of the azepine ring (Fig. 2; Lisgarten et al., 1989). Given the clinical importance of CBZ, there is a strong interest in improving its dissolution and bioavailability. Previous attempts to increase dissolution and bioavailability have focused on solid solutions (Hirasawa et al., 1999; Londhe and Nagarsenker, 1999; Naima et al., 2001), physical mixtures with surfactants (Jekone, 1998; Naima et al., 2001), trapping the drug in an amorphous state (Han and Suryanarayanan, 1998; Li et al., 2000), and conversion to less stable crystal forms (Kobayashi et al., 2000). The EPAS process utilizes the advantages of all of these techniques resulting in drug particles that have a small primary size, low crystallinity, and are intimately mixed with one or two surfactants.



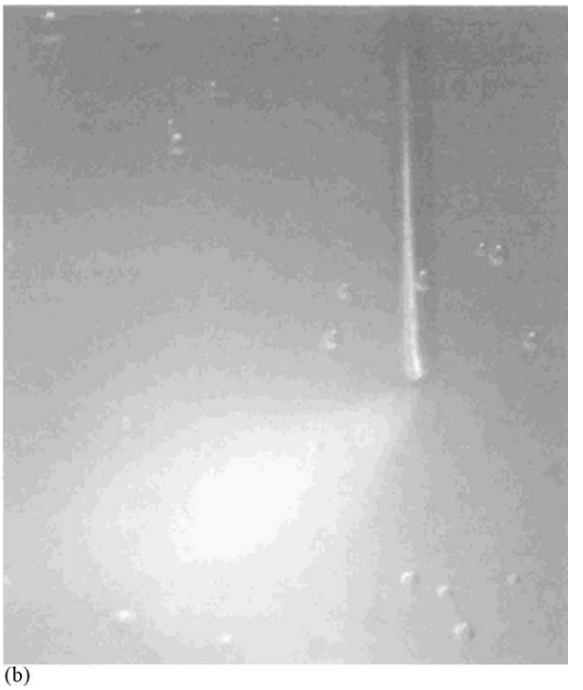

(b)

Fig. 1. EPAS process for the formation of aqueous suspensions of poorly water soluble drugs. Photograph showing intense atomization of the spray exiting the fine tapered nozzle into the aqueous solution.

2. Materials and methods

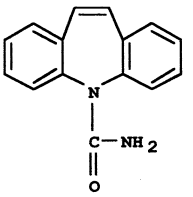
2.1. Materials

CBZ and poly(vinyl pyrrolidone) K15 (PVP) (MW 10 k) were purchased from Spectrum Chemical Manufacturing Corp (Gardena, CA). Dichloromethane (HPLC grade, Aldrich-Sigma, Milwaukee, WI), deoxycholic acid in the Na salt form (DCA, Aldrich-Sigma) and sodium dodecyl sulfate (SDS, Aldrich-Sigma) were used as received. Pluronic F127 was a gift from BASF Corp. (Mount Olive, NJ). Fig. 2 shows the structures of the polymers and surfactants used in this study.

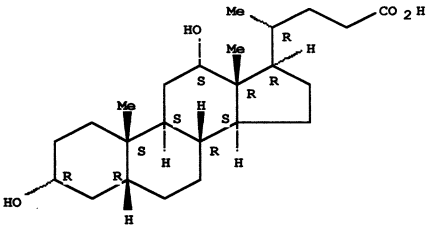
2.2. Methods

2.2.1. Particle formation using EPAS

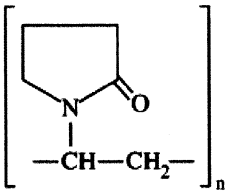
The EPAS experiments were conducted using the apparatus shown in Fig. 1a. All experiments were performed by spraying a 1.0% (w/w) solution of CBZ in dichloromethane via an HPLC pump through a preheating coil (0.45 m length, 0.762 mm internal diameter) into a 1.0 w/w% aqueous solution of surfactant. The preheating coil was placed in an acrylic water jacket, 250 mm in length and 25.4 mm inside diameter (id), (Altech, Deerfield, IL). The temperatures of both the water bath and the heating jacket were maintained at 87 °C. The nozzle shown in Fig. 1b was made following the procedure described by Young et al. (2000). The end of a piece of 1.61



Carbamazepine (CBZ)



Deoxycholic acid (DCA)



Poly(vinyl pyrrolidone) (PVP K-15)

$CH_3(CH_2)_{10}CH_2O\text{-}SO_3^-Na^+$

Sodium dodecyl sulfate (SDS)

$H(O\text{-}CH_2CH_2)_{\sim 98}(O\text{-}CH(CH_3)CH_2)_{\sim 67}(O\text{-}CH_2CH_2)_{\sim 98}OH$

Pluronic F127

Fig. 2. Molecular structures of carbamazepine (CBZ) and surfactants used in this study.

mm outer diameter (od) and 0.762 mm id stainless steel (SS 316) tubing was cut, crimping it shut. The crimped end was filed back until the required flowrate of 1 ml/min was achieved for a pressure drop of about 200 bar across the orifice. This type of nozzle produces a very rapid pressure drop across the orifice resulting in intense atomization of the drug solution at the tip of the nozzle. The nozzle was submerged 20–50 mm below the surface of the aqueous surfactant solution. The receiving vessel in most cases was a separatory funnel filled with 20 ml of the aqueous surfactant solution. In cases where the suspension was spray dried, the receiver was a 500 ml cylindrical vessel containing 100 ml of aqueous surfactant solution and a Teflon-coated stir bar driven by a magnetic stir plate to provide additional agitation. Since the solvent and aqueous solution in the receiving vessel were well above the solvent's normal boiling point, the solvent evaporated rapidly upon leaving the nozzle. During the spraying, the surfactant coated the drug particles and inhibited particle growth and crystallization. The high temperature also lowers the equilibrium solubility of dichloromethane in water with the mole fraction decreasing from 0.0019 to 0.0010 when the temperature is increased from 44 to 73 °C (Sorensen and Arlt, 1979). Visual observation showed that an excess dichloromethane phase did not form at the bottom of the vessel. For some experiments to reduce foaming and aid evaporation of the solvent, air at 120 psig was continuously flowed over the surface of the receiving solution (Young et al., 2000).

The aqueous microsuspension of CBZ was dried using one of the following techniques. (1) Spray drying: the suspension was dried using a Buchi 190 spray dryer (Biichi AG, Flawil, Switzerland) with an inlet air temperature of 150 °C and an outlet air temperature of 90 °C at an average liquid flow rate of 5 ml/min. (2) Ultrarapid freezing: the suspension was sprayed into liquid nitrogen, that was at its boiling point (−210 °C), to rapidly freeze it. The frozen particles

were collected and lyophilized in a VirTis Advantage (VirTis, Gardiner, NY) tray lyophilizer for 24 h. A typical lyophilization cycle consisted of the following steps: −40 °C for 3 h, −30 °C for 3 h, −20 °C for 4 h, +10 °C for 4 h, and +25 °C for 6 h. (3) Rapid freezing: the suspension was placed in a glass vial that was dipped in a Dewar flask filled with liquid nitrogen. After the suspension was completely frozen it was removed from the liquid nitrogen and lyophilized as before. (4) Filtration: In most cases the CBZ particles were in the micron size range and could not be recovered by filtration. However, in some cases, where the particles were not adequately stabilized the particles were filtered using a Fisherbrand P5 filter (Fisher Scientific, Pittsburgh, PA) with a particle retention of 5–10 μn and vacuum dried for 5 h at 35 °C. The ultra-rapid freezing and rapid freezing were carried out in closed systems and, hence, there could be no change in the drug:surfactant ratio during the procedure. However, for spray drying and filtration there was a possibility that the drug:surfactant ratio could change during drying.

2.2.2. Dissolution testing

Dissolution testing for CBZ samples was carried out in duplicate using a VanKel dissolution apparatus (Dissolution Test Station 7010, VanKel, Gary, NC) following the USP Apparatus II (paddle) method. During all dissolution tests, to ensure sink conditions, only 10–30% of the saturation solubility of the unprocessed bulk drug was added to the dissolution vessels. The appropriate amount of EPAS drug powder preparation was weighed and added to 900 ml of distilled water. Each sample was stirred at 50 rpm using a paddle-type stirrer. The dissolution apparatus was maintained at 37 °C throughout the experiment.

Samples in the amount of 5 ml were withdrawn at 10, 20, 30, and 60 min intervals. These samples were filtered using a 0.45 μm filter (Gelman GHP Acrodisc 0.45 μm, VWR, West Chester, PA). To ensure that no precipitation occurred during HPLC analysis, 0.5 ml of methanol was added to 3 ml of filtered sample. These were mixed using a vortex mixer at high speed for approximately 5 s and then refiltered using a 0.45 μm filter into an HPLC (Shimadzu, Columbia, MD) vial for analysis. HPLC analysis was carried out on a Shimadzu VP-AT series LC10 HPLC using a CIS Inertsil column (15 × 4.6 mm, 5 μm) with a 10:7:3 mixture of water, methanol and acetonitrile as the mobile phase. The elution time for CBZ, in the presence and absence of surfactants, was about 5 min using an injection volume of 50 μl and a flow rate of 1.5 ml/min. A photodiode array detector was utilized at 288 nm. In all cases the %RSD was less than 5.5% indicating good reproducibility.

2.2.3. X-ray diffraction studies

Wide angle X-ray scattering was employed to detect the crystallinity of CBZ. Cu$K\alpha_1$ radiation with a wavelength of 1.54054 Å at 40 kV and 20 mA from a Philips PW 1720 X-ray generator (Philips Analytical Inc., Natick, MA) was used. The samples were ground to a fine powder and well-mixed to minimize the effects of preferred orientation. A Philips goniometer was used to measure the reflected intensity at a 20 angle between 5 and 45° with a step size of 0.05° and a dwell time of 1 s. Since there is no clear method to quantify the degree of crystallinity of a powder containing multiple components, we developed a qualitative scale to determine the degree of crystallinity. Samples were labeled as L-low, M-medium, and H-high in crystaUinity depending on the intensity of the CBZ and CBZ dihydrate peaks relative to the background intensity and the intensity of the peaks of the other components.

2.2.4. SEM studies

The dried powders were mounted on aluminum stubs using double adhesive carbon conductive tabs (Ted Pella, Inc.) and coated with Au for 30 s using a Pelco Model 3 sputter-coaler under an Ar atmosphere. A Hitachi S-4500 scanning electron microscope (SEM) (Hitachi Instruments Inc., Irvine, CA) at an accelerating voltage of 10 kV with a secondary electron detector was used to obtain digital images of the samples.

2.2.5. Particle size measurements

The aerodynamic particle diameter of the final spray dried or lyophilized powder was measured using an Aerosizer LD (Amherst Process Instru-

ments, Inc., Amherst, MA) according to the time-of-flight in the fluidized state. The dual laser beam instrument measures the time taken by a fluidized particle to cover the distance between the two laser beams and calculates the particle size distribution using cross correlation techniques. The run time for each measurement was 300 s. The manufacturer recommended particle density of 1.35 g/cm^3 was used, and the particle size distribution was measured on a volume basis.

2.2.6. Contact angle measurements

The interaction between CBZ and the surfactants was investigated by measuring the contact angle between the processed samples and distilled water. Contact angle measurements were carried out for dried EPAS suspensions. The suspensions were first centrifuged in a Model TJ-6 centrifiige (Beckman Coulter Inc., Fullerton, CA) at 3000 rpm for 30 min. The supernatant was carefully poured out and the remaining solids were dried at 40 °C for 2 days. 100 mg of the dried powder was tabletted under a pressure of 1500 kg/m^2 using a Carver Laboratory Press, Model M (Fred S. Carver Inc, Wabash, IN). 5 μl of RO water was gently placed on the tablet and the contact angle was measured.

3. Results

During EPAS, the heated organic solution was sprayed into the aqueous solution through the custom-designed nozzle and the intense atomized spray (Fig. 1b) resulted in very fine droplets of dichloromethane. The spray diffused out rapidly and the plume disappeared approximately 20 mm from the nozzle. The extremely rapid evaporation of the organic droplets may be expected to produce high supersaturations of CBZ and, hence, high nucleation rates. The high exit velocity of the spray intensely mixed the receiving solution, thus, facilitating the migration of the aqueous surfactant to the drug particles. The growing drug particles were stabilized by the surfactants present in either medium. At the end of spraying, some small particles could be visually observed in the white opaque colloidal suspensions. The suspensions were then allowed to cool to ambient temperature. Since CBZ water-solubility increases with temperature, some CBZ precipitated during cooling increasing the size of the particles in the suspension. The particles that precipitated during cooling appeared to reflect more light suggesting greater crystallinity, and they gradually grew during the cooling period. The cooled suspension would settle completely in an hour and, thus, we did not attempt to measure particle sizes. All suspensions were easily redispersible with gentle shaking.

The drug suspensions obtained by EPAS were dried by four different methods: (1) spray drying, (2) ultra-rapid freezing into liquid nitrogen followed by lyophilization, (3)rapid freezing and (4) filtration followed by vacuum drying to produce powders suitable for solid dosage forms for oral delivery. The two drying methods used most frequently were ultra-rapid freezing into liquid nitrogen followed by lyophilization of the frozen powder and conventional spray drying. In both cases, a dry, free flowing powder was obtained for all samples. Dissolution rates were compared for the aqueous suspension produced by EPAS before drying versus the dried powders to determine how each step of the process influences the properties of the drug particles. During dissolution studies, it was observed that the unprocessed CBZ and physical mixtures initially floated on the surface of the dissolution medium while the EPAS processed powders were wetted readily and quickly dissolved. This increased wettability of the drug provided evidence of the adsorption of the surfactants onto the drug surface.

In Table 1 for the experiments with DCA as the only surfactant, the final aerodynamic particle size is nearly constant for the different drying techniques. However, there is a distinct difference in the dissolution rates and the particle crystallinities. The filtration technique gives the largest, most crystalline particles and the slowest dissolution rate. Filtration was carried out using a 5–10 μm-retention filter, thus, the residue consisted of relatively large particles which were not well stabilized and had grown and crystallized in solution. Thus, these particles had poor dissolution rates, despite the presence of the surfactant. This result

Table 1
Amount of drug released in 10 min and particle size of dried drug powder for EPAS experiments with no surfactant in the organic phase

Surfactant in aqueous phase	Drying technique	Drug released in 10 min (%)	Mean particle size in μm (S.D.)	Degree of crystallinity
None	Rapid freezing	26	16 (1.59)	–[c]
	Filtration + vacuum dry[a]	12	19 (1.65)	M
PhironicF127	Rapid freezing	56	–	–[c]
	Filtration + vacuum dry	57	16 (1.55)	H
DCA	Spray drying	86	11 (1.60)	L
	Rapid freezing	78	12 (1.53)	–[c]
	Ultra-rapid freezing[b]	90	13 (1.45)	–[c]
	Filtration + vacuum dry	34	17 (1.51)	M

Drug: surfactant in aqueous phase was (1:1.2) (w/w) at a concentration of 17.2 mg/ml of CBZ in the aqueous EPAS suspension.
[a] CBZ concentration 18.5 mg/ml.
[b] CBZ concentration 9.2 mg/ml at a CBZ:DCA wt ratio of 1:2.2.
[c] X-ray analysis not performed for these samples.

also reinforces the correlation between high drug crystallinity and low dissolution rates. The higher dissolution rate for ultra-rapid freezing versus rapid freezing and spray drying may be influenced by the drying technique and the modest difference in the drug/surfactant ratios.

The effect of the drying process is addressed further in Fig. 3. It shows dissolution profiles for CBZ with Pluronic F127 in the organic phase and DCA in the aqueous phase with a CBZ:Pluronic F127:DCA weight ratio of 1:0.5:0.5 in all cases except where the suspension was dried using the ultra-rapid freezing technique where the ratio was 1:0.5:1.08. For all of these EPAS samples, regardless of whether or not they were dried, more than 80% of the total CBZ dissolved within the first 10 min compared with just 3.7% for the unprocessed CBZ. The drug dissolution profile was very similar for the aqueous suspension produced by EPAS prior to drying and the EPAS suspension dried by ultra-rapid freezing. It was only slightly lower for the EPAS suspensions dried by spray drying. After 1 h, the amount of total drug added that went into solution approached 95% for all three EPAS samples versus only 23% for the bulk drug.

The profiles for the aqueous EPAS suspension and the dried suspensions, for both drying techniques, were very similar indicating that the agglomeration of primary particles and other processes taking place during water removal were not detrimental to the dissolution rates. Based on these results in Table 1 and Fig. 3, we chose to focus on ultra-rapid freezing as our primary drying technique.

EPAS experiments were carried out with no surfactant in either phase, a single surfactant in

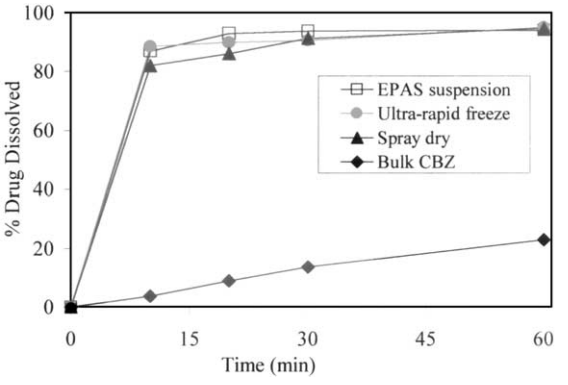


Fig. 3. Dissolution profiles of CBZ comparing the EPAS CBZ:Pluronic F127:DCA (1:0.5:0.5) (weight ratios) suspension with bulk, spray dried and ultra-rapid frozen EPAS powders. [a], Weight ratio for ultra-rapid frozen powder was 1:0.5:1.08.

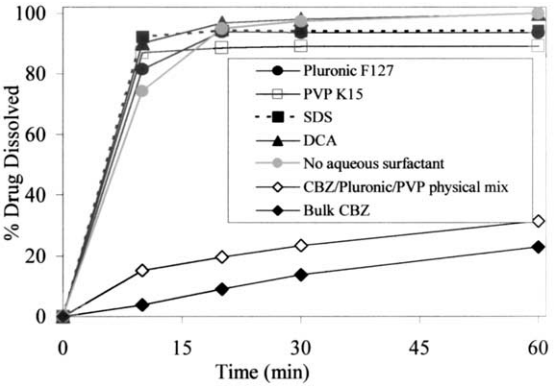


Fig. 4. Dissolution profiles of CBZ comparing the effect of surfactants in the aqueous phase with Pluronic F127 in the organic phase. The final CBZ:Pluronic F127:aqueous surfactant ratio by weight was 1:0.5:1.08. All suspensions were dried by ultra-rapid freezing into liquid nitrogen followed by cyophilization.

either phase or a surfactant in both phases. Of the surfactants studied, only Pluronic F127 and PVP K15 are soluble in both water and dichloromethane. This dual solubility allowed the option of dissolving these polymeric surfactants either in the organic phase with the drug or in the aqueous phase or in both phases. In all the data shown, unless otherwise specified, the drying technique used was ultra-rapid freezing followed by lyophilization.

The effect of different stabilizers in the aqueous medium was investigated with a given stabilizer in the organic phase. Pluronic F127 (0.5 wt%) was dissolved in the dichloromethane along with CBZ and sprayed into aqueous solutions containing a variety of low molar mass and polymeric stabilizers as shown in Fig. 4 and Table 2. The weight ratio of CBZ:PluronicF127:aqueous stabilizer was 1:0.5:1.08. These suspensions were all dried by the ultra-rapid freezing technique and all samples showed low residual crystallinity. For the system with Pluronic F127 in the organic phase and no surfactant added to the aqueous phase, the amount of drug dissolved was only 74% after 10 min. For the systems with added surfactant in the aqueous phase, after 10 min, 88, 87, 81, 92% of the added CBZ had dissolved for the systems containing DCA, PVP Kl 5, Pluronic F127, and SDS, respectively. However, after 20 min, a single stabilizer in the organic phase, Pluronic F127, was as effective as the examples that also included a surfactant in the aqueous phase. The addition of PVP K15 to the aqueous solution lowered the dissolution rate slightly versus the case with only Pluronic F127 in the organic phase. In comparison only 3.7% of the bulk CBZ and 15% of the CBZ from a physical mixture of CBZ:Pluronic F127:PVP K15 were dissolved in 10 min.

The effect of different aqueous surfactants when PVP Kl 5 is present in the organic phase is shown in Table 3. The dissolution rates are higher with Pluronic F127 (89%) and DCA (81%) than with PVP K15 (63%) present in both phases. The low dissolution rate of 63% was seen in spite of the feet that the crystallinity of each of the three powders was observed to be low.

A similar study on dissolution rates was conducted to compare the effect of different polymeric stabilizers in the organic phase for a given stabilizer in the aqueous phase, DCA. The dissolution profiles shown in Fig. 5 indicate that the addition of a polymer to the organic phase produces a significant increase in the amount released, compared with the case with DCA alone

Table 2
Amount of drug released in 10 min and particle size of dried drug powder for EPAS experiments with Pluronic F127 in the organic phase

Surfactant in aqueous phase	Drug released in 10 min (%)	Mean particle size in μm (S.D.)
None	74[b]	13[b] (1.54)
Pluronic F127	81	17 (1.65)
PVPK15	87	10 (1.45)
SDS	92	16 (1.60)
DCA	88	14 (1.55)
DCA	82[a]	14[a] (1.71)

Drug: Pluronic F127 in organic phase:surfactant in aqueous phase was (1:0.5:1.08) (w/w/w) at a concentration of 18.5 mg/ml of CBZ in the aqueous EPAS suspension. The suspensions were dried by using the ultra-rapid freezing technique. The crystallinity was determined to be low by X-ray diffraction in each case.

[a] Concentration of CBZ in EPAS suspension was 39.9 mg/ml at a CBZ:Pluronic F127:DCA wt. ratio of 1:0.5:0.5. The suspension was spray dried.

[b] CBZ:Pluronic F127 wt. ratio was 1:0.5.

Table 3
Amount of drug released in 10 min and particle sizes of dried drug powder for EPAS experiments with PVP K15 in the organic phase

Surfactant in aqueous phase	Drug released in 10 min (%)	Mean particle size in μm (S.D.)
Pluronic F127	89	–
PVPK15	63[a]	14[a] (1.57)
DCA	81	–

Drug:PVP K15:surfactant in aqueous phase weight ratio of (1:0.5:2.5) at a concentration of 7.9 mg/ml of CBZ in the aqueous EPAS suspension. The suspensions were dried by using the ultra-rapid freezing technique. The crystallinity was determined to be low by X-ray diffraction in each case.

[a] Concentration of CBZ in EPAS suspension was 13.8 mg/ml at a CBZ:PVP K15 organic phase:PVP K15 aqueous phase wt ratio of 1:0.5:2.85.

in the aqueous phase. The increase is greater for Pluronic F127 than for PVP K15 (88 vs. 81% in the initial 10 min).

Drug metabolism and availability can be affected by the crystal structure of CBZ (Ali, 1997). The high energy amorphous form can give higher activity and bioavailability, but also tends to be the less stable form. CBZ has been shown to convert to its dihydrate when exposed to high temperatures and high humidity levels (Han and Surayanarayanan, 1998; Kobayashi et al., 2000), During EPAS and the subsequent drying procedures, CBZ is exposed to both high temperature and high water concentrations and would be expected to be in the dihydrate form. Fig. 6 shows the X-ray diffraction patterns of pure CBZ before and after EPAS processing without any stabilizers in either phase. The pattern displayed in Fig. 6a shows the bulk unprocessed CBZ which is highly crystalline and shows the characteristic diffraction peaks at $2\theta = 15.3$ and 27.6° (PDF-2, 1998). The pattern shown in Fig. 6b is that of CBZ which has been processed by EPAS without any surfactants, filtered and vacuum dried. The peaks at $2\theta = 9.07$ and 19.0° match closely to those reported for CBZ dihydrate (Kobayashi et al., 2000), as expected. The patterns shown in Fig. 6c and d are those of CBZ EPAS processed with Pluronic F127 in the organic phase and DCA in the aqueous phase with Fig. 6c showing the spray dried powder and Fig. 6d showing the ultra-rapid frozen powder. Both these profiles are very flat and show an amorphous region from $2\theta = 25$–38°. The

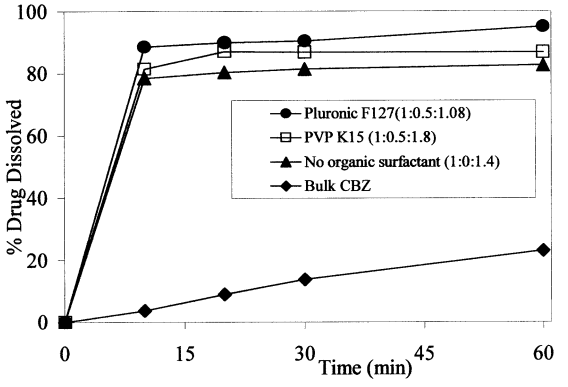


Fig. 5. Dissolution profiles of CBZ comparing the effect of surfactants in the organic phase with DCA in the aqueous phase. The weight ratios shown are CBZ:organic surfactant:DCA. All suspensions were dried by ultra-rapid freezing into liquid nitrogen followed by lyophilization.

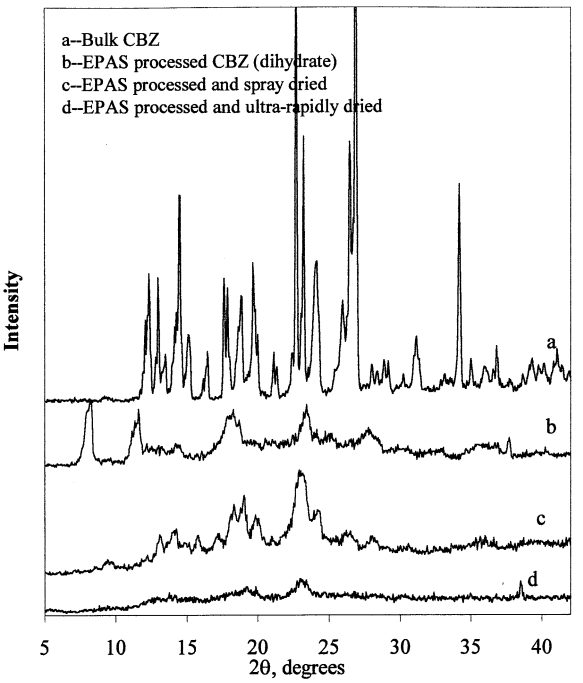


Fig. 6. X-ray diffraction patterns of CBZ formed by EPAS (a) control: bulk CBZ, (b) CBZ dihydrate formed without a stabilizer, (c) CBZrPluronic F127:DCA dried by spray drying, (d) CBZ:Pluronic F127:DCA dried by ultra-rapid freezing.

peaks corresponding to both crystalline CBZ and its dihydrate are mostly absent indicating that the crystallinity of the drug has been reduced substantially. The remaining peaks result primarily from the polymeric exciplents. The profile for the powder dried by ultra-rapid freezing is much flatter than for the spray dried powder indicating that the rapid freezing process is more efficient in retaining the amorphous character of the EPAS suspension. This slight variation in crystallinity could also be the reason for the small difference in dissolution rates between drying techniques (Table 2), with the less crystalline powder showing the higher dissolution rate.

The effect of the different stabilizers on the final crystalline structure of CBZ was studied using X-ray diffraction patterns shown in Fig. 7a–c. In all cases, 1 wt.% CBZ dissolved when CBZ with 0.5 wt.% Pluronic F127 in dichloromethane was sprayed into an aqueous surfactant solution and the resulting suspension was ultra-rapid frozen and lyophilized. The final powder had a CBZ:Pluronic F127:aqueous surfactant weight ratio of 1:0.5:1.08. All the profiles show the distinct broad featureless halo observed in amorphous and highly disordered crystalline materials. The small peak at $2\theta = 23.15°$ seen in all the profiles is characteristic of Pluronic F127. Additionally, the pattern displayed in Fig. 7a shows a peak at $2\theta = 38°$ which is characteristic of DCA. The patterns displayed in Fig. 7b and 7c where PVP K15 and SDS were the aqueous surfactants, respectively, also show amorphous halos and reduced crystallinity. SDS however, does show small peaks at $2\theta = 20°$ similar to those for CBZ dihydrate (Fig. 6b) indicating that SDS with the small amount of Pluronic F127 cannot completely retard CBZ dihydrate crystal formation. Based on the results presented in Fig. 4, SDS yields very good dissolution results indicating that a complete loss of crystallinity is not necessary for high dissolution rates.

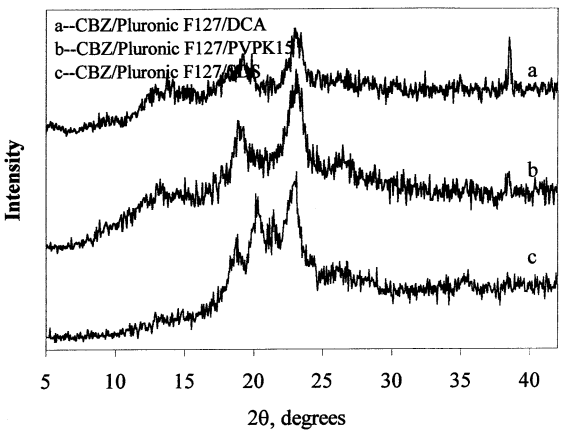


Fig. 7. X-ray diffraction patterns of EPAS processed CBZ with various surfactants. The ratios of CBZ:organic surfactant:aqueous surfactant were 1:0.5:1.08. The patterns clearly demonstrate the decrease in crystalline character of the processed CBZ.

To determine the nature of the interaction between CBZ and the surfactants, contact angle measurements were carried out on dried EPAS suspensions. The EPAS suspension corresponding to Table 2, row 1 was centrifuged, dried and formed into a compact for measuring contact angle. The measured contact angle was 24.6° indicating a relatively hydrophilic surface. Also, the contact angle of the corresponding physical mixture of CBZ and poloxamer was 37.5°, indicating a less hydrophilic surface. CBZ pure powder prior to EPAS processing could not be compacted, but it was observed that the powder was not wetted.

4. Discussion

The following discussion relates the dissolution rate data to the degree of crystallinity of the EPAS powders and to the intermolecular interactions in a qualitative manner. The molecular interactions between CBZ and the various stabilizers are complex and have not been characterized in detail in the literature. Consider the case where CBZ solutions were sprayed with no surfactant in either phase (Table 1). The dissolution rate, although better than for bulk CBZ is very low as expected, since, the dihydrate has been shown previously to have lower dissolution rates than the anhydrous forms of CBZ (Khankari and Grant, 1995; Kobayashi et al., 2000). Thus, this small improvement in dissolution rate after EPAS processing may be attributed to the relatively low crystallinity (M) of the resulting dihydrate.

Next we consider the effect of Pluronic F127 when it is utilized only in the aqueous phase, or only in the organic phase. In Pluronic F127, the ethylene oxide (EO) block is hydrophilic whereas the central propylene oxide (PO) block is hydrophobic (Fig. 2). The PO block adsorbs onto the hydrophobic surface of the drug while the EO block may be solvated by water providing steric stabilization. Based on the dissolution rate results, the amphiphilic character of Pluronic F127 appears to be sufficiently well-balanced to provide both adsorption onto the drug particle and steric stabilization (Rouchotas et al., 2000). When Pluronic F127 is fed in the organic phase the drug to surfactant ratio remains constant (1:0.5) during the duration of the experiment. Here the Pluronic F127 is in the same phase as the CBZ when it precipitates from the evaporating organic droplets, and, hence, requires a relatively short time to diffuse to the drug surface and to stabilize the drug particles. When Pluronic F127 is originally present in the aqueous phase, because of the continuous addition of CBZ, the drug to surfactant ratio in the aqueous phase is constantly increasing from zero to the final value of 1:1.2 over the duration of the spray. Even though this ratio is lower than in the above case, the dried sample shows a lower dissolution rate (56% in 10 min) and a higher degree of crystallinity. This result can be explained by the difference in drying techniques. Both rapid freezing and filtration have been shown to be less effective than ultra-rapid freezing (Table 1) at producing high dissolution rates. The lower dissolution rates could also be influenced by the location from which the surfactant is fed. When the surfactant is present in the aqueous phase alone, it must diffuse through the aqueous phase and across the organic-water interface into the evaporating dichloromethane droplets to adsorb onto the precipitating drug. In this particular case, the proximity of the surfactant to the precipitating drug particles appears to be more important for arresting growth and stabilizing the drug particles than the total surfactant concentration in the aqueous medium. In addition, the local concentration of the surfactant around the drug particle may be expected to be higher in the case where the surfactant is introduced with the organic phase containing the API.

When Pluronic F127 is added in both phases even higher dissolution rates and lower crystallinity are observed than when it is present in only one of the phases (Tables 1 and 2). In this case, the drug to surfactant ratio (1:1.58) was also lower, which favors higher dissolution rates. Finally in all cases with Pluronic F127 as the surfactant, the average particle sizes of the powders are in the range 10–19 μm (the bulk CBZ has an average diameter of 39 μm with a S.D. of 2.15) and, hence, would be expected to have little influence on the dissolution rates. These powders were agglomerates of much smaller primary particles, as has been seen by dynamic light scattering studies of particles produced by a similar process (Young et al., 2000). Thus, even when the aerodynamic particle sizes are similar, the primary particle sizes could be different and influence the dissolution rates.

The experiments with Pluronic F127 demonstrate the importance of drug crystallinity in controlling dissolution rates. In all cases except the one where vacuum drying was used the degree of crystallinity was low and the dissolution rates were high. In the single case where crystallinity was high (Table 1), dissolution rates were low even at a drug to surfactant ratio of 1:1.2.

Consider the cases with Pluronic F127 in the organic phase and various surfactants in the aqueous phase (Table 2 and Fig. 4). In each case, the addition of the second surfactant to the aqueous phase increases the dissolution rate. In these systems, it is likely that some of the Pluronic F127 adsorbs to the growing drug surface in the sprayed droplets before the second surfactant reaches the surface. SDS produces the highest initial dissolution rate. SDS has been shown to bind very strongly to Pluronic F127 (Li et al., 2000). The ability of SDS to bind to the Pluronic F127 may be expected to contribute to this high dissolution rate by providing a high surface coverage of the surfactant layers about the drug particles. The ionic charge on SDS provides electrostatic stabilization of the CBZ-Pluronic F127 suspension in addition to steric stabilization, which may further inhibit crystallization. In addition it promotes high dissolution rates by favoring wetting and solvation of the particle–surfactant complexes with a highly hydrophilic surface.

It is instructive to compare the different intermolecular interactions with the CBZ surface for DCA and Pluronic F127. The carboxamide groups on CBZ can H-bond with each other and are known to participate in CBZ dimer formation (Lisgarten et al., 1989). The hydroxyl groups on DCA can act as H-bond donors and acceptors with the CBZ carboxamide groups. This complex will have considerable hydrophilic character, because of the ionized DCA molecule, which may contribute to the high dissolution rates observed with DCA. The Pluronic F127 molecule contains only a limited number of H-bond donors in the terminal OH groups, however, it can attach itself to the CBZ molecule via strong hydrophobic interactions between its PO groups and CBZ (Rouchotas et al., 2000), thus, imparting a hydrophilic surface to CBZ. These factors contribute to the higher dissolution rates for the mixture of Pluronic F127 and DCA versus Pluronic F127 alone as a dissolution enhancing surfactant.

Next, consider the interaction of PVP K15 with CBZ. The PVP ring contains a tertiary amide N that can be protonated only under very low pH conditions below pH 1 (Molyneux, 1984). Thus, under the conditions of EPAS, PVP is not ionized. PVP has been shown to be a strong crystallization inhibitor for numerous drugs including sulfathiazole (Simonelli et al., 1970), sulfisoxazole and sutfamethizole (Sekikawa et al., 1979), and sulfamerazine (Sekikawa et al., 1978). When PVP was added to supersaturated solutions of sulfathiazole, the growth of the seeded crystals initially slowed down and then completely stopped. Simonelli et al.(Simonelli et al., 1970) proposed a model where PVP adsorbs onto the drug particles and inhibits further growth of the crystals. A similar mechanism is likely for the CBZ-PVP K15 systems studied. PVP may coat the CBZ particles before significant crystal growth occurs, trapping them in a primarily amorphous form, as observed in the X-ray data. In the case where PVP K15 is the only surfactant present, in this case in both phases (Table 3), the dissolution rate (63% in 10 min) is lower than for the other systems in Table 3 even though the powder has very low crystallinity. We observed that PVP Kl 5 dissolves in water more slowly than the other surfactants when preparing aqueous solutions. Thus, the binding of the high molecular weight PVP Kl 5 to the CBZ may retard its diffusion into the aqueous medium resulting in lower dissolution rates. However, these dissolution rates are extremely rapid compared with those reported on a CBZ-crosslinked PVP (1:2) mixture prepared by solvent evaporation from a 3:1 (v/v) ethanol:acetone solution (Machiste et al., 1995), where 50% of the drug dissolved in 10 min. Several reasons may explain the faster dissolution rates. The more rapid evaporation and atomization in the EPAS process, along with the proximity of the aqueous stabilizer to the nascent drug particles, may lead to smaller particles and more intimate contact between drug and stabilizer. In EPAS, the surfactant migrates to the drug-water interface during particle formation. In solvent evaporation techniques that do not use water, this driving force for forming a hydrophilic coating on the particle is not present.

Considering the stabilization mechanism of DCA when it is used with other surfactants, DCA is a much smaller molecule (MW of the ionic species is 391) than PVP K15 and has a critical micellar concentration (CMC) of about 1 g/l (Morgan et al., 1998). Thus, in all cases we are above the CMC of DCA. The small size of DCA allows it to diffuse more quickly to the surface of CBZ and, hence, may help stabilize it before crystallization sets in. Further, as discussed earlier, it can H-bond with the CBZ, preventing dimer formation, increasing the disorder in the crystal lattice of CBZ and, hence, increase the amorphous character of the final powder. These factors may explain why DCA can by itself give high CBZ dissolution rates without a second surfactant in the organic phase (Table 1 and Fig. 5). In contrast, the more slowly diffusing molecule Pluronic F127 by itself in the aqueous phase did not provide high dissolution rates. For DCA in water, the addition of PVP K15 provides only a very slight improvement in dissolution rate whereas Pluronic F127 gives a substantial improvement (Fig. 5). Again the lower dissolution rate with PVP K15 could be due to the slower dissolution kinetics of PVP K15 versus the other surfactants.

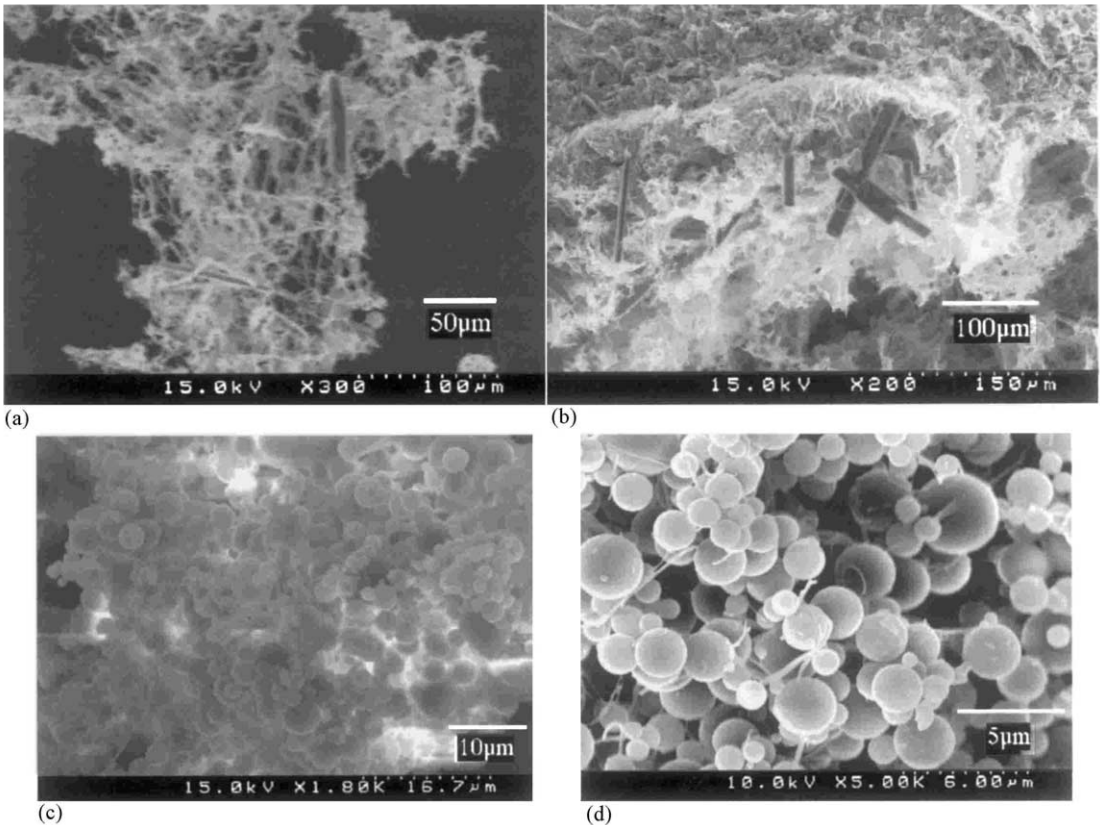


Fig. 8. SEM images of EPAS processed and spray dried and ultra-rapid frozen CBZ. (a) CBZ:Pluronic F127:DCA (1:0.5:1.08) drying technique: ultra-rapid freezing (b) CBZ:Pluronic F127:PVP K15 (1:0.5:1.08) Drying technique: Ultra-rapid freezing (c) CBZ:Pluronic F127:DCA (1:0.5:0.5) Drying technique: Spray drying (d) CBZ:DCA (1:0.76) Drying technique: Spray drying.

Fig. 8 shows SEM micrographs of CBZ which was spray dried and dried by the ultra-rapid freezing technique. Fig. 8a and c are powders of CBZ with the same excipients (Pluronic F127 and DCA) and compare the two drying techniques. The spray dried powder (8c) is in the form of monodisperse micron sized spherical particles while that from ultra-rapid freezing (8a) contains a few small crystals embedded in a polymer matrix shown in the SEM. In many regions in the SEMs (not shown), the crystals were not observed. The X-ray diffraction patterns for both these morphologies show low values of crystallinity (Fig. 6c and d), consistent with the SEM micrographs. In Fig. 8a and b, as well as Fig. 8c and d, the primary particles, on the order of a few microns in diameter, are flocculated to form the large aggregates. The small size of the primary particles may be expected to contribute to the high dissolution rates. Fig. 8b and d show two more examples of differences in particle morphology due to the drying technique for other stabilizers. The morphologies in the four examples in Fig. 8 are influenced more by the drying technique than the particular choice of surfactant stabilizers.

5. Conclusions

The new EPAS process produces surfactant stabilized aqueous suspensions that may be dried to form CBZ powder with rapid dissolution rates. For PVP K15 stabilized powders, these dissolution rates are much faster than those produced

earlier by solvent evaporation without an aqueous phase (Machiste et al., 1995). In EPAS, the surfactant migrates to the drug-water interface during particle formation, and the hydrophilic segment is oriented outwards towards the aqueous continuous phase. In solvent evaporation techniques that do not use water, this driving force for forming a hydrophilic coating on the particle is not present. In EPAS, the rapid nucleation of the drug followed by adsorption of surfactant at the drug-aqueous solution interface leads to colloidal suspensions of micron-sized drug particles coated by a hydrophilic stabilizer. The stabilizer inhibits crystallization of the growing particles. The surface of the powder formed after drying is considerably more hydrophilic than that of a physical mixture, on the basis of contact angle measurements. The hydrophilic surface facilitates wetting and increases dissolution rates. Rapid dissolution rates could be achieved with a variety of ionic and nonionic low molecular weight and polymeric stabilizers present originally in the organic phase, aqueous phase or both. The ability to utilize a surfactant in the organic phase to inhibit particle growth and crystallization and a second organic-insoluble surfactant in the aqueous phase to stabilize the suspension is advantageous in achieving high dissolution rates. Hydrogen bonding and/or hydrophobic interactions between CBZ and the stabilizers provided intimate contact and much higher dissolution rates than obtained from a simple physical mixture of the two. The crystallinity of the particles produced by EPAS was low for all of the drying techniques except filtration and vacuum drying. In summary, the increase in dissolution rates is due to a combination of the small primary particle size, the hydrophilic coating on the particles that favors wetting and, the low crystallinity. These factors are interrelated, as suspensions of small primary particles could not be formed without a surfactant.

Acknowledgements

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