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

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Abstract

Objective: The aim of this study was to evaluate the applicability of POVACOAT™, a hydrophilic PVA co-polymer, 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 A1-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.

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 bioavailability1-3. 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 reduction5-8.

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 profiles. 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 dispersion1-2.

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 materials2. 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
40,000 and an average degree of polymerization of 500. POVC\textsuperscript{TM} is soluble only in water. POVC\textsuperscript{TM} is a thermoplastic polymer and is used as a dry SD matrix. In Japan, it has been reported that POVC\textsuperscript{TM} was employed to prepare SDs in ultrasound assisted compaction and melt indexer methods\textsuperscript{8}, and the experimental results suggested that POVC\textsuperscript{TM} could be efficiently applied to obtain SD formulations with a high performance. Bifendate (4,4\textdegree-dimethoxy-5,6,5\textdegree,6\textdegree-bi(methylenedioxy)-2,2-bicabomethoxybiphenyl, Figure 1b), is a synthetic intermediate derived from schisandrin C (a component of Fructus schizandae) 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 \textmu g/mL) and slow dissolution rate. Due to its physicochemical properties, the bioavailability of DDB was only 10–30\% after oral administration\textsuperscript{9}. 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\textsuperscript{10,11}, mixed micelles\textsuperscript{12}, microemulsions\textsuperscript{13} and proovesicular powders\textsuperscript{14}.

In this study, bifendate was hot-melt extruded by a co-rotating twin-screw extruder with POVC\textsuperscript{TM} in order to enhance its solubility and dissolution rate. POVC\textsuperscript{TM} 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 POVC\textsuperscript{TM} 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 (POVC\textsuperscript{TM}, Type F, MW = 40,000; Daido Chemical Corporation, Osaka, Japan) was supplied as a 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 POVC\textsuperscript{TM} 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 POVC\textsuperscript{TM} 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, POVC\textsuperscript{TM}, were prepared by HME using a Coperion KEYA TE-20 (Nanjing, Jiangshu, 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 ID 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

![Figure 1. Chemical structure of: (a) POVC\textsuperscript{TM} and (b) bifendate.](image-url)
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-Kα 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 2θ range from 5° to 45°.

**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 FT-IR spectra were obtained on a BRUKER IFS 55 FT-IR system (Bruker, Switzerland, Germany) using the KBr disk method. The resolution was 1 cm⁻¹.

**HPLC analysis**

The HPLC analysis was performed using an Agilent Technologies 1200 liquid chromatography system with a C18 column (250 × 4.6 mm², 5 μm, 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 & Connors. 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 μm cellulose acetate 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 μg/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 μm 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 μm 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 temperatures. 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...
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 drug. 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
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 groups. 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=O 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.
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 SD. 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>
<thead>
<tr>
<th>Concentration of POVACOAT™ (mg/mL)</th>
<th>Concentration of DDB (µg/mL)</th>
<th>S/S∞</th>
<th>ΔG° (J/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2.56</td>
<td>1.00</td>
<td>0.00</td>
</tr>
<tr>
<td>1</td>
<td>3.64</td>
<td>1.42</td>
<td>−903.92</td>
</tr>
<tr>
<td>2</td>
<td>4.32</td>
<td>1.69</td>
<td>−1352.65</td>
</tr>
<tr>
<td>5</td>
<td>6.51</td>
<td>2.54</td>
<td>−2402.94</td>
</tr>
<tr>
<td>10</td>
<td>10.39</td>
<td>4.06</td>
<td>−3611.98</td>
</tr>
</tbody>
</table>

Ks (mL/mg) 1209.89
The phase solubility of DDB at 37 °C of 1:1 drug–carrier interactions. 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. The computed slope was less than unity suggesting the formation of weakly soluble complexes, the co-solvent effect of the carrier and/or the micellar solubilization owing to the amphiphilic structure of POVACOAT. 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 recrystallization.

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 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
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.\textsuperscript{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 growth.\textsuperscript{26}

Obviously, the precipitation rate decreased as the POVACOAT\textsuperscript{TM} concentration increased, suggesting that POVACOAT\textsuperscript{TM} could play a role in inhibiting crystal growth and the efficiency was dependent on the polymer concentration. The higher the POVACOAT\textsuperscript{TM} 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\textsuperscript{TM} at all concentrations relative to distilled water without POVACOAT\textsuperscript{TM}.

The inhibition of crystallization and crystal growth by polymers has been observed previously.\textsuperscript{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,\textsuperscript{25,27} drug/polymer interaction,\textsuperscript{18} fluid viscosity,\textsuperscript{18} and protective colloidal effect\textsuperscript{8} 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 material.\textsuperscript{10} 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\textsuperscript{TM} to generate and maintain supersaturated drug solutions.\textsuperscript{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\textsuperscript{22,28} and are presented in Table 3. It can be seen that SDs containing 95% POVACOAT\textsuperscript{TM} showed the highest initial dissolution rate 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 ($C_{300\text{ min}}$) were only 1.08 and 0.86 μg/mL, respectively. As POVACOAT\textsuperscript{TM} 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\textsuperscript{TM} did not markedly enhance the dissolution during a short period. In the SD dissolution curves, the DDB concentration quickly reached the maximum supersaturated concentration ($C_{\text{max}}$) 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\textsuperscript{TM} on stabilizing the

![Figure 10. Dissolution profiles of the bifendate–POVACOAT\textsuperscript{TM} system](image)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Initial dissolution rate (μg/mL min)</th>
<th>$C_{\text{max}}$ (μg/mL)</th>
<th>$C_{\text{max}}/S_0$</th>
<th>$C_{300\text{ min}}$ (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DDB</td>
<td>0.00</td>
<td>0.86</td>
<td>0.34</td>
<td>0.86</td>
</tr>
<tr>
<td>10% DDB-PM</td>
<td>0.04</td>
<td>1.08</td>
<td>0.42</td>
<td>1.08</td>
</tr>
<tr>
<td>5% DDB-SD</td>
<td>2.49</td>
<td>18.86</td>
<td>7.37</td>
<td>10.55</td>
</tr>
<tr>
<td>10% DDB-SD</td>
<td>1.94</td>
<td>14.89</td>
<td>5.82</td>
<td>9.53</td>
</tr>
<tr>
<td>15% DDB-SD</td>
<td>1.52</td>
<td>11.98</td>
<td>4.68</td>
<td>8.76</td>
</tr>
<tr>
<td>20% DDB-SD</td>
<td>1.29</td>
<td>10.59</td>
<td>4.14</td>
<td>8.39</td>
</tr>
<tr>
<td>30% DDB-SD</td>
<td>0.89</td>
<td>8.33</td>
<td>3.25</td>
<td>8.02</td>
</tr>
<tr>
<td>50% DDB-SD</td>
<td>0.64</td>
<td>7.80</td>
<td>3.05</td>
<td>7.52</td>
</tr>
</tbody>
</table>
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 SDs. 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 \( \mu g/mL \) 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. Consequently, it
was found in this study that with the increase of drug loading, i.e.
the decrease of POVACOAT 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
POVACOAT by HME technology.

**Conclusions**

In this article, POVACOAT, a new hydrophilic PVA co-
polymer, was successfully applied to prepare SDs by HME
technology to improve the dissolution of DDB. The TGA analysis
showed that POVACOAT 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_{\chi}-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 POVACOAT demonstrated the spontaneity
of the transfer. Furthermore, POVACOAT 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

![Figure 11. Dissolution profiles of 10% DDB-SD after storage and \( C_{max} \) at different months as a function of time.](image1)

![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) POVACOAT.](image2)
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).

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