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Preparation of Budesonide-Poly (Ethylene Oxide) Solid Dispersions Using Supercritical Fluid Technology

Hui Liu
Department of Pharmacy, Wuhan General Hospital, Wuhan, P.R. China and
School of Pharmacy, Shenyang Pharmaceutical University, Shenyang, P.R. China

Li-Li Zhou
School of Pharmaceutical Engineering, Shenyang Pharmaceutical University, Shenyang, P.R. China

Lan-Lan Wei, Hong-Guo, Shu-Fang Nie, and Xing-Gang Yang
School of Pharmacy, Shenyang Pharmaceutical University, Shenyang, P.R. China

Ren Tang
Department of Pharmacy, Wuhan General Hospital, Wuhan, P.R. China

Wei-San Pan
School of Pharmacy, Shenyang Pharmaceutical University, Shenyang, P.R. China

The purpose of this study was to investigate the possibility of preparing solid dispersions of the poorly soluble budesonide by supercritical fluid (SCF) technique, using poly (ethylene oxide) (PEO) as a hydrophilic carrier. The budesonide-PEO solid dispersions were prepared, using supercritical carbon dioxide (SC CO_2) as the processing medium, and characterized by scanning electron microscopy (SEM), powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), solubility test and dissolution test in order to understand the influence of the SCF process on the physical status of the drug. The endothermic peak of budesonide in the SCF-treated mixtures was significantly reduced, indicating that budesonide was in amorphous form inside the carrier system. This was further confirmed by SEM and PXRD studies. The enhanced dissolution rates of budesonide were observed from SCF-treated budesonide-PEO mixtures. The amorphous characteristic of the budesonide, the better mixing of drug and PEO powders in the presence of SC CO_2, together with the improved wettability of the drug in PEO, produced a remarkable enhancement of the in vitro drug dissolution rate. Thus, budesonide-PEO solid dispersions with enhanced dissolution rate can be prepared using organic solvent-free SCF process.

Keywords supercritical fluid; poly (ethylene oxide); solid dispersions; budesonide

Address correspondence to Wei-San Pan, School of Pharmacy, Shenyang Pharmaceutical University, 103 Wenhua Road, P.O. Box 122, Shenyang 110016, P.R. China. E-mail: pharmacymanLH@163.com

INTRODUCTION

The bioavailabilities of poorly soluble drugs are often limited by their dissolution rates in the gastrointestinal tract. The solid dispersion method is one of the pharmaceutical approaches most commonly employed to improve the dissolution of poorly soluble drugs (Leuner & Dressman, 2000; Löbenberg & Amidon, 2000; Broman et al., 2001). Various methods for preparing solid dispersions including coprecipitation, lyophilization, spray drying, solvent evaporation, fusion and powder mixing methods have been reported (Serajuddin, 1999). However, besides its tremendous potential in improving drug dissolution, the solid dispersion system prepared by conventional methods has serious limitations on large scale production, including difficult removal of residual organic solvent, decomposition of the drug, problems of grinding and physical instabilities of the solid dispersions on storage (Greenhalgh, et al., 1999; Serajuddin, 1999). Supercritical fluid technology provides a novel alternative for preparing solid dispersions with easier producing procedure, smaller particle size, lower residual organic solvent level, better flowability and thus overcomes some of the problems faced in conventional methods (Moneghini et al., 2001; Nijlen et al., 2003).

A supercritical fluid (SCF) can be defined as a substance existing as a single fluid phase above its critical temperature (T_c) and pressure (P_c). Carbon dioxide (CO_2) is regarded as a favorable processing medium and is commonly used in SCF for pharmaceutical applications because it is chemically inert,

non-flammable and inexpensive, and generally recognized as safe (GRAS). Moreover, CO_2 has relatively mild critical parameters (T_c = 31.1°C, P_c = 73.8 bar) and thus exhibits solubilization and plasticization effects that can be varied continuously by moderate changes in pressure and temperature (Vemavarapu et al., 2005).

Budesonide is a potent glucocorticosteroid with a high topical anti-inflammatory activity and low systemic effects, as a result of its strong affinity for corticosteroid receptors and its rapid first pass metabolism in the liver (Edward, 2003). Budesonide is currently marketed as a nasal spray (Rhinocort®), a dry powder inhaler (Pulmicort®), a ileal release capsule (Entocort®), and a ointment (Preferid®) for the treatment of asthma, allergic rhinitis, inflammatory bowel disease, Crohn's disease and inflammatory dermatoses, respectively (Mutlu et al., 2002; Pearlman, 2003). Budesonide, with a log *P* of 3.2 and ionic strength of 0.01, is practically insoluble in water at physiological pH, which may confine the therapeutical potential of budesonide (Edward, 2003). Therefore, solid dispersion techniques, and especially those using SC CO_2, which lead to an increase in the specific surface area and the improvements of solubility of budesonide, would be very valuable in order to allow a high topical concentration and bioavailability to come in contact with inflamed tissue.

Hydrophilic synthetic polymers have been widely investigated as carrier substances for solid dispersions (Sethia & Squillante, 2003). Polyethylene oxide (PEO, a higher molecular weight polymer composed of the same monomeric unit as polyethylene glycol) is a crystalline, non-ionic, hydrophilic polymer family commonly used in agricultural engineering, food, cosmetics and pharmaceutical controlled release applications (The Dow Chemical Company, 2002). Although the chemical structure of its repeat unit is identical to that of polyethylene glycol (PEG), the PEO family is distinguished by significantly higher molecular weights compared to PEG. Similar to semi-crystalline PEG polymers, a relatively low melting point and high compatibility for the drug of PEO has generated highlighted interest in the use of PEO in solid dispersions (Ozeki et al., 1997; Schachter et al., 2004).

With all these consideration in mind, the aims of this study were to determine the feasibility of using SCF process with supercritical CO_2 (SC CO_2) as a processing medium to prepare solid dispersions of budesonide in PEO and further to investigate the effects of varying molecular weight of PEO on physiochemical properties and dissolution behavior of budesonide-PEO solid dispersions. The different powder forms were characterized with scanning electron microscopy (SEM), powder X-ray diffraction (PXRD) and differential scanning calorimetry (DSC), in order to understand the influence of SCF process on the physical and morphological state of budesonide. The pharmaceutical performance of the different powder forms was evaluated using an in vitro dissolution method.

MATERIALS AND METHODS

Materials

PEO N10, N80, and N750 with approximate molecular weight of 100 000, 200 000, and 300 000 Da, respectively, were obtained from The Dow Chemical Company. Budesonide (BUD) was kindly donated by Lunan Pharmaceutical Co. Ltd (Shandong, China). Carbon dioxide (CO_2), with 99.9% minimum purity, was purchased from Dongyu Supercritical Co. Ltd. (Shenyang, China). All solvents used were of high-performance liquid chromatography (HPLC) grade. All other chemicals were analytical grade.

SCF Process for the Preparation of Solid Dispersions

The experimental apparatus (Dongyu Supercritical Co. Ltd., Shenyang, China) for the SCF process used to prepare the solid dispersions of BUD-PEO is illustrated in Figure 1. The equipment can be divided into four units: autoclave, high pressure pump, carbon dioxide reservoir and thermostatic bath with valves at appropriate locations to controlled SC CO_2 flow. The autoclave unit was loaded with accurately weighted amounts of BUD-PEO mixture (1:10, BUD:PEO, W/W). The temperature of the system was controlled with an accuracy of ±0.1°C by a heater circulator (Apparatus Inst., Shenyang, China) that was placed in the thermostatic bath. The system pressure was controlled by a syringe pump. The pressure of the system was monitored using a pressure transducer coupled to a pressure indicator (Trust Pressure Instrument Co. Ltd., Shenyang, China).

CO_2 from a cylinder was fed into pump B (V1 was opened, V2 and V3 were shut, respectively). Once the required pressure was reached, CO_2 from the pump B entered into the autoclave (V2 was opened, V1 and V3 were shut, respectively). The autoclave filled with BUD and PEO mixture was equilibrated at the desired pressure and temperature for at least 5 min prior to commencing the solid dispersions formation. The procedure was also used to remove moisture and air in the autoclave. Then V2 was closed and the autoclave was isolated and left in a static mode under the predetermined conditions (V1 and V3

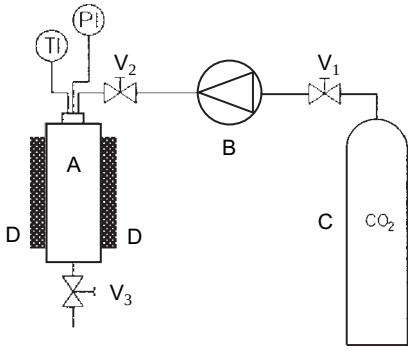

FIGURE 1. Laboratory apparatus for preparing solid dispersions with SCF process (A: autoclave; B: high pressure pump; C: carbon dioxide reservoir; D: thermostatic bath; TI: thermoelement with digital screen; PI: manometer and V_1, V_2, V_3: valves 1, 2 and 3, respectively).

were shut, respectively). Following the SCF procedure, the system was depressurized to atmospheric pressure by opening V3. The depressurization step was usually completed within 5 min. The operating parameters in a static mode used for preparing BUD-PEO were: temperature, 40°C; pressure, 200 bar; exposure time, 18 hr. All the experiments were repeated 3 times.

Preparation of Physical Mixtures

Physical mixtures were prepared by mixing BUD and PEO (1:10, BUD:PEO, W/W) thoroughly during 10 min in a mortar until homogeneous mixtures were obtained.

Scanning Electron Microscopy (SEM)

The morphologies of drug, physical mixtures and SCF-processed physical mixtures were observed by scanning electron microscope (XL-30, Philips-FEI, Holland). Samples were sputter-coated with Au/Pd under an argon atmosphere using a gold module in a vacuum evaporator and were examined using SEM set at 15 kV.

Powder X-Ray Diffractometry (PXRD)

PXRD patterns of samples were recorded using a diffractometer (D/MAX-2A, Rigaku, Japan) with Ni filtered Cu Kα line as the source of radiation. The scanning angle ranges from 5 to 45° of 2θ, steps were of 0.04° of 2θ, and the counting time was 1 s per step. The current and voltage used were 20 mA and 40 kV, respectively.

Differential Scanning Calorimetry (DSC)

Thermal analyses of samples were performed in a differential scanning calorimeter (DSC-60, Shimadzu, Japan). A known mass of sample (≈5 mg) was weighed in a standard open aluminum pan. An empty pan of the same type was utilized as the reference. Samples were heated from 25 to 300°C at a heating rate of 10°C/min, while being purged with nitrogen atmosphere (flow rate 20 mL/min). Calibrations of temperature and heat flow were performed with indium.

Solubility Measurements

An excess amount of BUD was added to capped test tubes containing 10 mL of aqueous solutions and the samples were agitated at the rate of 50 times $\cdot$ min^{-1} in a thermostatically controlled magnetic stirrer at 25°C for 48 hr. Subsequently, the suspension was centrifuged at 15000*g* for 10 min and the supernatant was analyzed by HPLC after diluting with the mobile phase. The results of triplicate measurements and their means were reported.

In Vitro Drug Dissolution Studies

In vitro dissolution studies were performed for pure BUD, its physical mixtures with PEO, and the solid dispersions formed by SCF process, respectively, following the Chinese Pharmacopeia 2005 paddle method in 900 mL of PBS (pH 7.4) at 37°C and 50 rpm. Accurately weighted samples containing the equivalent of 9 mg of BUD were spread over the dissolution medium surface. At predetermined time intervals, 5 mL aliquot samples were withdrawn with the same volume of fresh dissolution medium replacement to maintain a constant volume. The samples were filtered (pore size 0.45μm) and the concentrations of BUD in the withdrawn samples were determined by measuring the absorbance at λ = 240 nm using UV-9100 spectrophotometer (Reili Instrument Co. Ltd., Beijing, China). PEO did not interfere with the UV analysis. Experimental data were the average of three replicates, and standard deviations (SD) did not exceed 3% of mean value. Dissolution profiles were compared to that pure BUD, at the same experimental conditions.

HPLC Analysis

A previously reported HPLC method was referred (Hou et al., 2001) for quantifying BUD. 20 μl of the resulting sample was injected into an HPLC Apparatus (Prominence, Shimadzu Co., Kyoto, Japan) consisting of a photodiode array detector (SPD-M20A, Shimadzu Co., Kyoto, Japan), dual liquid chromatography pump (LC-20AB, Shimadzu Co., Kyoto, Japan), a injector (7725i, Rheodyne Co., CA), on-line degasser (DGU-20A$_3$, Shimadzu Co., Kyoto, Japan) and a LC solution single workstation (Shimadzu Co., Kyoto, Japan). The analysis was carried out using a Nucleosil C_{18} column (250 mm × 4.6 mm I.D., 5 μm, Phenomenex Inc.) and ethanol/acetonitrile/0.0256 mM phosphate buffer (pH 3.4, 25.6 mM) (2 : 32 : 66, v/v) as the mobile phase. The flow rate was 1.5 mL/min and the system was maintained at 30°C (Temperature Controller TC-100, China). The detection limit was 0.4 μg/mL. Commercial BUD is an epimeric mixture of two isomers which have the same pharmacological activity. The retention times for *R*-epimer and *S*-epimer were 17.5 ± 1.0 min and 19.0 ± 1.0 min, respectively. The resolution between the peaks corresponding to *R*-epimer and *S*-epimer was not less than 1.5.

Data Analysis

Results were expressed as mean values and standard deviation (±SD) and the significance of the difference observed was analyzed by two-way analysis of variance (ANOVA), a probability value of $p < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

Physicochemical Characterization of BUD-PEO Solid Dispersions with Various PEO Molecular Weights

The physical state of BUD within the PEO matrices (solid dispersions and physical mixtures) was studied by SEM, PXRD and DSC.

SEM Photographs

The shape and surface characteristics of the samples before and after SCF process had been observed with SEM. The particles of untreated pure BUD showed cube-like shaped crystals and were less agglomerated with particle sizes ≤100 μm (Figure 2A). However, the SCF-treated pure BUD was larger and highly agglomerated than the untreated BUD (Figure 2E). In the SCF-untreated BUD-PEO physical mixtures, discrete crystals of BUD could be easily recognized together with a few porous PEO agglomerates (Figures 2B–D). After SCF process, however, the formation of large agglomerates increased obviously and the crystals of BUD could not be recognized (Figure 2F, G, H).

PXRD Patterns

The PXRD analysis was conducted to study the solid state of BUD and to check whether the changes in the crystal morphology corresponded to an amorphous transition. The PXRD patterns of pure BUD before (Figure 3a) and after SCF process (Figure 4a) showed that BUD existed in a crystalline form all the time and no evidence of significant changes from crystalline BUD into noncrystalline state could be attested after the SCF treatment. The high-molecular weight carrier PEO with SCF-treated (Figures 4b–d) show the same diffraction peaks as compared with those with SCF-untreated (Figures 4b–d). The diffraction peaks of BUD were clearly observed in all the SCF untreated physical mixtures (Figures 3e–g), although with a lower intensity, which meant that the simple mixture of BUD and PEO had no influence on the physical state of BUD. However, the diffraction peaks of BUD in the SCF-treated mixtures were decreased significantly (Figures 4e–g). These PXRD results suggested that BUD in the SCF-treated mixtures may exist in essentially non-crystalline form.

In evaluation of solid dispersions prepared by the SCF process using PEO of different molecular weights, PEO N750 was found to give less diffraction peaks than PEO N10 and PEO N80 at a mixing ratio of 1:10 (BUD:PEO), indicating that PEO N750 has more ability to form the solid dispersions than others (Figures 4e–g). The cause of the least crystallinity of BUD in solid dispersions using PEO N750 may be that PEO of this grade is more cross-linked than the two other grades when molten, and for this reason the crystal of the drug was more readily inhibited and resulted in the complete formation of amorphous BUD in solid dispersions when treated by SCF process.

DSC Curves

DSC analysis, an alternative method to investigate the physical state of powders, was carried out to confirm the results by PXRD. The DSC curves for pure BUD and PEO before (Figures 5a–d) and after SCF process (Figures 6a–d) showed characteristic endothermic peaks at 255–260°C and 65–70°C, respectively, indicating that BUD and PEO existed in a crystalline form and SCF process did not alter the crystallinity of BUD and PEO. The DSC curve for the SCF-untreated physical mixtures (Figures 5e–f, g) show two endothermic peaks, an endothermic peak at 65–70°C corresponding to PEO, followed by the endothermic peak at 255–260°C, characteristic of crystalline BUD, which intensities were reduced as a result of blending with semi-crystalline PEO polymer. The DSC curves for the SCF-treated BUD-PEO mixtures (Figure 6e–d) indicated the endothermic peak corresponding to PEO at 65–70°C, but the corresponding endothermic peak for BUD was considerably reduced. These DSC results suggested that BUD in the SCF-treated mixtures may be present in primarily amorphous form. This was in line with our findings from SEM photographs and PXRD patterns.

It was theorized that the following factors may result in the formation of drug-PEO solid dispersions with SCF process. Previous studies observed a reduction of the melting point and glass transition temperature of PEO and a transformation of PEO to a molten phase enabling the interaction between drug and carrier (Weidner et al., 1997; Mishim et al., 1998; Broman et al., 2001), due to the SC CO_2 solubility into this polymer. In addition, solubilization of the drug in the SC CO_2 also facilitated solid dispersions formation. Upon SCF process, the SC CO_2 may enhance the drug solubility, the extent of which in the SC CO_2 was influenced by the supercritical conditions (i.e., temperature and pressure). Indeed, significant solubility of BUD at 40°C and pressure greater than 139 bar in CO_2 had been reported (Martin et al., 2002). Following solubilization of the drug in SC CO_2, molecular dispersion of the drug in PEO was possible due to the high affinity of the drug dissolved in SC CO_2 to PEO matrices. This could result in a high partitioning of the dissolved drug between molten PEO and the supercritical fluid phase. This solubility enhancement of BUD in conjunction with the transformation of the PEO to a molten state likely facilitated the amorphous transition of the drug in PEO carrier through the SCF process and induced dispersion formation. The data obtained in SEM, PXRD and DSC analysis, clearly proved the formation of BUD-PEO solid dispersions upon SCF process.

Aqueous Solubility

Aqueous solubilities of pure BUD were 20.8 μg/mL and 21.2 μg/mL for SCF-untreated and SCF-treated, respectively, which indicated that SCF process had no effect on the intrinsic solubility of pure BUD. SCF-untreated physical mixtures of BUD and different molecular weight PEO increased the solubility of BUD, though the increase was marginal. After SCF process, the significant increases of BUD solubility at mixtures with PEO N10, PEO N80, and PEO N750 were seen to be approximately 19-, 22- and 30- fold, respectively (as compared to SCF treated pure BUD; Table 1). The increase in solubility of BUD by PEO may be due to the formation of solid dispersions between hydrophilic polymeric carrier and poorly soluble

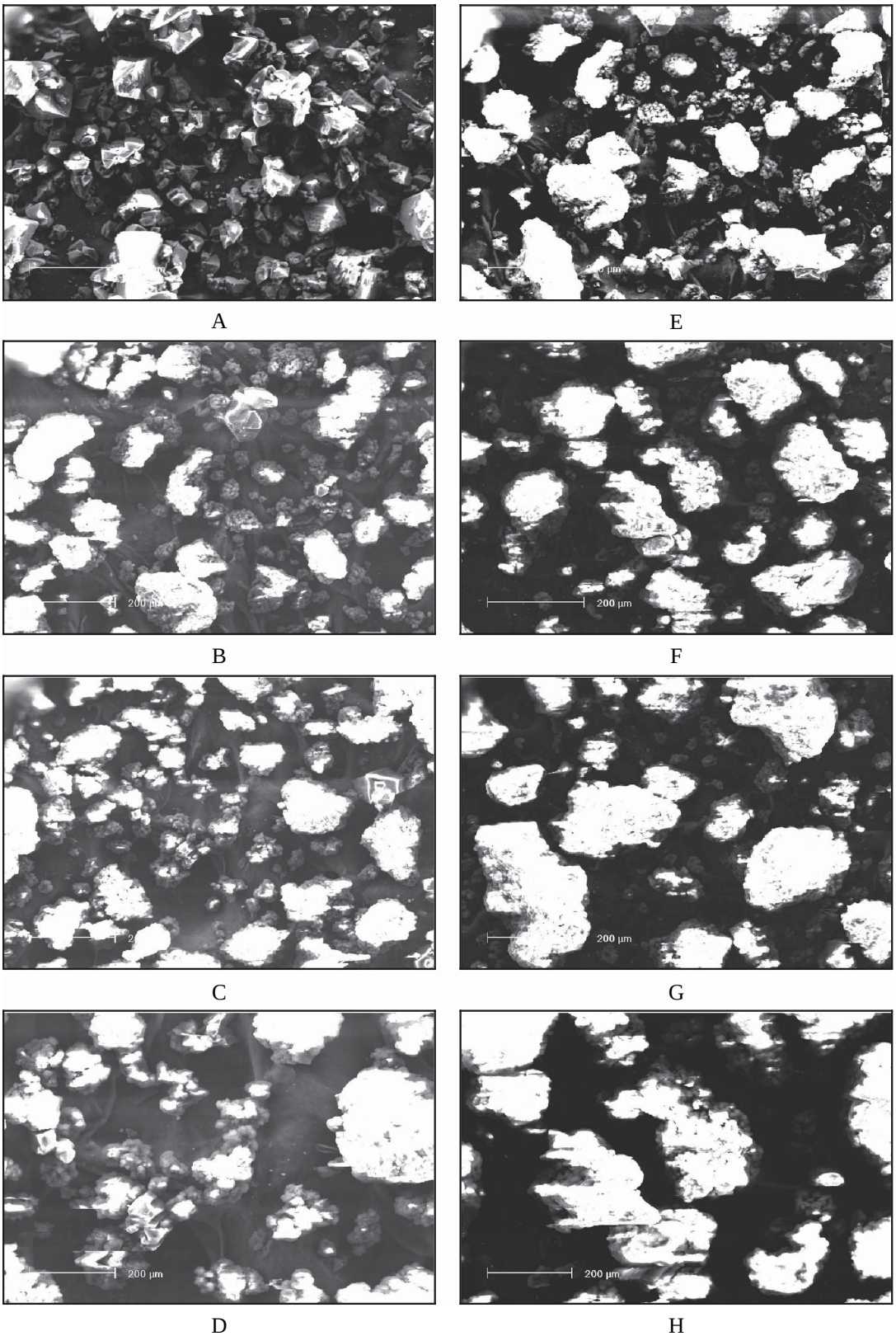

FIGURE 2. SEM photographs of (A) SCF-untreated BUD; (B) SCF-untreated physical mixture of BUD-PEO N10; (C) SCF-untreated physical mixture of BUD-PEO N80; (D) SCF-untreated physical mixture of BUD-PEO N750; (E) SCF-treated BUD; (F) SCF-treated mixture BUD-PEO N10; (G) SCF-treated mixture BUD-PEO N80; (H) SCF-treated mixture BUD-PEO N750.

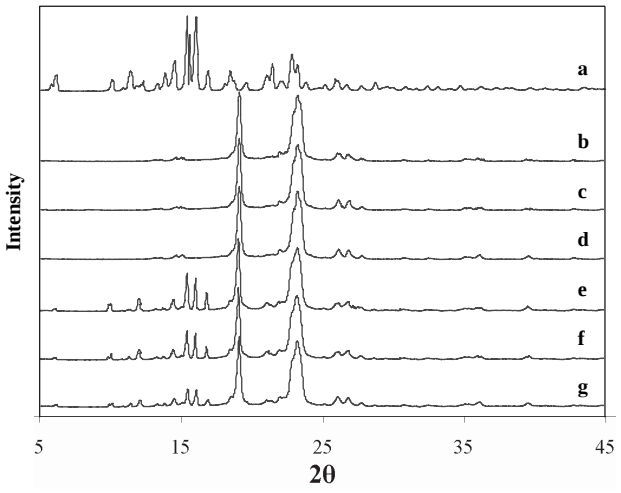

FIGURE 3. PXRD patterns of (a) BUD; (b) PEO N10; (c) PEO N80; (d) PEO N750; (e) BUD-PEO N10 physical mixture; (f) BUD-PEO N80 physical mixture; (g) BUD-PEO N750 physical mixture with SCF-untreated process.

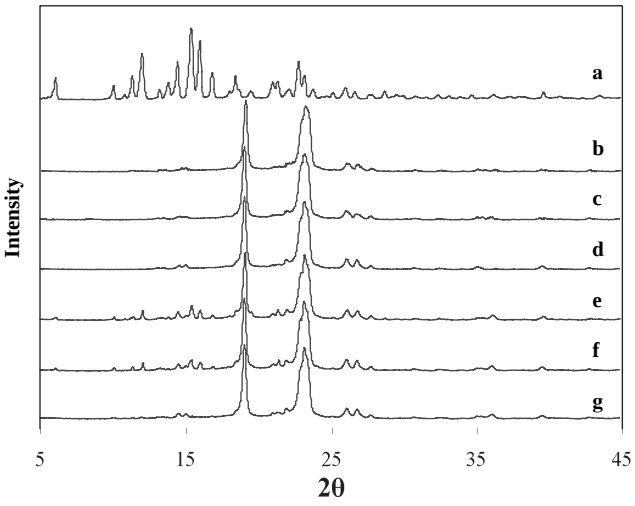

FIGURE 4. PXRD patterns of (a) BUD; (b) PEO N10; (c) PEO N80; (d) PEO N750; (e) BUD-PEO N10 mixture; (f) BUD-PEO N80 mixture; (g) BUD-PEO N750 mixture with SCF-treated process.

drug. PEO may enhance the solubility of BUD either by improving the wettability of the hydrophobic BUD or by preventing aggregation of individual drug particles exhibiting high solid–liquid surface tension by reducing the hydrophobic interaction or by both processes.

Dissolution Studies

The in vitro pharmaceutical performance of the different powders was investigated by determining their dissolution profiles. After 120 min, for the SCF-untreated pure BUD, the amount of dissolved drug was very small, with 15.2 ± 1.3%

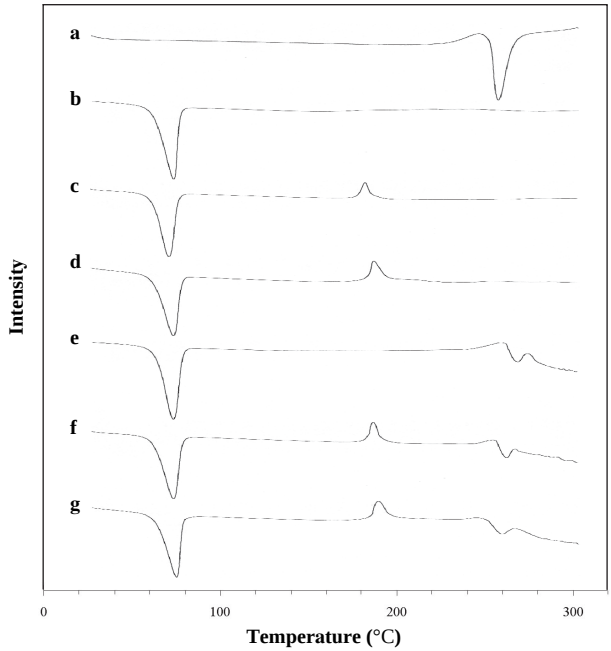

FIGURE 5. DSC curves of (a) BUD; (b) PEO N10; (c) PEO N80; (d) PEO N750; (e) BUD-PEO N10 physical mixture; (f) BUD-PEO N80 physical mixture; (g) BUD-PEO N750 physical mixture with SCF-untreated process.

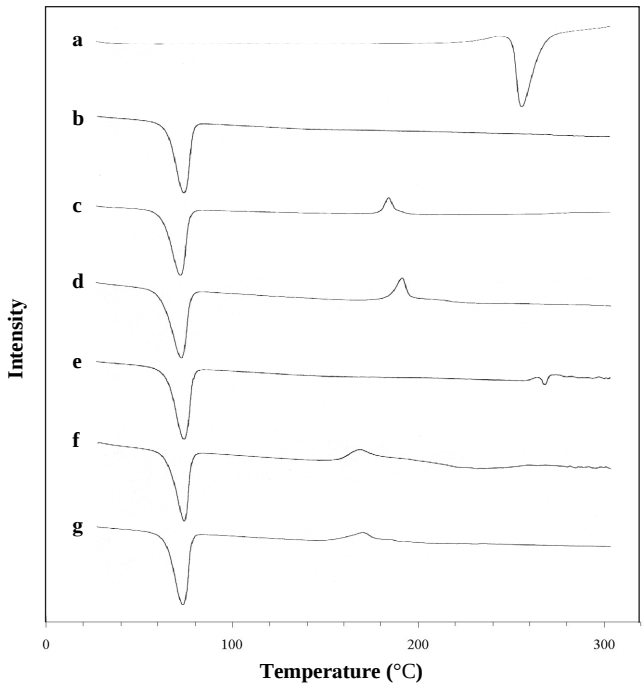

FIGURE 6. DSC curves of (a) BUD; (b) PEO N10; (c) PEO N80; (d) PEO N750; (e) BUD-PEO N10 mixture; (f) BUD-PEO N80 mixture; (g) BUD-PEO N750 mixture with SCF-treated process.

TABLE 1
Aqueous Solubility of BUD

	Solid Containing BUD	Aqueous Solubility (μg /ml)[a] at 37°C
SCF-untreated	Pure BUD	20.8 ± 2.5
	BUD-PEO N10	26.5 ± 2.8
	BUD-PEO N80	24.3 ± 2.1
	BUD-PEO N750	37.2 ± 4.3
SCF-treated	Pure BUD	21.2 ± 3.2
	BUD-PEO N10	397.8 ± 32
	BUD-PEO N80	467.8 ± 39
	BUD-PEO N750	645.2 ± 43

[a]Each solubility data represents mean ± S.D. (n =3).

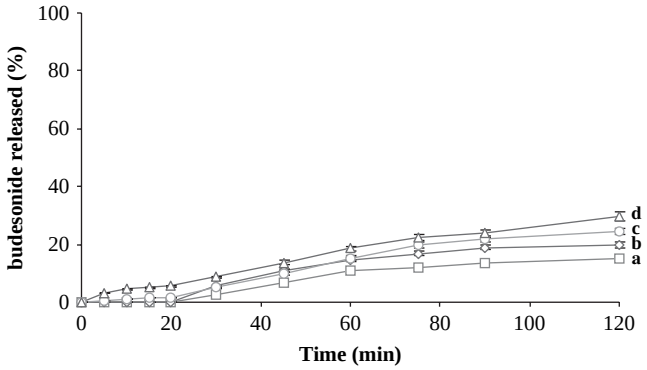

FIGURE 7. Dissolution profiles of SCF-untreated pure BUD (□), physical mixtures of BUD-PEO N10 (◇), BUD-PEO N80 (○), BUD-N750 (△) in 900 ml of PBS (pH 7.4) at 37°C and a stirring of 50 rpm. Results were expressed as mean ± S.D. (n =3).

dissoluted (Figure 7a). A similar dissolution profile was obtained for the SCF-treated BUD (21.3 ± 3.5% dissolution after 120 min; Figure 8a), in spite of the difference in particle size. There was no difference in dissolution rates between SCF-untreated and treated BUD ($p > 0.05$), illustrating that SC CO_2 treatment did not enhance the dissolution of pure BUD. SCF-untreated BUD-PEO physical mixtures had not improved dissolution patterns as compared with the SCF-untreated BUD significantly ($p > 0.05$; Figures 7b–d). The SCF-treated BUD-PEO solid dispersions, however, showed significant improvement in BUD dissolution as compared with the SCF-treated BUD ($p < 0.05$; Figures 8b–d).

To evaluate differences in the dissolution rates according to the grade of PEO, two-way analysis of variance (ANOVA) was performed for the dissolution systems. For SCF-untreated BUD-PEO physical mixtures, no significant effects on the dissolution rates of BUD among the PEO N10, PEO N80, PEO N750 physical mixtures were found ($p > 0.05$). For SCF-

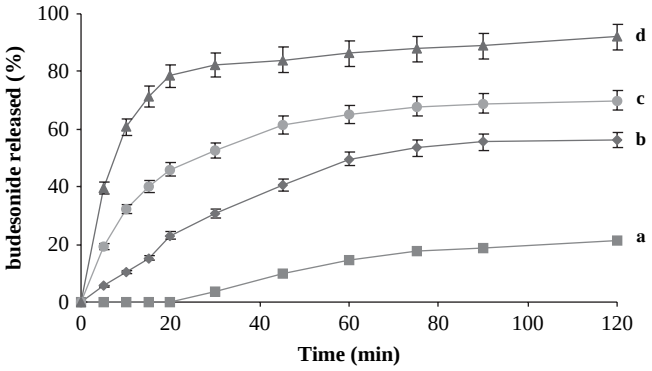

FIGURE 8. Dissolution profiles of SCF-treated pure BUD (■), solid dispersions of BUD-PEO N10 (◆), BUD-PEO N80 (●), BUD-N750 (▲) in 900 ml of PBS (pH 7.4) at 37°C and a stirring of 50 rpm. Results were expressed as mean ± S.D. (n =3).

treated BUD-PEO mixtures, the dissolution rates were in order: PEO N10 < PEO N80 < PEO N750. The PEO N750 showed the fastest rate, 4.3-fold of that of SCF-treated BUD. PEO is a rather special polymer with unique properties in the solid, gel and solution. The swelling and erosion properties of PEO have been shown to vary consistently with molecular weights of PEO. It was calculated that the results that the enhancing effects of PEO on solubility and dissolution of BUD were in line with the order of molecular weights of PEO may be in relation to above-mentioned characteristics of PEO.

It should be noted that in this study the products were not sieved or ground prior to the dissolution tests. Based on the SEM analysis, the particle sizes of the SCF-treated mixtures were found to be larger than those of the SCF-untreated physical mixtures. As a result, the reduction in particle size may not be a major determinant of the dissolution characteristics of BUD. It has been suggested that, for drugs with a low solubility, the release of the drug was primarily controlled by the relative magnitude of the rate of swelling/erosion of the polymer (Kim, 1998). The enhanced contact time of PEO with the drug due to gel formation may thus enhance the wetting of the drug, providing access of the dissolution medium to the drug surface and prevent aggregation of particles and subsequent decrease in surface area. In addition to wetting, an amorphous transformation of the drug to a more soluble form when present as a solid dispersion formation may be considered (Mehta et al., 2002). Another possible explanation for the observed dissolution enhancement was the formation of sufficient mixture of drug and PEO powders in the presence of SC CO_2. On the whole, we believed that a combination of factors including the amorphous characteristic of the BUD, the improved wettability effect of hydrophilic PEO on BUD and the better mixing of drug and PEO powders contributed to the enhancement in dissolution rate of drug. This result indicated that PEO could be used as a carrier in the solid dispersion to enhance the dissolution rate of the drug.

CONCLUSION

In this study, the feasibility of preparing the BUD-PEO solid dispersions using SCF technology was investigated. The physical characteristics of the solid state of the drug before and after SCF treatment was analyzed by way of SEM, PXRD, and DSC. The results verified the amorphous nature of the BUD in the SCF-processed mixture, suggesting the formation of drug-PEO solid dispersions. These solid dispersions, prepared with various molecular weights of PEO as carrier, were able to remarkably improve the dissolution characteristics of poorly soluble BUD. The extent of improved dissolution of BUD in the SCF-treated mixtures was consistent with the order of the molecular weights of PEO. The mechanism of the enhanced dissolution was attributable to the amorphous nature of the product, the better mixture of the drug and PEO carrier and the improved wettability of drug when the polymer was dissolved. Since SCF process showed advantages over conventional methods for solid dispersions preparation by avoiding the use of organic solvents and heat, yielding the solid dispersions in one step and the final product was in powdered form it has been proved to be a viable and alternative means of preparing BUD-PEO solid dispersion. Presently in vivo studies are being performed to support these in vitro findings.

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