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Preparation, Characterization and In Vitro Evaluation of Solid Dispersions Containing Docetaxel

Jie Chen
College of Pharmaceutical Sciences, Zhejiang University, Hangzhou, People's Republic of China and Zhejiang Xianju Pharmaceutical Technology Co., Ltd, Hangzhou, People's Republic of China

Liyan Qiu, Minxin Hu, Yi Jin, and Jieru Han
College of Pharmaceutical Sciences, Zhejiang University, Hangzhou, People's Republic of China

Solid dispersions using water-soluble carriers were studied for improving the dissolution of docetaxel, a poorly soluble compound. In order to obtain the most optimized formulation, we prepared many solid dispersions with different carriers, different solvents, or at a series of drug-to-carrier ratios, and compared their dissolution. The accumulative dissolution of docetaxel from poloxamer 188 was more excellent than that from PVP_{k30} and glyceryl monostearate, and the dissolution of docetaxel from solid dispersion was markedly higher than that of pure docetaxel; meanwhile the increased dissolution was partly dependent on the ratios of docetaxel and poloxamer 188. The ethanol used to prepare solid dispersion is of more significant effect on the dissolution of docetaxel than that of acetone. The docetaxel/poloxamer 188 system was characterized by differential scanning calorimetry (DSC), X-ray diffractometry (XRD), and environmental scanning electron microscope (ESEM). The results of DSC, XRD, and ESEM analyses of docetaxel/poloxamer 188 system showed that there are intermolecular interactions between docetaxel and poloxamer, and the crystallinity of docetaxel disappeared. These results show that solid dispersion is a promising approach of developing docetaxel drug formulates.

Keywords docetaxel; solid dispersion; poloxamer 188; solubility; dissolution; crystallinity

INTRODUCTION

Docetaxel (Figure 1), which is a white or almost-white powder with an empirical formula of $C_{43}H_{53}NO_{14,}$ is in the taxane class of anticancer agents. Docetaxel, which was identified in 1986 as an alternative to paclitaxel and has a renewable resource, is a semisynthetic derivative of a compound isolated from the needles of the European yew plant (Bissery, 1995; Clarke & Rivory, 1999).

Address correspondence to Yi Jin, College of Pharmaceutical Sciences, Zhejiang University, Hangzhou 310058, P. R. China. E-mail: jinyizju@hotmail.com

Over the past several decades, docetaxel has become one of the most important chemotherapeutic agents, whose antitumor activity is due to its ability to disrupt the normal process of microtubule assembly and disassembly (Clarke & Rivory, 1999; Ringel & Horwitz, 1991). In clinical trial, docetaxel was successfully applied, mostly against ovarian carcinoma, advanced breast cancer, lung cancer, and head/neck cancer (Clarke & Rivory, 1999; Nuijen et al., 2001; Ringel & Horwitz, 1991; Takigawa & Segawa, 2004; Tham & Gomez, 2005). Docetaxel, which is highly lipophilic and practically insoluble in water, was prepared using Tween 80 (polysorbate 80) and ethanol (Sanofi aventis website, 2007). However, acute hypersensitivity reactions have been found in the majority of patients treated in the clinical trials (Markman, 2003; Nanan & Huizing, 1997), and previous research has showed that Tween 80 may result in some more serious adverse effects than the drug itself (Albert et al., 2003).

Because of the drawbacks presented by the presence of Tween 80 in drug formulation, some new preparations, including liposomes (Maria et al., 2003) and nanoparticle (Musumeci et al., 2006), have been developed to avoid and/or alleviate these effects. Another attractive approach to overcome the drawbacks of Tween 80 resulted from systemic administration is to develop oral formulations, which have more advantages than intravenous dosage, including reduction of the potential toxicity caused by Tween 80 and the times of outpatient visits. However, preclinical studies have suggested that docetaxel was not significantly absorbed after oral administration, and the bioavailability in mice was less than 3.6% (Bardelmeijer et al., 2002). Many reasons have been proposed to account for the poor oral bioavailability of docetaxel, but the most likely explanation is its poor solubility. In order to improve the solubility of docetaxel, and thus increase the absorption of the drug in the gastrointestinal tract, the technical methods of solid dispersion are applied in our study. They are defined as the dispersion of one or two more active ingredients in an inert

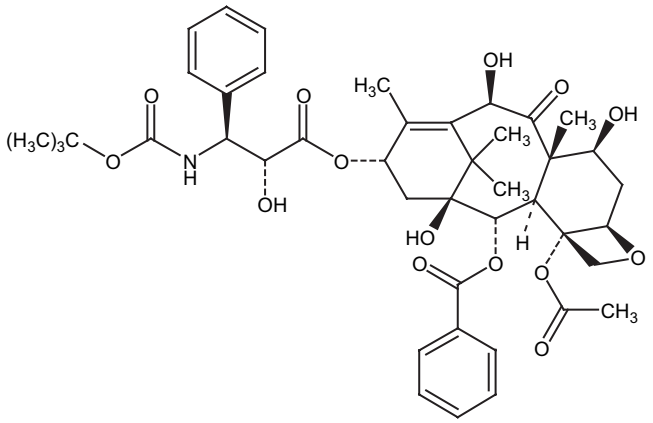

FIGURE 1. Chemical structure of docetaxel.

hydrophilic carrier or matrix with solid state, prepared by the fusion, solvent, or solvent-fusion method (Leuner & Dressman, 2000; Sheen, Khetarpal, Cariola, & Rowlings, 1995). These systems provide the possibility of reducing the particle size of the drugs to a molecular level, and locally increasing the saturation solubility and/or of transforming the drug from the crystalline to the amorphous state.

Poloxamer 188 is one of the commercial grades of poloxamers, which are water soluble nonionic surfaceactive copolymers (Rowe, Sheskey, & Weller, 2003). In this paper, the preparation, characterization, and in vitro evaluation of docetaxel solid dispersions using poloxamer 188 as a carrier were reported. Besides which are stated, all ratios and percentages are expressed as w/w. The desired dosage of docetaxel (10%, w/w) forms a uniform solid dispersion in polymeric carrier.

MATERIALS AND METHOD

Chemicals and Reagents

Docetaxel was provided by Jiangsu JARI PHARM CO., Ltd. Poloxamer 188 was purchased from Nanjing WELL Chemical Co., Ltd. Polyvinylpyrrolidone K_{30} (PVP_{k30}) was obtained from Shanghai Hengxin Chemical Reagent Co., Ltd., and glyceryl monostearate was purchased from Sinopharm Chemical Reagent Co., Ltd. All other chemicals were reagent grade and were used without further purification.

Preparation of Physical Mixtures and Solid Dispersion

Physical Mixtures

Docetaxel and poloxamer 188 were accurately weighed at a ratio of 10:90, pulverized, and then mixed thoroughly in a mortar with a pestle until homogeneous mixtures were obtained. The mixtures were passed through a 280 μm sieve for further experiments.

Solid Dispersion

Solid dispersions of docetaxel in glyceryl monostearate and PVP_{k30} contain the same ratio of 10:90, but in poloxamer 188 they contain four different ratios of 25:75, 15:85, 10:90, and 5:95. All of them were prepared by the solvent method. Briefly, docetaxel and excipients were dissolved in an appropriate amount of solvent (absolute ethanol and acetone) separately. After complete dissolved, they were mixed with magnetic stirring. Solvents were evaporated under reduced pressure at 40°C in a rotary evaporation meter. Subsequently, the solid dispersions were stored in vacuum over silica gel for 12 h at room temperature. After dried, the solid dispersion were ground with liquid nitrogen in a mortar, and then passed through a 280 μm sieve. The samples were stored in a desiccator for further investigation.

Determination of Equilibrium Solubility of Docetaxel/Poloxamer 188 in Distilled Water

Excessive amounts of pure docetaxel, physical mixture and solid dispersion, were added into distilled water. The suspension was rotated vertically at 37°C for at least 48 h to obtain the equilibrium solubility. The suspensions were filtered through 0.45 μm filters. The concentration of the filtrate was determined by a HPLC method. The sample were carried out in triplicate, therefore only mean values with *SD* error are reported.

HPLC Analysis

The analysis was performed using an Agilent 1100 series HPLC. The column was Diamonsil C_{18} (4.6 mm × 25 cm, 5 μm). The mobile phase was water, acetonitrile, and methanol (42:24:34), and the flow rate was 1 mL/min. The wavelength of the UV detector was at 232 nm, and the injection volume was 20 μL.

Differential Scanning Calorimetry (DSC)

DSC curves of the docetaxel, poloxamer 188, the physical mixture, and solid dispersion, were measured with a DSC instrument (Model DSC Q100, New Castle). The samples were accurately weighed and heated in closed aluminum crimped cells at a rate of $10\,°C \cdot min^{-1}$ between 30 and 340 °C temperature under a nitrogen gas flow of $40\ mL \cdot min^{-1}$ during the study.

X-Ray Diffraction (XRD)

The powder samples were packed in the X-ray holder from the top before analysis. X-ray powder diffraction patterns were recorded on a Rigaku-D/MAX-2550PC diffractometer (Rigaku Co., Ltd., Japan) using Nifiltered, Cu Kα radiation, a voltage of 40 kV and a 300 mA current. These samples were continuously spun and scanned at a rate of $0.02°\ s^{-1}$ over a 2 θ range of 3–50°.

Environmental Scanning Electron Microscope (ESEM)

Morphology of the docetaxel/poloxamer 188 system was characterized by an environmental scanning electron microscope XL30 (PHILIPS, Netherlands) operating at 20.0 KV accelerating voltage. Samples were coated by gold before examination (cathode dispersion).

Dissolution Test

Dissolution profiles of pure docetaxel and solid dispersions as well as physical mixtures were evaluated according to the method in the Ch.P-2005 (Appendix XC, No.3 method at 100 rpm). Briefly, 5 mg of free docetaxel or equivalent amount of physical mixtures or solid dispersion were filled into gelation capsules, and 900 mL distilled water at 37.0 ± 0.5°C was added in a ZRS-8G Dissolution Apparatus (Precision Instruments, Tianjing Universituy, China). At predetermined time, suitable solutions were withdrawn and equivalent amounts of distilled water were added. Samples were filtered (0.45 μm pore size) and analyzed by HPLC. Experiments were carried out in triplicate, therefore only mean values with *SD* are reported, and analysis of variance (ANOVA) was performed to clarify the differences in dissolution rates.

RESULTS AND DISCUSSION

Optimizing the Formulation of Solid Dispersion

Screening of Water-Soluble Carrier

Glyceryl monostearate, $PVP_{k30,}$ and poloxamer 188 have been generally accepted as polymeric carriers to enhance the dissolution characteristics of poorly soluble drugs and hence, their oral bioavailability (Franco & Trapani, 2001; Franco & Zhang, 2004). In order to obtain a suitable carrier to solubilize docetaxel, the new formulation with three excipients were prepared by solvent method in our research, and the dissolution profiles of the three new formulations are shown in Figure 2. Important differences in dissolution behavior can be observed among the different preparations. The formulation containing poloxamer 188 showed an instantaneous dissolution of the drug; approximately 60% was released within the first 20 min. The dissolution of docetaxel from PVP_{k30} or glyceryl monostearate was much lower, lower than 15%. Interestingly, the dissolution of docetaxel that used poloxamer 188 as carrier was the highest after 2 h, which was more than 90% ($p < 0.05$). On the other hand, although the dissolution of docetaxel that used PVP_{k30} as carrier was lower than 80%, it was higher than that of docetaxel that used glyceryl monostearate as carrier ($p < 0.05$). It was proposed that the change of crystal structure of drug in solid dispersions and the solubilizing effect of carriers were attributable to the high dissolution rate (Kim et al., 2006). Considering its outstanding solubilization effect, poloxamer 188 was chosen as drug-carrier in the study.

Screening of Solvent

Figure 3 shows the dissolution profile of solid dispersion (10:90) prepared with absolute ethanol and acetone. It was observed that the solid dispersion with absolute ethanol improved dissolution profiles with more than 20% drug released over the solid dispersion with acetone after 1 h ($p < 0.05$), although there was little difference between the initial dissolution rate. The solvent dissolving the drug and carrier may lead to different interactions between them while forming solid dispersions, then may affect the final dissolution amount of docetaxel from solid dispersions.

Screening of the Drug-to-Carrier Composition Ratio

To investigate the effect of the amount of carrier on the formation of solid dispersion, different docetaxel/poxolamer 188 were prepared at the drug-to-carrier composition ratios (w/w) of 0:100, 5:95, 10:90, 15:85, 25:75, and 100:0, and their crystalline phase characteristics and dissolution profiles were studied by XRD method and dissolution test, respectively. Figure 4A

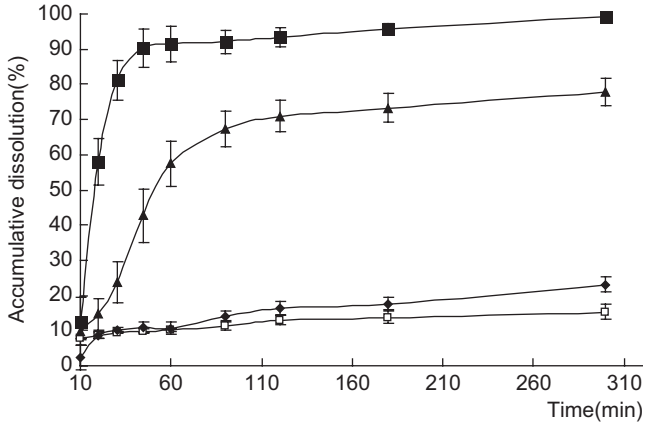

FIGURE 2. Dissolution profiles of docetaxel from solid dispersions prepared using different carriers: glyceryl monostearate(□), pure docetaxel (◆), PVP_{k30} (▲), and poloxamer 188 (■); (n = 3).

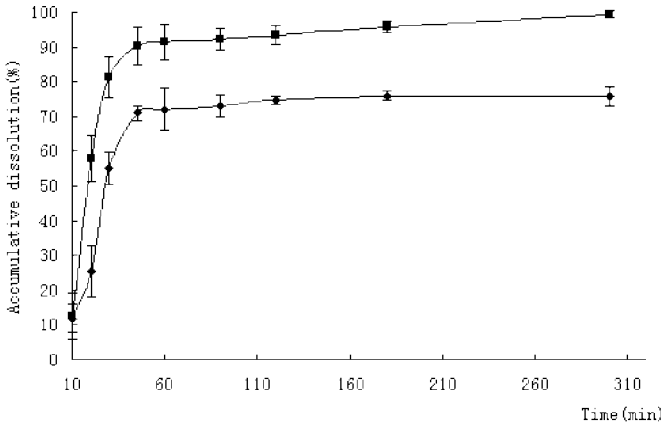

FIGURE 3. Dissolution profiles of docetaxel from solid dispersions prepared using different solvents: absolute ethanol (■) and acetone (●); (n = 3).

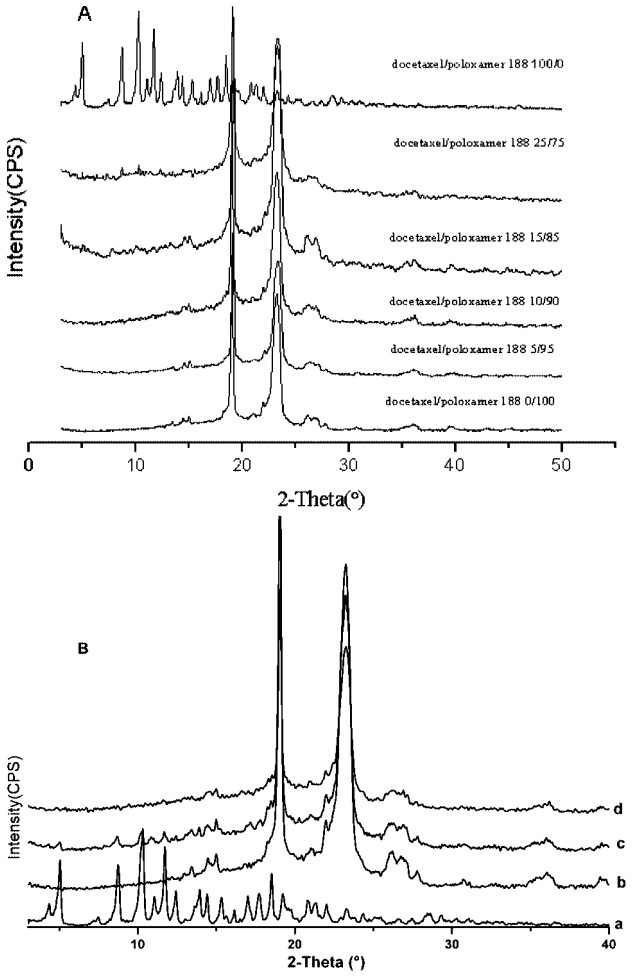

FIGURE 4. Representative XRD patterns of docetaxel/poloxamer 188 system: (A) solid dispersion at different drug-to-carrier composition ratios; (B) a: docetaxel; b: poloxamer 188; c: physical mixtures of docetaxel and poloxamer 188(10:90); d: solid dispersion (10:90).

showed XRD result of formulations containing different ratios of docetaxel. Diffraction peaks of both docetaxel and poloxamer 188 were sharp, and no amorphous halo was observed, which indicated negligible amophous content and high crystallinity of both components. The compositions of docetaxel and poloxamer 188 at the ratio of 5:95 and 10:90 only showed characteristic diffraction peaks of carrier, this indicates that docetaxel was not present as a crystalline state. On the other hand, with the decrease of the amount of poloxamer 188, the diffraction peaks of docetaxel appeared gradually. At the ratio of 15:85 and at higher ratios, the XRD curves showed diffraction peaks, indicating the presence of crystalline docetaxel. Interestingly, the spectrum of physical mixture (Figure 4B[c]) also showed diffraction peaks at 2 θ of 5.04, 8.72, 10.28, and 11.7, which disappeared in spectrum of solid dispersion (10:90). These results imply that docetaxel may be presented in an amorphous form in docetaxel/poloxamer 188 solid dispersion (10:90).

The thermal curves of docetaxel/poloxamer system are shown in Figure 5. In Figure 5(a), DSC measurements showed one broad endothermic peak near 81.2°C corresponding to the vaporation of water of docetaxel, which was a compound with tri-hydrong (Bissery, 1995), and a small endothermic peak at 169°C corresponding to the transconformation of the molecule, and the irregular peaks above 210°C corresponding to the decomposition of docetaxel [Merckindex]. Poloxamer 188 presented crystalline structures composed of multi-color sea-urchin like patterns (Jannin, Pochard, & Chambin, 2006). In Figure 5(b), there was a single and sharp exothermic peak at 53.9°C, that corresponds to the melting point of poloxamer 188 (Rowe et al., 2003). In the DSC curve of the docetaxel/poloxamer 188 solid dispersion, the endothermic peak of docetaxel at 170°C was not observed, whereas the slight transition peak was shown in physical mixture of Figure 5(c). The DSC curves of the solid dispersion and the physical mixture showed a sharp peak, and their temperature of melting point appeared somewhat different from that of poloxamer 188.

In conclusion, the relative enthalpy change may be considered to correspond to the energy loss of crystallinity transformation. It may be that the drug molecules are dispersed in the poloxamer 188 matrix of the solid dispersion and that the thermal property was changed.

To observe the morphology of pure docetaxel, poloxamer 188, the physical mixtures of docetaxel and poloxamer 188 (10:90), and solid dispersion (10:90), our study applied ESEM to the system and the results are shown in Figure 6. Docetaxel existed in lamellar-like crystals, whereas poloxamer 188 consisted of large crystalline particles of rather irregular size. In the physical mixtures, the characteristic docetaxel crystals, which were mixed with excipient particles or adhered to their surface, were clearly detected, thus, confirming the presence of crystalline drug. On the contrary, the solid dispersions

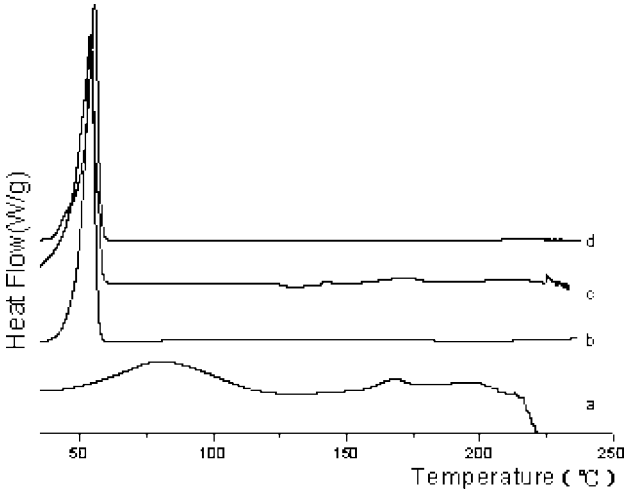

FIGURE 5. DSC curves of (a) docetaxel, (b) poloxamer 188, (c) physical mixtures of docetaxel and poloxamer 188 (10:90) and (d) solid dispersion (10:90).

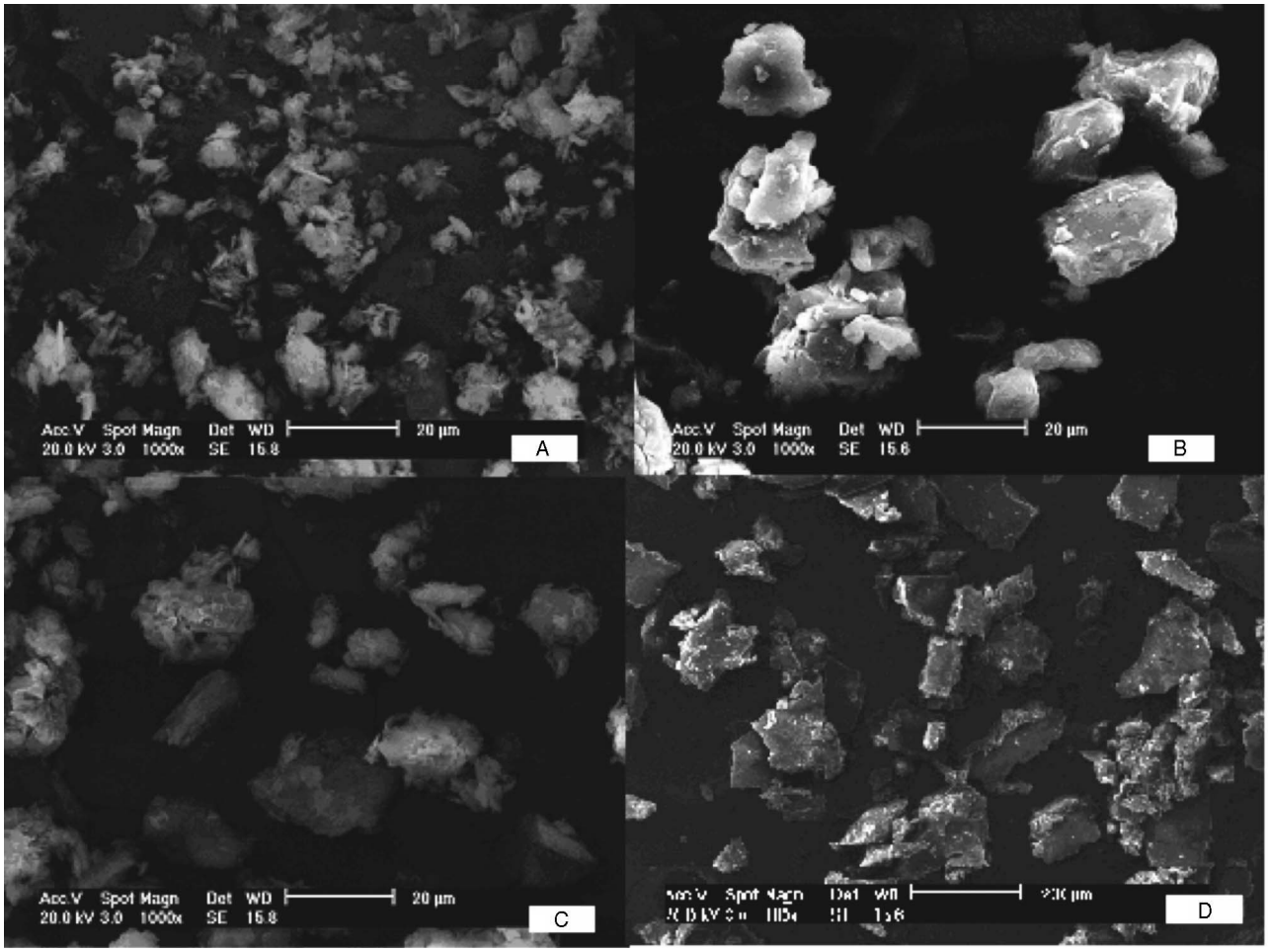

FIGURE 6. ESEM of (A) pure docetaxel crystalline power, (B) poloxamer 188, (C) physical mixtures of doxetaxel and poloxamer 188, and (D) solid dispersion (10:90).

appeared in the form of irregular particles and the original morphology of both components disappeared, which corresponds to DSC and XRD data. (In Figure 5, the melting point of SD (50.2°C) was lower than that of carrier (53.9°C); in Figure 4B, the characteristic peaks of drug disappeared in solid dispersion.) These results demonstrated that docetaxel in solid dispersion was integrated into poloxamer 188 swollen with ethanol and was homogeneously dispersed into poloxamer at the molecular level.

The dissolution profiles of docetaxel, physical mixture of docetaxel/poloxamer 188, and solid dispersion are illustrated in Figure 7. At each time point, dissolved amount of docetaxel in solid dispersion was significantly higher than that of pure docetaxel. The dissolved amount of pure docetaxel was less than 10 wt.% after 1 h, while the docetaxel dissolved amount from solid dispersions were more than 50 wt.% except for solid dispersion at ratio of 25:75, which rapidly and markedly exceeded the pure docetaxel ($p < 0.05$); in the solid dispersions, at the ratios of 5:95 and 10:90, dissolution profiles increased to more 75% than that of pure docetaxel powder ($p < 0.05$), however, there was no significant difference between that of the dissolution profiles (Figure 7). Therefore, we chose the lower drug/polymer ratio system (10:90) which is of adequate dissolution and physicochemical properties for the further analysis and development.

It is interesting to note that even though the quantity ratio (10:90) of the drug and carrier for dissolution was the same, the dissolution rate of docetaxel from the solid dispersion was significantly enhanced when compared with that of physical mixture. This was supported by the previous research that formulation in solid dispersions could, theoretically, further improve the dissolution by reducing the drug particle size, formation of drug/polymer solid solutions, transformation of the drug to the diffluent amorphous state and by a more intimate contact between the polymer and the drug, compared with physical mixtures (Verheyen, Blaton, Kinget, & Mooter, 2002).

In order to further illustrate the dissolution curves, the percentage of docetaxel dissolved in distilled water after 20 min (D_{20})

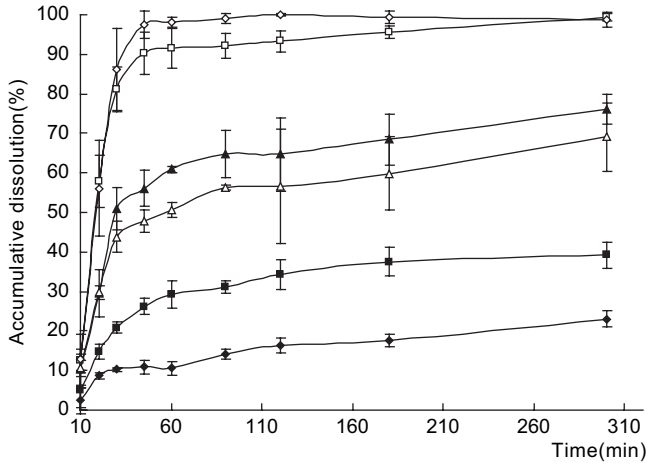

FIGURE 7. Dissolution profiles of pure docetaxel crystalline power (◆), physical mixtures of doxetaxel and poloxamer 188 (■), solid dispersion (25:75) (△), solid dispersion (15:85) (▲), solid dispersion (10:90) (□), and solid dispersion (5:95) (◇) in distilled water at 37.0°C; (n = 3).

and the characteristic time for 50% dissolution of docetaxel initial amount ($T_{50\%}$) were calculated and are shown in Table 1. After 20 min, the dissolutions of docetaxel from all solid dispersions were more than 30%, while the dissolution of pure docetaxel was 8.7%. Formation of 10:90 and 5:95 (w/w) solid dispersion advanced the $T_{50\%}$ value from 32.1 min (15:85 solid dispersion) to 18.6 min and 18.5 min, respectively. $T_{50\%}$ decreased with the reducing of percentage of docetaxel in solid dispersion. Similar observations have been reported for solid dispersions of Nifedipine in poloxamer 407 (Chutimaworapan et al., 2000).

Determination of Equilibrium Solubility of Docetaxel/ Poloxamer 188 System in Distilled Water

The equilibrium solubility of docetaxel/poloxamer 188 system in distilled water is shown in Figure 8. The solid dispersion (SD) and the physical mixture (PM) can improve the solubility of

TABLE 1
Dissolution Properties of Docetaxel, the Physical Mixtures and Solid Dispersions with Poloxamer 188

	$M \pm SD$	
Sample	D_{20} (%)[a]	$T_{50\%}$ (min)[b]
Pure docetaxel	8.7 ± 0.8	–
Physical mixtures	14.8 ± 1.7	–
Solid dispersion (15:85)	29.5 ± 5.9	32.1 ± 6.1
Solid dispersion (10:90)	57.9 ± 6.6	18.6 ± 1.9
Solid dispersion (5:95)	56.0 ± 4.5	18.5 ± 3.0

[a]Amount of docetaxel dissolved after 20 min.
[b]Time when 50% of initial amount of docetaxel was dissolved.

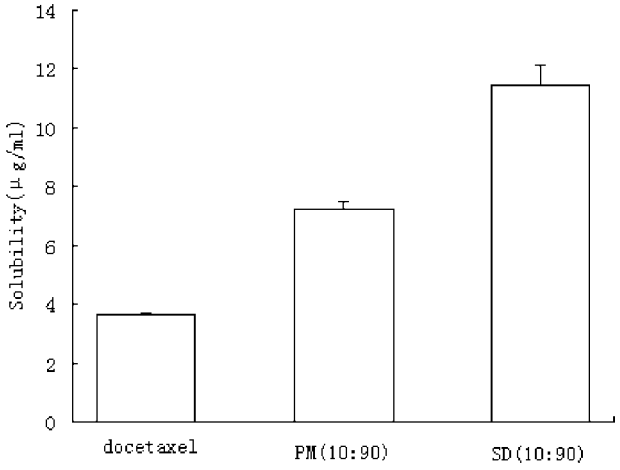

FIGURE 8. Equilibrium solubility of docetaxel/poloxamer 188 system in distilled water; (n = 3).

docetaxel from 3.66 μg · mL^{-1} (pure docetaxel) to 11.45 μg · mL^{-1} and 7.23 μg · mL^{-1} separately. These results indicated that main mechanisms of the increasing solubility of docetaxel in poloxamer 188 solid dispersion compared with the pure drug are most likely due to wettability and emulsifying effects and the change of crystallinity (Chutimaworapan et al., 2000; Franco & Trapani, 2001; Shin et al., 2003).

Stability Testing

To assess the stability of solid dispersion (optimizing formulation), a stability study was conducted. The sample (solid dispersion 10:90) was stored in desiccator at ambient temperature for 30 d. The stability of solid dispersion was assessed by HPLC method and dissolution test. HPLC analysis showed that no degradation products were formed, indicating that the drug substance was chemically stable under the storage conditions for 30 days. Figure 9 illustrates the dissolution profile of solid dispersion (10:90) stored for 0 day and 30 days. After 45

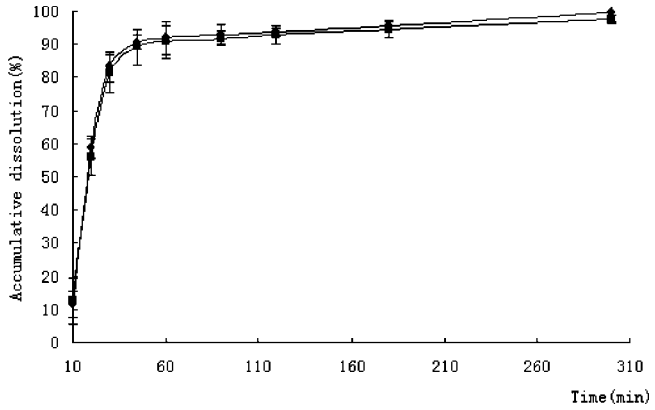

FIGURE 9. Dissolution profiles of docetaxel from solid dispersions: 30 d (■) and 0 d (●).

min, the acculumative dissolution of docetaxel from solid dispersion (30 d) was more than 80%. However, there was no significant difference between that of solid dispersion (0 d). These observations indicated that the solid dispersion prepared by solvent method of docetaxel and poloxamer 188 (10:90) was chemically and physically stable for 30 days at ambient temperature.

CONCLUSION

The solubility and dissolution rate of docetaxel from solid dispersion prepared with poloxamer 188 were markedly improved in comparison to pure docetaxel and its physical mixtures. The results of XRD, DSC, and ESEM indicated that the physico-chemical interaction, such as an association between the functional groups of docetaxel and poloxamer 188, might occur in the molecular level and there was not any crystallinity of docetaxel in the solid dispersion at ratio of 10:90(docetaxel and poloxamer 188), or in the increase of the solubility and the dissolution of docetaxel from the solid dispersion. The solid dispersion using poloxamer 188 as carrier provides a promising way to increase the solubility and dissolution rate of poorly soluble drugs.

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