

RESEARCH ARTICLE

Application and functional characterization of POVACOAT, a hydrophilic co-polymer poly(vinyl alcohol/acrylic acid/methyl methacrylate) as a hot-melt extrusion carrier

Ming Xu, Chungang Zhang, Yanfei Luo, Lishuang Xu, Xiaoguang Tao, Yanjiao Wang, Haibing He, and Xing Tang

Department of Pharmaceutics, Shenyang Pharmaceutical University, Shenyang, China

Abstract

Objective: The aim of this study was to evaluate the applicability of POVACOAT™, a hydrophilic PVA copolymer, as a solid dispersion (SD) carrier for hot-melt extrusion (HME).

Methods: Bifendate (DDB), a water-insoluble drug, was chosen as the model drug. DDB was hot-melt extruded by a co-rotating twin screw extruder with POVACOAT™. The SD formability of POVACOAT™ was investigated by varying the composition ratios. Solid state characterization was evaluated by differential scanning calorimetry, powder X-ray diffraction, scanning electron microscopy and Fourier transformation infrared spectroscopy. In order to have a better knowledge of the mechanism of dissolution enhancement, dissolution study, phase solubility study and crystallization study of DDB from supersaturated solutions were performed. In addition, the storage stability of the extrudate containing 10% DDB was investigated.

Results: Physical characterizations showed that DDB was amorphous up to 15% drug loading. The phase solubility study revealed an A_L-type curve. Moreover, POVACOAT™ was found to have an inhibitory effect on crystallization from supersaturated solutions. Compared with the pure DDB and physical mixture, the dissolution rate and solubility of extrudates were significantly enhanced and the drug loading markedly affected the dissolution of SDs. Furthermore, the stability test indicated that 10% DDB-SD was stable during storage (40 °C/75% RH).

Conclusion: The results of this study demonstrate that POVACOAT™ is a valuable excipient for the formulation of solid dispersions prepared by HME to improve dissolution of poorly water-soluble drugs.

Keywords

Bifendate, hot-melt extrusion, POVACOAT, solid dispersion, solubilization, supersaturation

History

Received 20 June 2012
Revised 14 November 2012
Accepted 15 November 2012
Published online 21 January 2013

Introduction

Due to the emergence of high-throughput screening in drug discovery, at least 50% of the new chemical entities (NCEs) are limited to use in clinical therapy as a result of poor solubility. There has been a sharp decline in the number of NCEs discovered with optimal oral bioavailability^{1–3}. However, a number of water-insoluble drugs are highly bioactive. As a result, improvement of drug solubility and dissolution rate is an important issue, especially for biopharmaceutics classification system (BCS) Class II compounds⁴. Nowadays, a variety of approaches have been used to enhance the solubility and dissolution rate of poorly water-soluble drugs, such as solid dispersion (SD), salt formation, solubilization, the use of inclusion compounds based on cyclodextrin and particle size reduction^{3,5}.

The SD method is one of the most commonly used pharmaceutical approaches to enhance the oral bioavailability of drugs with low aqueous solubility. The traditional method using

organic solvent has been widely investigated, but this method has a potential problem of residual organic solvent⁴.

The hot-melt extrusion (HME) technique has been developed to prepare SDs over the past two decades. HME is one of the most widely used processing techniques in the plastics industry². Building on knowledge from the plastics industry, formulators can extrude combinations of drugs, polymers and plasticizers into various final forms to achieve the desired drug-release profiles⁶. HME gains much attention and offers some distinct advantages over other traditional methods. For example, it is solvent free, involves continuous dry processing (necessitating fewer processing steps), offers better content uniformity and can greatly improve bioavailability due to a higher degree of dispersion^{2,6}.

Recently, a polyvinyl alcohol (PVA) co-polymer (POVACOAT™), a new aqueous PVA derivative, which is grafted with acrylic acid and methyl methacrylate, was developed as a film-coating polymer with a good film-forming ability without plasticizers, hard capsules with the characteristics of oil resistance and oxygen barrier and wet granulation binder materials⁷. The chemical structure is shown in Figure 1(a). Learning from an introduction brochure, POVACOAT™ is supplied as Type R with a molecular weight of 200 000 and an average degree of polymerization of 1400 and Type F with a molecular weight of

Address for correspondence: X. Tang, Department of Pharmaceutics, Shenyang Pharmaceutical University, Wen Hua Road No. 103, Shenyang 110016, People's Republic of China. Tel: +86 024 23986343. Fax: +86 024 23911736. E-mail: tangpharm@yahoo.com.cn

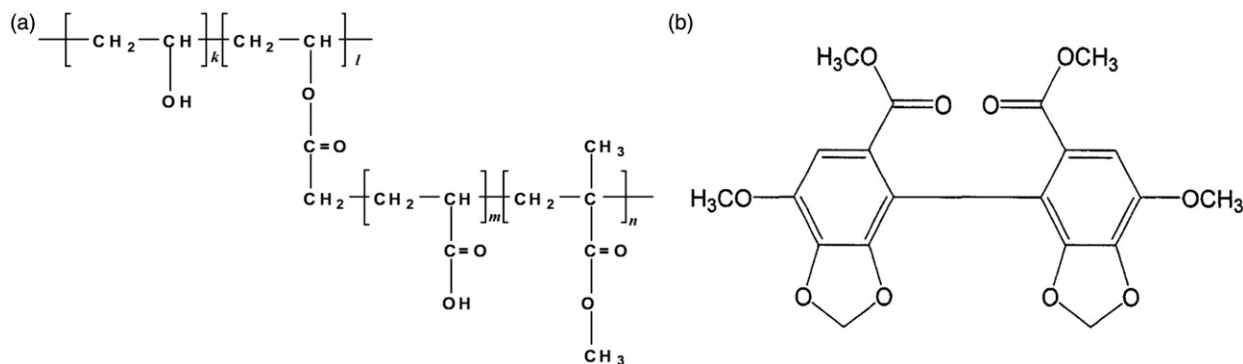


Figure 1. Chemical structure of: (a) POVACOAT™ and (b) bifendate.

40 000 and an average degree of polymerization of 500. POVACOAT™ is soluble only in water. POVACOAT™ is a thermoplastic polymer and is used as a dry SD matrix. In Japan, it has been reported that POVACOAT™ was employed to prepare SDs in ultrasound assisted compaction and melt indexer methods⁸, and the experimental results suggested that POVACOAT™ could be efficiently applied to obtain SD formulations with a high performance.

Bifendate (4,4'-dimethoxy-5,6,5',6'-bi(methylenedioxy)-2,2-bicabomethoxybiphenyl, Figure 1b), is a synthetic intermediate derived from schisandrin C (a component of *Fructus schizandrae*) which is widely used in China for the treatment of chronic hepatitis by lowering alanine transaminase in patients. It is rapidly absorbed from the gastrointestinal tract after oral administration. However, the application of DDB in clinical situations has been limited due to its extremely poor aqueous solubility (about 2.5–4.0 µg/mL) and slow dissolution rate. Due to its physicochemical properties, the bioavailability of DDB was only 10–30% after oral administration⁹. Given the fact that its permeability is adequate, bifendate is categorized as a BCS Class II drug according to the BCS. Consequently, several attempts are reported in literature to enhance the solubility and dissolution of DDB via SDs^{10,11}, mixed micelles¹², microemulsions¹³ and provesicular powders¹⁴.

In this study, bifendate was hot-melt extruded by a co-rotating twin-screw extruder with POVACOAT™ in order to enhance its solubility and dissolution rate. POVACOAT™ is expected to be applicable as an HME SD matrix based on its thermoplasticity. The purpose of this study was to evaluate the applicability of POVACOAT™ as a SD carrier for HME. In order to elucidate the mechanism of dissolution enhancement, solid-state characteristics of extrudates were investigated. The crystallinity of DDB was examined using differential scanning calorimetry (DSC) and powder X-ray diffractometry (PXRD). Scanning electron microscopy (SEM) was performed to observe the surface morphology of the hot-melt extrudates. Moreover, Fourier transformation infrared (FT-IR) spectroscopy was carried out to elucidate drug/polymer interactions in SDs. In order to better understand the mechanisms involved during the dissolution of DDB from SDs, dissolution testing was carried out, as well as phase solubility study and crystallization study of bifendate from supersaturated solutions. Furthermore, an accelerated stability study under stress conditions (40 °C/75% RH) was performed to determine the physical stability of SDs under the influence of the environmental factors, temperature and humidity.

Materials and methods

Materials

The PVA co-polymer (POVACOAT™, Type F, MW = 40 000; Daido Chemical Corporation, Osaka, Japan) was supplied as a

Table 1. Processing conditions for HME.

Parameters	Temperature (°C)				Die	Rate (rpm)
	Zone 1	Zone 2	Zone 3	Zone 4		
P1	120	160	160	160	100	36
P2	150	190	190	190	130	36
P3	150	190	190	190	130	24

carrier after milling and then passing through a no. 80 mesh sieve as described in the Chinese Pharmacopoeia (Ch. P, 2010). Bifendate (DDB) was purchased from Taizhou Haixiang Pharmaceutical Co. Ltd (Taizhou, Zhejiang, China). All the other reagents were of either analytical or chromatographic grade.

Preparation of physical mixtures

DDB and POVACOAT™ were accurately weighed, and then were mixed in a polyethylene bag by hand for 10 min to obtain a homogeneous physical mixture (PM; X% DDB-PM). The SD formability of POVACOAT™ was investigated by varying the composition ratios. The concentrations of drug in the formulations were 5%, 10%, 15%, 20%, 30% and 50% (w/w).

Preparation of SDs by HME

Bifendate SDs (X% DDB-SD) consisting of DDB and a polymeric carrier, POVACOAT™, were prepared by HME using a Coperion KEYA TE-20 (Nanjing, Jiangsu, China) co-rotating twin-screw extruder. The extruder consisted of a hopper, barrel, die, kneading screw and heaters distributed over the entire length of the barrel. The barrel *L/D* ratio (barrel length/barrel diameter) of the extruder used was 32:1. The materials introduced into the hopper were carried forward by the feed screw, kneaded under high pressure by the kneading screw and then extruded from the cylindrical die. The temperature, feed rate and screw rate were controlled by an external operation system. To optimize the extrusion process parameters, the temperature and the rates (screw and feed rates) were mainly investigated. The detailed process parameters are presented in Table 1. The extrudate was collected and allowed to cool at room temperature, then pulverized with a laboratory micromill and passed through a no. 80 mesh sieve. The SD powder was subjected to further investigation.

Thermogravimetric analysis

Thermogravimetric analysis (TGA) was used in the study to investigate the thermal decomposition of DDB and

POVACOAT™. The TGA measurements were carried out using a Thermal Analyzer-60 WS and Thermogravimetric Analyzer-50 (Shimadzu, Kyoto, Japan). Tests were performed at a scan speed of 10 °C/min over a range from 30 °C to 330 °C. Nitrogen was used as the purging gas during all TGA experiments.

Differential scanning calorimetry

DSC was used to characterize the thermal properties of the polymer, drug, PMs and hot-melt extrudates. DSC analysis was carried out using a Thermal Analyzer-60 WS, DSC-60 (Shimadzu, Kyoto, Japan). Samples between 5.0 and 10.0 mg were accurately weighed, placed into crimped aluminum pans and analyzed using a heating rate of 10 °C/min from 30 °C to 240 °C. Nitrogen was used as the purging gas at a flow rate of 40 mL/min.

Powder X-ray diffraction

PXRD was used to assess the physical state of bifendate in PM and SDs. PXRD was performed using a D/Max-2400 X-ray fluorescence spectrometer (Rigaku, Osaka, Japan) with a Cu-K α line as the source of radiation, and standard runs using a voltage of 56 kV, a current of 182 mA and a scanning rate of 2°/min over a 2 θ from 5° to 45°.

Scanning electron microscopy

A SEM (SSX-550, Shimadzu, Kyoto, Japan) was used to examine the surface morphology of the SDs, which were placed on carbon specimen holders, air dried and then coated with platinum in a vacuum before being subjected to SEM. An accelerating voltage of 15 kV was used.

Fourier transformation infrared spectroscopy

FT-IR spectra were obtained on a BRUKER IFS 55 FT-IR system (Bruker, Switzerland, Germany) using the KBr disk method to investigate the interactions between the drug and the carrier. The scanning range was from 4000 to 400 cm⁻¹ and the resolution was 1 cm⁻¹.

HPLC analysis

The concentration of bifendate was determined according to the Ch. P (2010) by HPLC using a Hitachi L-2130 intelligent pump (Hitachi, Tokyo, Japan). An Agilent™ C18 column (250 × 4.6 mm², 5 μ m, Agilent Technologies, Palo Alto, CA) was used with a mobile phase consisting of methanol–water (60:40, v/v). A Hitachi UV detector L-2400 (Hitachi, Tokyo, Japan) was set at 278 nm and the chromatographic analyses were performed at 35 °C at a flow rate of 1.0 mL/min.

Effect of POVACOAT™ on the solubility of bifendate

The equilibrium solubility of crystalline bifendate in purified water was measured at 37 °C in the presence and absence of POVACOAT™. Phase solubility study was performed according to the method reported by Higuchi & Connors¹⁵. An excess amount (900 mg) of crystalline bifendate was dispersed in 900 mL of water, in which POVACOAT™ had been previously dissolved, and stirred at 100 rpm. Samples of 5 mL were withdrawn from each vessel at predetermined time intervals (24, 48 and 72 h) and filtered through a 0.15 μ m cellulose acetate-type membrane filter. At each time point, the same volume of fresh medium was replaced. The concentration of bifendate in the solutions was determined by HPLC analysis. The solubility of DDB in water in the absence of POVACOAT™ was also determined. All measurements were carried out in triplicate.

Inhibitory effect of POVACOAT™ on recrystallization from supersaturated solutions

The effect of the polymer on the solution concentration–time profile was also evaluated following the generation of supersaturated solutions of bifendate. A concentrated solution of DDB in dimethyl sulfoxide (DMSO) was prepared by dissolving 45 mg of crystalline DDB in 5 mL of DMSO which was subsequently added to 900 mL of purified water at 37 °C. This generated an initial drug solution concentration of 50 μ g/mL in water, into which 1710, 810, 510, 360, 210 or 90 mg of POVACOAT™ had been previously dissolved, leading to a final POVACOAT™ concentration of 1.90, 0.90, 0.57, 0.40, 0.23 or 0.10 mg/mL, respectively. The solution was stirred with a rotating paddle at 100 rpm; 5 mL samples were withdrawn from each vessel at predetermined time intervals and filtered through a 0.15 μ m cellulose acetate membrane filter. At each time point, the sample withdrawn was replaced with an equivalent amount of fresh dissolution medium. The concentration of DDB in each sampled aliquot was determined by HPLC. The same experiment was performed in purified water in the absence of POVACOAT™.

Dissolution studies

The dissolution testing was performed according to dissolution test method 2 as described in the Ch. P (2010). The dissolution test was carried out at 37 °C in 900 mL of distilled water using a ZRS-8G dissolution apparatus. The paddle speed was 50 rpm and all experiments were carried out in triplicate. Samples equivalent to 90 mg of DDB were added to 900 mL of test fluid. Samples of 5 mL were withdrawn from each vessel at predetermined time intervals. All samples taken were filtered through a 0.15 μ m cellulose acetate membrane filter. At each time point, the same volume of fresh medium was replaced. The concentration of DDB in each sampled aliquot was determined by the HPLC method as described above.

Stability test

The stability of 10% DDB-SD was performed in a drug stability test chamber (LRH-150(250)-Y, Shenzhen, Guangdong, China) maintained at 40 °C and 75% RH. The extrudate containing 10% (w/w) bifendate was sealed tightly in aluminum foil packing. The duration of the study was six months. The stability was evaluated by dissolution testing and DSC analysis at zero, one, two, three and six months.

Results and discussion

HME with POVACOAT™

Thermal stability

TGA is a very rapid analytical technique that can determine mass loss as a function of temperature. Before preparing SDs by HME, the thermal stability of DDB and POVACOAT™ was measured by TGA. As shown in Figure 2, all materials used in this study exhibited acceptable thermal stability up to approximately 250 °C and significant decomposition was observed at higher temperature. Therefore, DDB and POVACOAT™ were thermostable during HME under 200 °C.

Optimization of extrusion process parameters

For HME, the main process parameters are the extrusion temperature, screw rate and feed rate. In this study, in order to simplify the course of optimization, the screw and feed rates were set at the same value and the ratio of DDB to POVACOAT™ was fixed at 10:90. From the dissolution profiles shown in Figure 3, as the extrusion temperature increased, the dissolution rate and

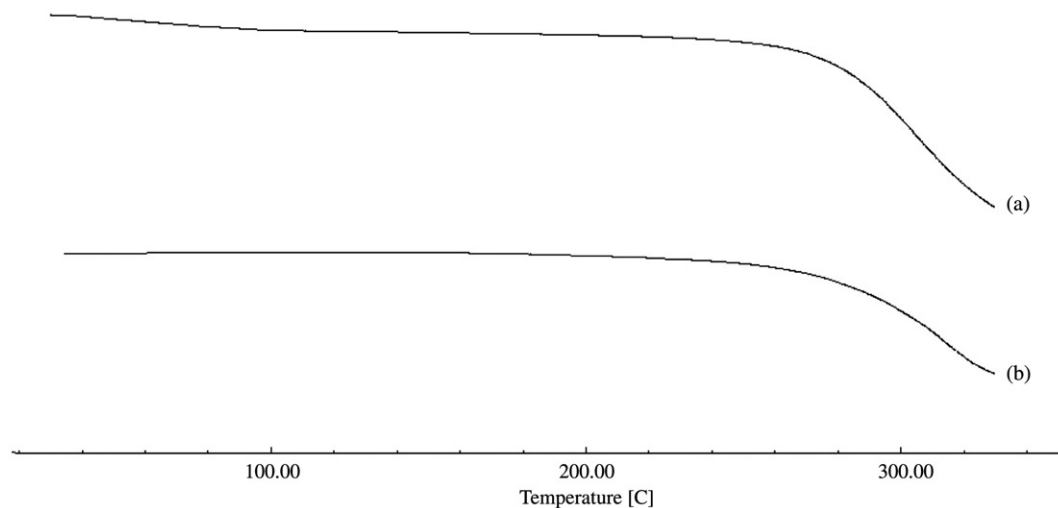


Figure 2. TGA thermograms of raw materials: (a) POVACOAT™ and (b) DDB.

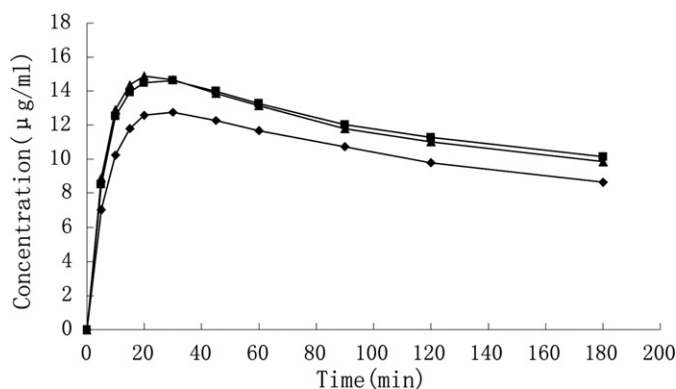


Figure 3. Dissolution profiles of 10% DDB-SD extruded at different process parameters. (♦) P1; (■) P2 and (▲) P3.

maximum supersaturated concentration were both enhanced. Judging from the dissolution curves, the screw speed in a certain range had no effect on the dissolution. However, the screw rate determined the residence time of material in the barrel. If it was too low, the material would be heated for a long time, maybe giving rise to degradation. As a result, the temperatures were finally set at 150 °C, 190 °C, 190 °C, 190 °C and 130 °C for Zone1, Zone2, Zone3, Zone4 and the die, respectively. The screw and feed rates were both set at 36 rpm.

Physical characterizations of SDs

The crystallinity of DDB in the DDB/POVACOAT™ binary system was examined by DSC and PXRD. SEM was used to study the surface morphology of the hot-melt extrudates and FT-IR was used to study intermolecular interactions between DDB and POVACOAT™ in SDs.

DSC study

The DSC thermograms for the bulk polymer, pure DDB, DDB-POVACOAT™ PM and extrudates processed at different drug loadings are shown in Figure 4. Bifendate crystals exhibited a sharp endothermic peak at 186 °C resulting from melting of DDB crystals and so did the PM. However, in the SD curves, it was found that an endothermic peak around 186 °C was present at 20%, 30% and 50% drug loadings, while in the case of 5%, 10%

and 15% drug loadings, the DSC thermograms exhibited a complete suppression of the drug fusion peak, indicating the amorphous state of DDB in SDs.

In order to investigate the maximum loading amount of amorphous DDB in the SD formulation, formulations with different drug loadings were prepared. From the DSC results, it can be observed when the drug loading was over 15%, there was an endothermic peak. It was inferred that when the ratio of DDB to POVACOAT™ was 20:80, the carrier could not dissolve the entire drug and part of the drug was in a crystalline form instead of amorphous form. This is because the carrier has a limited ability to dissolve the drug¹⁶. As a result, DDB in DDB/POVACOAT™ SDs could be amorphous up to 15% drug loading.

PXRD study

The PXRD patterns of the samples were recorded to confirm the loss of drug crystallinity in the SDs. The PXRD patterns of polymer, DDB, PM and SDs are shown in Figure 5. Pure drug showed a series of characteristic peaks of crystalline DDB at 2θ angles of 12.013°, 19.567°, 20.669°, 23.527° and 24.998°. POVACOAT™ exhibited amorphous characteristics and no crystalline peak could be seen. The diffraction patterns of the PM with apparent peaks were similar to that of the pure drug, indicating only a simple mixing of drug and carrier which did not change the crystallinity of DDB. With regard to extrudates, PXRD showed the similar results to the DSC thermograms. It can be observed from Figure 6 that when the drug loading was over 15%, there were still a certain weak diffraction peaks, indicating that some part of the drug was not present in the amorphous form, but in the microcrystalline form. When the drug loading was under 20%, no detectable diffraction peak of DDB was observed, suggesting that DDB was in an amorphous state in SDs.

Scanning electron microscopy

The SEM photomicrographs of pure DDB, POVACOAT™, PM of DDB/POVACOAT™ (1:9, w/w) and SDs were utilized to study their surface morphological characteristics (Figure 7). Figure 7(a) and (b) revealed that POVACOAT™ and pure bifendate existed in irregular particles and cubic crystal structure, respectively. The PM showed the presence of drug in the crystalline form along with irregular particles of POVACOAT™ (Figure 7c). As far as the extrudates were concerned, bifendate crystals were not observed at lower drug loadings (Figure 7d–f). Also, the surface

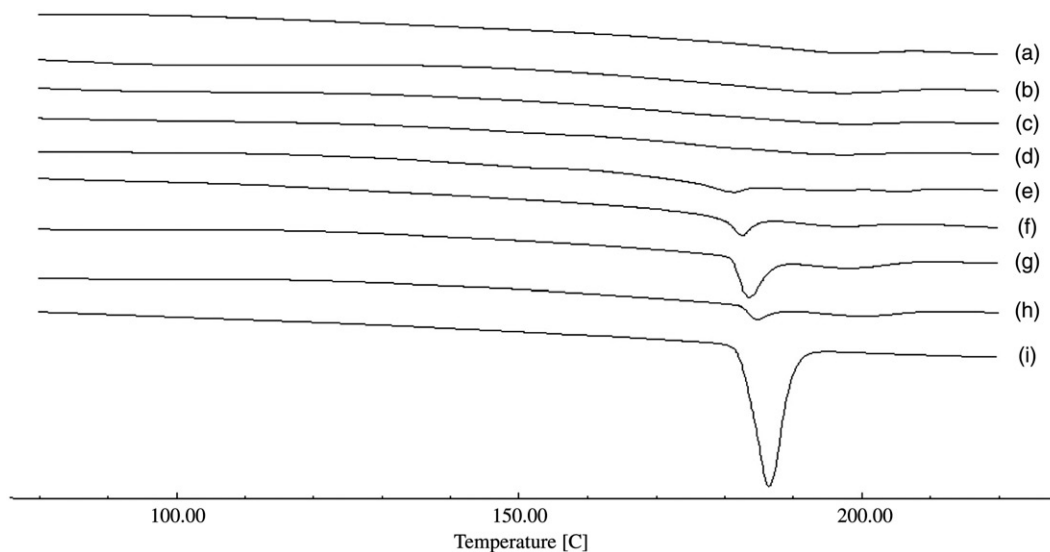


Figure 4. DSC profiles of the bifendate-POVACOAT™ system: (a) POVACOAT™; (b) 5% DDB-SD; (c) 10% DDB-SD; (d) 15% DDB-SD; (e) 20% DDB-SD; (f) 30% DDB-SD; (g) 50% DDB-SD; (h) 10% DDB-PM and (i) DDB.

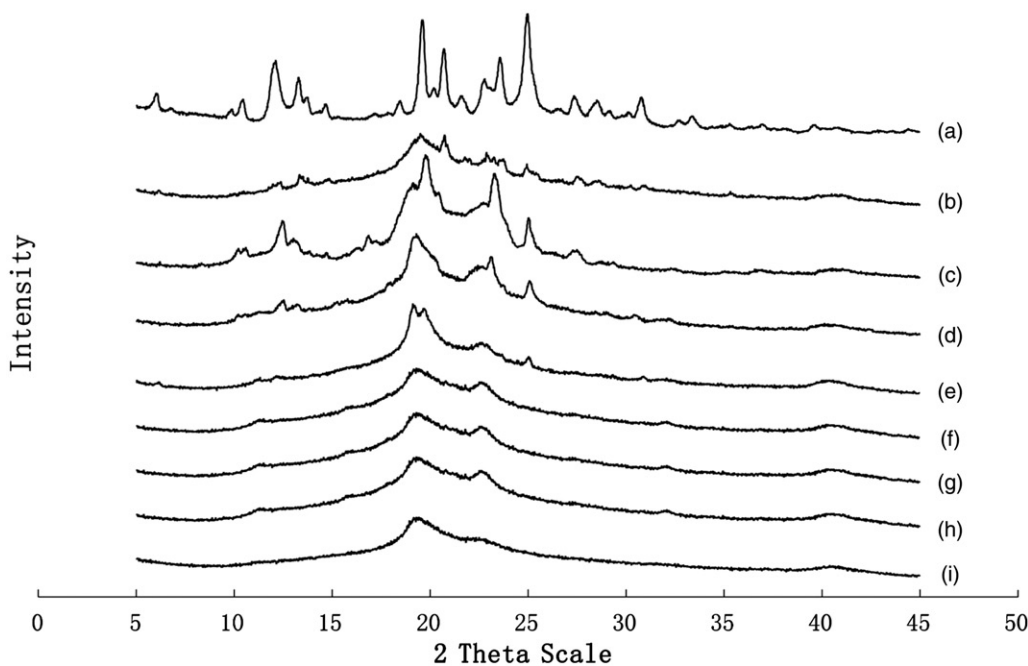


Figure 5. PXRD patterns of the bifendate-POVACOAT™ system: (a) DDB; (b) 10% DDB-PM; (c) 50% DDB-SD; (d) 30% DDB-SD; (e) 20% DDB-SD; (f) 15% DDB-SD; (g) 10% DDB-SD; (h) 5% DDB-SD and (i) POVACOAT™.

of the extrudates was smooth and homogeneous. This observation confirmed the formation of amorphous SDs and supported the conclusions from DSC and PXRD results. However, at higher drug loadings (Figure 7g–i), microcrystals of DDB were clearly observed and the number of crystals increased as the drug loading increased. These results obtained from SEM were consistent with the other characterizations above.

FT-IR spectrometry

In order to study the possible interactions between POVACOAT™ and DDB in the solid state, FT-IR spectra were recorded. From the chemical structures, hydrogen bonding could be expected between the hydroxyl groups of POVACOAT™ and the carbonyl groups of DDB and also between the hydroxyl group of POVACOAT™ and the ether-oxygens of DDB. These interactions

would result in peak broadening and a bathochromic shift of the absorption bands of the interacting functional groups¹⁷. The infrared spectra of pure DDB, bulk POVACOAT™, SD (10% drug loading) and the corresponding PM are presented in Figure 6. The FTIR spectrum of DDB showed an intense peak at 1716.9 cm^{-1} which was related to carbonyl stretching. Also, two distinct peaks were observed at 1595.9 and 1638.5 cm^{-1} which were assigned to vibrations of the C=C aromatic stretching. These three peaks were the main characteristic bands used in evaluating any interactions between drug and polymer. For POVACOAT™, the carbonyl absorption band was at 1734.7 cm^{-1} . Compared with DDB and POVACOAT™, the FT-IR spectra of the PM seemed to be only a summation of the drug and carrier. This suggested that in the case of the PM, there are no hydrogen-bonding interactions between the drug and carrier. However, regarding the spectra of the extrudate, it was found to be very similar to that of the carrier.

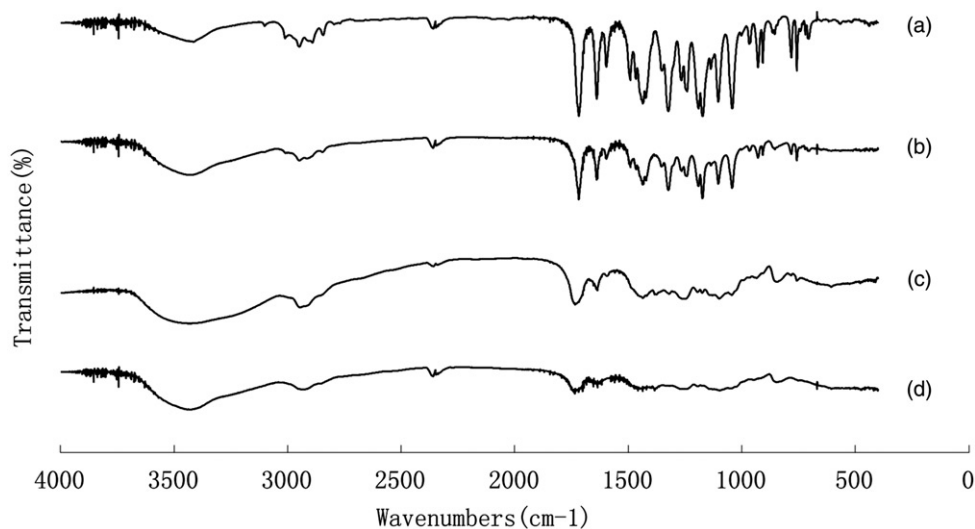


Figure 6. FTIR spectra of: (a) DDB; (b) 10% DDB-PM; (c) 10% DDB-SD and (d) POVACOAT™.

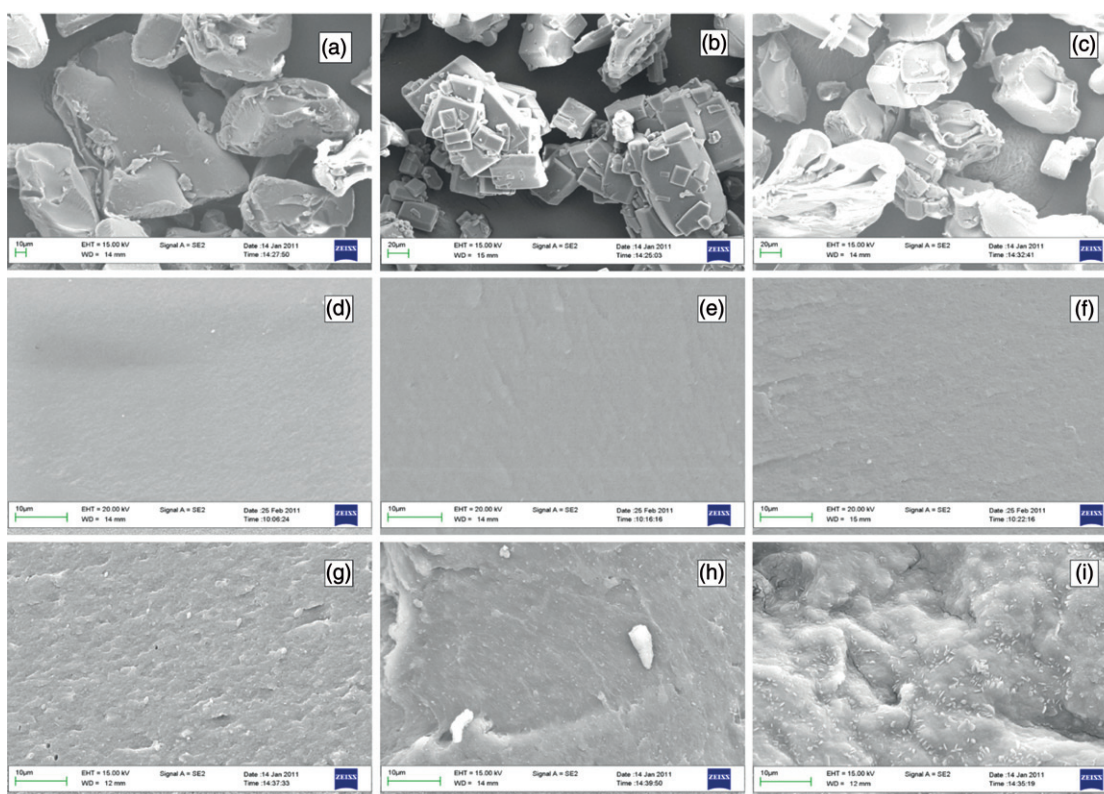


Figure 7. SEM micrographs of the surface morphology of the bifedate-POVACOAT™ system: (a) POVACOAT™; (b) bifedate; (c) 10% DDB-PM; (d) 5% DDB-SD; (e) 10% DDB-SD; (f) 15% DDB-SD; (g) 20% DDB-SD; (h) 30% DDB-SD and (i) 50% DDB-SD.

At the same time, some detectable absorption bands almost remained largely as in the spectra of the PM, although their intensities became very weak. These results indicated the absence of hydrogen-bonding interactions between DDB and POVACOAT™.

Phase solubility study

The solubility of the drug in the presence of concentrated solutions of a polymeric carrier can help determine the mechanism of dissolution from a SD¹⁸. To investigate the solubilization power of POVACOAT™, the equilibrium solubility of crystalline DDB in distilled water containing 1.0, 2.0, 5.0 and 10.0 mg/mL of polymer was determined and compared with the

Table 2. Phase solubility and thermodynamic parameters of bifedate at different concentrations of POVACOAT™.

Concentration of POVACOAT™ (mg/mL)	Concentration of DDB (μg/mL)	S_s/S_o	ΔG_{tr}° (J/mol)
0	2.56	1.00	0.00
1	3.64	1.42	-903.92
2	4.32	1.69	-1352.65
5	6.51	2.54	-2402.94
10	10.39	4.06	-3611.98
K_s (mL/mg)	1209.89		

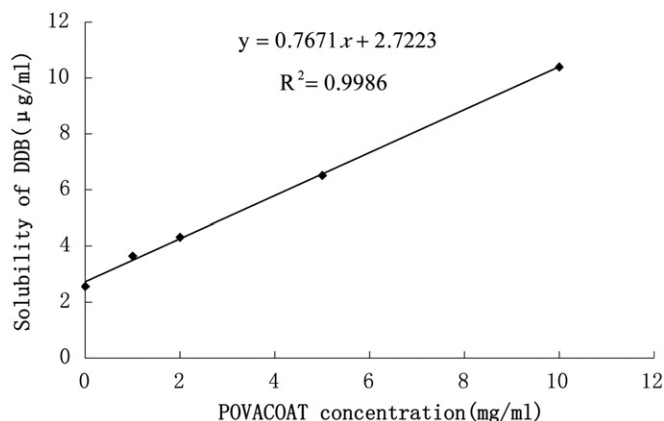


Figure 8. Phase solubility diagram of bifendate in aqueous solutions of POVACOAT™.

equilibrium solubility in water in the absence of POVACOAT™. All solutions could reach the equilibrium after 72 h. Interestingly, POVACOAT™ yielded a slightly emulsified opalescent solution when dissolved in water. The solubility of DDB in water at 37 °C was 2.56 µg/mL. Therefore, DDB could be considered to be a water-insoluble drug according to the Ch. P (2010). As presented in Table 2, there was a significant increase in the equilibrium solubility of DDB when POVACOAT™ was present at 1.0 (1.42-fold), 2.0 (1.69-fold), 5.0 (2.54-fold) and 10.0 mg/mL (4.06-fold). These results indicate that POVACOAT™ has a solubilizing effect on DDB. The phase solubility of DDB at 37 °C was observed as a function of the POVACOAT™ concentration (Figure 8). The phase solubility diagram corresponded to an A_L-type system as the computed slope was less than unity suggesting the formation of 1:1 drug-carrier interactions^{15,19}. Hydrophilic carriers are known to interact with drug molecules in solution mainly by electrostatic forces (ion-ion, ion-dipole and dipole-dipole bonds) and occasionally by other types of forces like van der Waals forces and hydrogen bonds^{18,20}.

An indication of the process of transfer of DDB from pure water to aqueous solution of POVACOAT™ was obtained from the values of the Gibbs free energy change¹⁹. The Gibbs free energy of transfer (ΔG_{tr}°) of DDB from pure water to aqueous solutions of POVACOAT™ was calculated using the following equation:

$$\Delta G_{tr}^{\circ} = -2.303RT \log \left(\frac{S_c}{S_o} \right) \quad (1)$$

where S_c/S_o is the ratio of the molar solubility of DDB in aqueous solution of POVACOAT™ to that of pure water, R the general gas constant and T the absolute temperature.

The value of the apparent stability constant, K_s , between the drug-carrier combination was calculated from the phase solubility profiles²⁰, as described below:

$$K_s = \frac{\text{slope}}{\text{intercept}(1 - \text{slope})} \quad (2)$$

The obtained values of ΔG_{tr}° and apparent stability constants (K_s) are presented in Table 2. The ΔG_{tr}° values show whether the reaction condition is favorable or unfavorable for drug solubilization in the aqueous carrier solution. Negative ΔG_{tr}° values indicate favorable conditions that the drug solubilization is spontaneous²¹. ΔG_{tr}° values were all negative for POVACOAT™ at all concentrations, unequivocally indicating the spontaneous nature of DDB solubilization. The values showed a declining trend with an increase in the carrier concentration, demonstrating that the

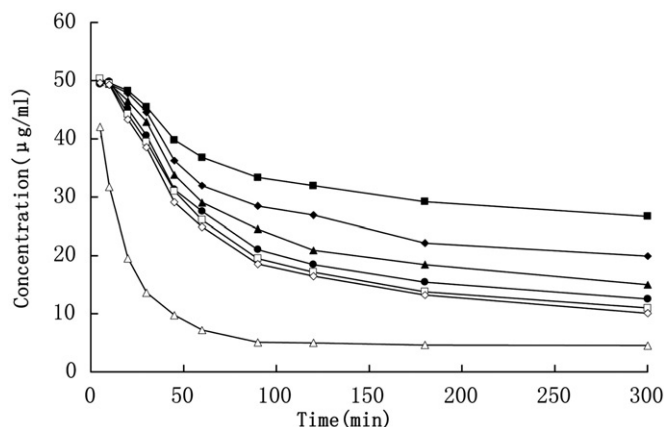


Figure 9. Inhibitory effect of POVACOAT™ on recrystallization of a supersaturated solution of bifendate (DDB; 50 µg/mL) in the water containing 1.90 (■), 0.90 (◆), 0.57 (▲), 0.40 (●), 0.23 (□) and 0.10 (○) (mg/mL) of POVACOAT™ and in the absence of POVACOAT™ (△).

process of DDB transfer from pure water to carrier solution was more favorable at higher carrier levels.

The enhancement of solubility might be ascribed to the improved wettability of the water-soluble polymer, the formation of weakly soluble complexes¹⁸, the co-solvent effect of the carrier²⁰ and/or the micellar solubilization owing to the amphiphilic structure of POVACOAT™^{20,22}. According to the classification of SDs, third generation SDs refer to those in which the dissolution profile can be improved if the carrier has surface activity or self-emulsifying properties. Therefore, the SD using POVACOAT™ as the carrier is classified as third generation SDs. These third generation SDs are intended to achieve the highest degree of bioavailability for poorly soluble drugs and to stabilize the SD, avoiding drug recrystallization²³.

Inhibitory effect of POVACOAT™ on recrystallization from supersaturated solutions

The inhibitory effect of POVACOAT™ on recrystallization of DDB from a supersaturated solution was evaluated by adding a concentrated solution of DDB to distilled water, in which the polymer had been predissolved and then by monitoring the solution concentration as a function of time. Figure 9 shows the results obtained at different POVACOAT™ solution concentrations, 1.90, 0.90, 0.57, 0.40, 0.23 and 0.10 mg/mL, which corresponded to the POVACOAT™ solution concentrations that would be produced by total dissolution of SDs at drug/polymer ratios of 5:95, 10:90, 15:85, 20:80, 30:70 and 50:50, respectively. The result obtained for distilled water without POVACOAT™ is shown for reference.

The initial solution concentration of DDB that was generated by dilution of the concentrated DMSO drug solution was 50 µg/mL. As shown in Figure 9, in the absence of polymer, the DDB concentration decreased rapidly, reaching 13.64 µg/mL after 30 min, and then continued to decrease and reached a plateau after 300 min with a concentration close to the equilibrium solubility of crystalline DDB. This rapid decrease in DDB concentration suggested that DDB recrystallized immediately from a supersaturated concentration.

Interestingly, in the presence of POVACOAT™, the initial drug concentrations, within the first 10 min after addition of a concentrated solution of DDB, all remained around 50 µg/mL. In spite of the supersaturated solution, compared with the case of the absence of POVACOAT™, the drug concentration did not decline immediately. It could be inferred that POVACOAT™ might inhibit or delay the nucleation. As stated in the literature, in

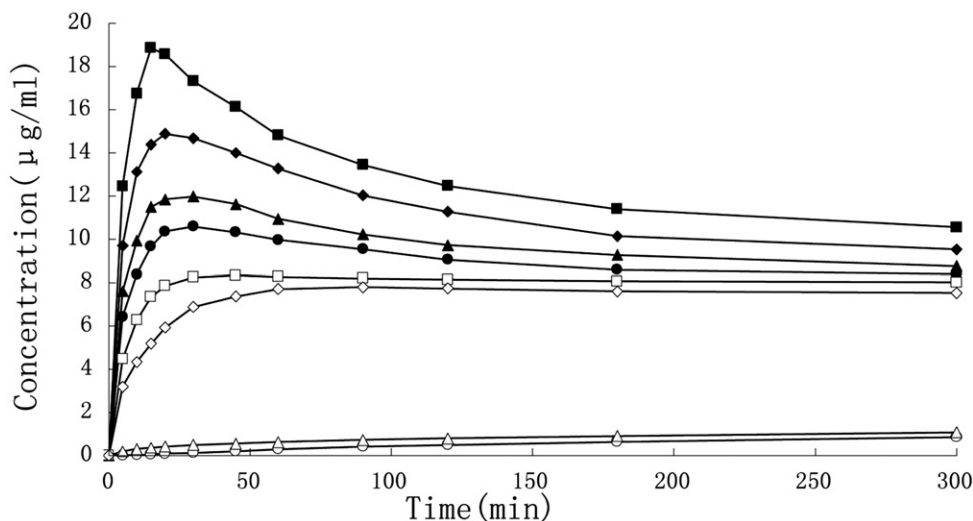


Figure 10. Dissolution profiles of the bifendate-POVACOAT™ system (■, 5% DDB-SD; ◆, 10% DDB-SD; ▲, 15% DDB-SD; ●, 20% DDB-SD; □, 30% DDB-SD; ◇, 50% DDB-SD; △, 10% DDB-PM and ○, DDB).

some cases, supersaturated solutions may show a metastable zone (giving an apparent higher solubility), within which spontaneous nucleation is not likely to occur until the metastable limit^{24,25}. Significant differences were observed after 10 min. The supersaturated concentration decreased gradually under stirring. Hence, this implied that crystal growth could start immediately in the supersaturated solution on condition that the nucleation process took place prior to crystal growth²⁶.

Obviously, the precipitation rate decreased as the POVACOAT™ concentration increased, suggesting that POVACOAT™ could play a role in inhibiting crystal growth and the efficiency was dependent on the polymer concentration. The higher the POVACOAT™ concentration was, the more efficient the inhibition was. Moreover, the DDB concentrations achieved after 5 h were significantly higher than the equilibrium solubility of crystalline DDB (2.56 µg/mL). These results indicated that there was a very marked recrystallization inhibition due to the presence of POVACOAT™ at all concentrations relative to distilled water without POVACOAT™.

The inhibition of crystallization and crystal growth by polymers has been observed previously^{18,25,27–29}. However, the mechanisms remain poorly explained and unclear, perhaps because this retardation of DDB recrystallization was a complex process and resulted from several simultaneous mechanisms, such as polymer adsorption^{25,27}, drug/polymer interaction¹⁸, fluid viscosity¹⁸ and protective colloidal effect⁸ as possible contributing factors.

Dissolution studies

Resulting from the change in free energy of the system, amorphous SDs are capable of providing significantly enhanced dissolution rates compared with the crystalline material³⁰. *In vitro* dissolution testing of SDs, as well as unprocessed crystalline DDB and the PM, were characterized under nonsink conditions in order to evaluate the ability of POVACOAT™ to generate and maintain supersaturated drug solutions^{18,30,31}. The dissolution profiles are shown in Figure 10. Critical dissolution parameters for each formulation were also calculated and are presented in Table 3. The initial dissolution rates were calculated from the concentration of bifendate after the first 5 min of dissolution^{22,28} and are presented in Table 3. It can be seen that SDs containing 95% POVACOAT™ showed the highest initial dissolution rate

Table 3. Summary of dissolution parameters for pure DDB and its PM and SDs.

Parameters	Initial dissolution rate (µg/mL min)	C_{max} (µg/mL)	C_{max}/S_0	C_{300min} (µg/mL)
DDB	0.00	0.86	0.34	0.86
10% DDB-PM	0.04	1.08	0.42	1.08
5% DDB-SD	2.49	18.86	7.37	10.55
10% DDB-SD	1.94	14.89	5.82	9.53
15% DDB-SD	1.52	11.98	4.68	8.76
20% DDB-SD	1.29	10.59	4.14	8.39
30% DDB-SD	0.89	8.33	3.25	8.02
50% DDB-SD	0.64	7.80	3.05	7.52

and that the initial dissolution rate decreased with a decrease in polymer concentration in the SD.

From the dissolution profiles in Figure 10, it can be seen that the dissolution rate of SDs was much higher than that of the PM and bifendate crystals. During *in vitro* dissolution testing, the PM and the DDB crystals exhibited very slow release and the concentrations at 300 min (C_{300min}) were only 1.08 and 0.86 µg/mL, respectively. As POVACOAT™ had an effect on the DDB solubilization, the dissolution rate of PM was a bit higher than that of DDB crystals. However, it was found that only the solubilization effect of POVACOAT™ did not markedly enhance the dissolution during a short period. In the SD dissolution curves, the DDB concentration quickly reached the maximum supersaturated concentration (C_{max}) and the maximum bifendate concentrations of SDs at 5%, 10%, 15%, 20%, 30% and 50% drug loadings were 18.86, 14.89, 11.98, 10.59, 8.33 and 7.80 µg/mL, respectively. From these results, it was found as the drug loading increased, the maximum concentration became smaller and smaller. Because the amorphous is superior to the crystalline in terms of solubility and dissolution rate, it was concluded that the drug loading markedly affected the degree of dispersion and the drug state (molecular, amorphous and/or microcrystalline form) in dispersions and then impacted the dissolution. However, a burst release followed by a gradual decline in SDs dissolution at drug loadings <30% could be explained by the release of DDB in an amorphous or molecular state followed by the formation of drug particles, namely recrystallization because of supersaturation. However, this retarded recrystallization was supposed to be due to the protective colloidal effect of POVACOAT™ on stabilizing the

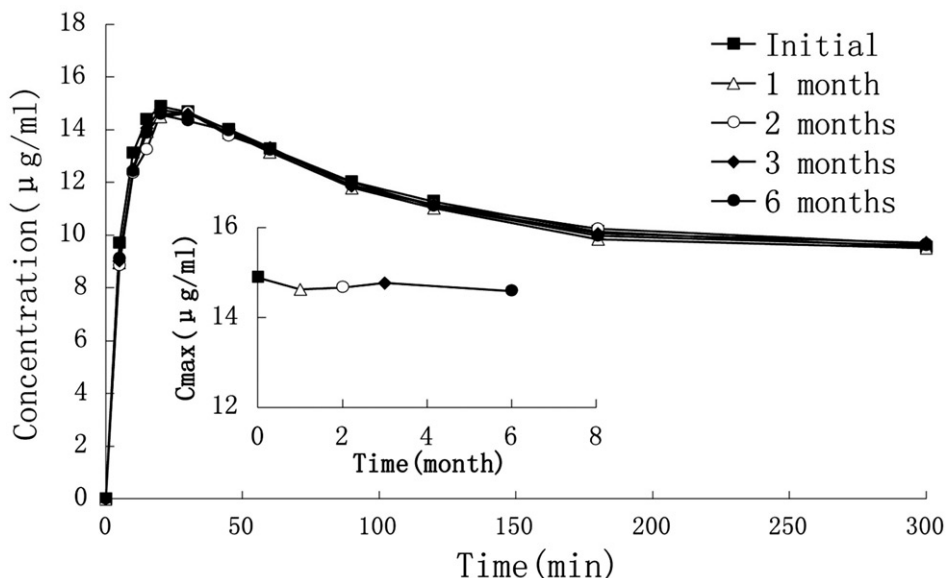


Figure 11. Dissolution profiles of 10% DDB-SD after storage and C_{max} at different months as a function of time.

crystal nuclei and suppressing the particle growth. The crystal growth inhibition during dissolution may be an important consideration to achieve the full benefits of the dissolution enhancement of SDs³². On the other hand, in the case of SDs at 30% and 50% drug loadings, there were no peaks in the dissolution curves. The drug in the SDs was released to the maximum concentration and then the concentration maintained at about 8.0 and 7.5 $\mu\text{g/mL}$ for 30% and 50%, respectively. This could be related to the state of the drug in the SDs, because the drug was mostly present in the form of crystals at high drug loadings.

Knowledge of the mechanism of drug release from SDs is essential for understanding the enhancement in the dissolution rate of a poorly water-soluble drug. As stated in literature with respect to the release mechanism, polymer-controlled dissolution (high-polymer concentrations) and drug-controlled dissolution (high-drug loadings) have been defined^{31,33,34}. Consequently, it was found in this study that with the increase of drug loading, i.e. the decrease of POVACOATTM concentration, amorphous or molecular dispersions shifted to microcrystalline dispersions and the release mechanism gradually shifted from carrier-controlled to drug-controlled dissolution.

Stability study

Dissolution testing

After storage (40 °C, RH 75%) for six months, dissolution testing of 10% DDB-SD at several time intervals was carried out. The results are shown in Figure 11. It can be observed clearly from the figure that after storage, the dissolution profiles were similar to the initial state and the maximum supersaturated concentration (C_{max}) was found to be relatively constant under storage, so it could be concluded that the amorphous state of DDB in 10% DDB-SD was not destroyed and ageing did not take place during storage, which indicated that 10% DDB-SD was stable.

Physical characterization

DSC recordings of 10% DDB-SD before and after storage (40 °C, RH 75%) are shown in Figure 12. It can be observed that there was no endothermic peak around 186 °C after storage. These results showed that DDB remained amorphous during storage, which proved the good stability of SD prepared using POVACOATTM by HME technology.

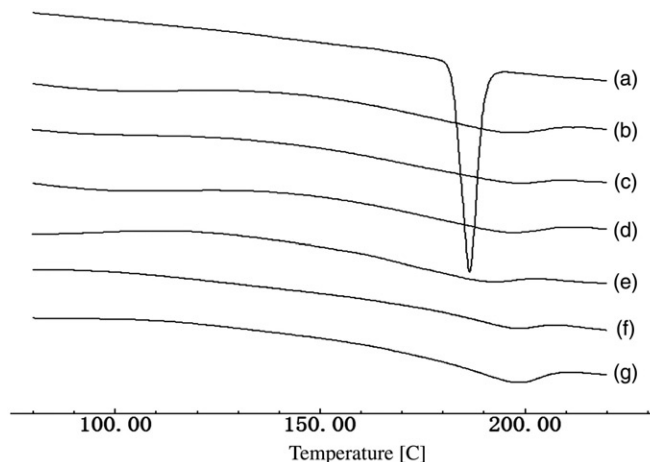


Figure 12. DSC thermograms of 10% DDB-SD after storage: (a) DDB; (b) initial; (c) one month; (d) two months; (e) three months; (f) six months and (g) POVACOATTM.

Conclusions

In this article, POVACOATTM, a new hydrophilic PVA copolymer, was successfully applied to prepare SDs by HME technology to improve the dissolution of DDB. The TGA analysis showed that POVACOATTM was thermostable enough to be hot-melt extruded under 200 °C. PXRD, DSC and SEM studies indicated that in SDs DDB was present in the amorphous form up to 15% drug loading, while part of the drug existed in the crystalline form at high-drug loadings. The phase solubility studies revealed an A_L -type curve, indicating a linear increase in drug solubility with carrier concentration. The negative values of the Gibbs free energy of transfer for DDB from water to an aqueous solution of POVACOATTM demonstrated the spontaneity of the transfer. Furthermore, POVACOATTM was found to have an inhibitory effect on crystallization from supersaturated solutions and stabilize the supersaturated drug concentration generated by the dissolution of amorphous drug during dissolution and the efficiency was dependent on the polymer concentration. From the dissolution results, the dissolution rate and solubility were greatly enhanced compared with pure DDB and the PM and the drug

loading observably affected the dissolution of DDB from SDs. The stability test showed that the amorphous SD (10% DDB-SD) remained stable after storage. The results of this study indicate that POVACOAT™ is a valuable and promising excipient in the formulation of SDs of bifendate prepared by HME.

Acknowledgements

Dr David B. Jack is gratefully thanked for correcting this article. The authors are grateful to Dr Dongchun Liu for his guidance and help in this study. At the same time, the authors are thankful to Daido Chemical Corporation (Japan) for providing the gift sample of POVACOAT™ to support this study.

Declaration of interest

The authors report no conflicts of interest.

This study was financially supported by Liaoning Provincial Science and Technology Department (2009ZX09301-012).

References

- Kerns EH. High throughput physicochemical profiling for drug discovery. *J Pharm Sci* 2001;90:1838–58.
- Repka MA, Shah S, Lu J, et al. Melt extrusion: process to product. *Expert Opin Drug Deliv* 2012;9:105–25.
- Singh A, Worku ZA, van den Mooter G. Oral formulation strategies to improve solubility of poorly water-soluble drugs. *Expert Opin Drug Deliv* 2011;8:1361–78.
- Srinarong P, de Waard H, Frijlink HW, Hinrichs WL. Improved dissolution behavior of lipophilic drugs by solid dispersions: the production process as starting point for formulation considerations. *Expert Opin Drug Deliv* 2011;8:1121–40.
- Fahr A, Liu X. Drug delivery strategies for poorly water-soluble drugs. *Expert Opin Drug Deliv* 2007;4:403–16.
- Coppens KA, Hall MJ, Mitchell SA, Read MD. Hypromellose, ethylcellulose, and polyethylene oxide use in hot melt extrusion. *Pharm Technol* 2006;30:60–71.
- Fujii T, Noami M, Tomita K, Furuya Y. PVA copolymer: the new coating agent. *Pharm Technol Eur* 2008;20:32–9.
- Uramatsu S, Shinike H, Kida A, et al. Application of poly(vinylalcohol/acrylic acid/methyl methacrylate) (PVA copolymer) as a solid dispersion matrix. 1st Asian Pharmaceutical Science and Technology Symposium ABSTRACT BOOK; 2007:280–2.
- Zhipeng C, Jiabi Z, Hongxuan C, et al. Distribution of liposomal bifendate in liver following intravenous injection in mice. *J Drug Target* 2010;18:627–36.
- Moon JH, Chun IK. Enhanced dissolution and permeation of biphenyl dimethyl dicarboxylate using solid dispersions. *J Korean Pharm Sci* 1999;29:227–34.
- Jia F, Lishuang X, Renchao G, et al. Evaluation of polymer carriers with regard to the bioavailability enhancement of bifendate solid dispersions prepared by hot-melt extrusion. *Drug Dev Ind Pharm* 2012;38:735–43.
- Chi SC, Yeom DI, Kim SC, Park ES. A polymeric micellar carrier for the solubilization of biphenyl dimethyl dicarboxylate. *Arch Pharm Res* 2003;26:173–81.
- Kim CK, Cho YJ, Gao ZG. Preparation and evaluation of biphenyl dimethyl dicarboxylate microemulsions for oral delivery. *J Control Release* 2001;70:149–55.
- Aburahma MH, Abdelbary GA. Novel diphenyl dimethyl bicarboxylate provesicular powders with enhanced hepatocurative activity: preparation, optimization, *in vitro/in vivo* evaluation. *Int J Pharm* 2012; 422:139–50.
- Higuchi T, Connors KA. Phase-solubility techniques. *Adv Anal Chem Instrum* 1965;4:117–212.
- Jijun F, Lili Z, Tingting G, et al. Stable nimodipine tablets with high bioavailability containing NM-SD prepared by hot-melt extrusion. *Powder Technol* 2010;204:214–21.
- Andrews GP, AbuDiak OA, Jones DS. Physicochemical characterization of hot melt extruded bicalutamide-polyvinylpyrrolidone solid dispersions. *J Pharm Sci* 2010;99:1322–35.
- Abu-Diak OA, Jones DS, Andrews GP. An investigation into the dissolution properties of celecoxib melt extrudates: understanding the role of polymer type and concentration in stabilizing supersaturated drug concentrations. *Mol Pharm* 2011;8:1362–71.
- Aggarwal AK, Singh S. Physicochemical characterization and dissolution study of solid dispersions of diacerein with polyethylene glycol 6000. *Drug Dev Ind Pharm* 2011;37:1181–91.
- Ahuja N, Katare OP, Singh B. Studies on dissolution enhancement and mathematical modeling of drug release of a poorly water-soluble drug using water-soluble carriers. *Eur J Pharm Biopharm* 2007;65:26–38.
- Maulvi FA, Dalwadi SJ, Thakkar VT, et al. Improvement of dissolution rate of aceclofenac by solid dispersion technique. *Powder Technol* 2011;207:47–54.
- Mehanna MM, Motawaa AM, Samaha MW. In sight into tadalafil – block copolymer binary solid dispersion: mechanistic investigation of dissolution enhancement. *Int J Pharm* 2010;402:78–88.
- Vasconcelos T, Sarmiento B, Costa P. Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. *Drug Discovery Today* 2007;12:1068–75.
- Brouwers J, Brewster ME, Augustijns P. Supersaturating drug delivery systems: the answer to solubility-limited oral bioavailability? *J Pharm Sci* 2009;98:2549–72.
- Tajarobi F, Larsson A, Matic H, Abrahmsen-Alami S. The influence of crystallization inhibition of HPMC and HPMCAS on model substance dissolution and release in swellable matrix tablets. *Eur J Pharm Biopharm* 2011;78:125–33.
- Janssens S, Nagels S, Armas HN, et al. Formulation and characterization of ternary solid dispersions made up of Itraconazole and two excipients, TPGS 1000 and PVPVA 64, that were selected based on a supersaturation screening study. *Eur J Pharm Biopharm* 2008;69:158–66.
- Tanno F, Nishiyama Y, Kokubo H, Obara S. Evaluation of hypromellose acetate succinate (HPMCAS) as a carrier in solid dispersions. *Drug Dev Ind Pharm* 2004;30:9–17.
- Konno H, Handa T, Alonzo DE, Taylor LS. Effect of polymer type on the dissolution profile of amorphous solid dispersions containing felodipine. *Eur J Pharm Biopharm* 2008;70:493–9.
- Lindfors L, Forssén S, Westergren J, Olsson U. Nucleation and crystal growth in supersaturated solutions of a model drug. *J Colloid Interface Sci* 2008;325:404–13.
- DiNunzio JC, Brough C, Miller DA, et al. Fusion processing of itraconazole solid dispersions by kinetisol dispersing: a comparative study to hot melt extrusion. *J Pharm Sci* 2010;99:1239–53.
- Alonzo DE, Gao Y, Zhou D, et al. Dissolution and precipitation behavior of amorphous solid dispersions. *J Pharm Sci* 2011;100:3316–31.
- Kanaujia P, Lau G, Ng WK, et al. Nanoparticle formation and growth during *in vitro* dissolution of ketoconazole solid dispersion. *J Pharm Sci* 2011;100:2876–85.
- Craig DQM. The mechanisms of drug release from solid dispersions in water-soluble polymers. *Int J Pharm* 2002;231:131–44.
- Albers J, Alles R, Mattheé K, et al. Mechanism of drug release from polymethacrylate-based extrudates and milled strands prepared by hot-melt extrusion. *Eur J Pharm Biopharm* 2009;71:387–94.