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INTRODUCTION

Solid dispersion can be classified based on physicochemical state of drug and polymeric carrier. Among several systems of solid dispersion, solid solution is of particular interest to pharmaceutical industry because it can overcome typical problems such as poor oral bioavailability due to poor drug solubility, drug polymorphism, and poor chemical (solution) stability, found in drug product development. Also, the state of the drug in solid solution can be kinetically and thermodynamically stabilized. To date, it is feasible to manufacture solid solution through spray drying and hot melt extrusion processes. However, formation of solid solution is not always possible. Evaluation of drug-polymer miscibility is often useful in guiding successful solid solution formulation[1-4]. In this study, miscibility between benzocaine (BZC), drug, and poly l-lactide (PLLA), polymeric carrier was predicted by comparison the calculated solubility parameters of the drug and polymer and by experimental determination using differential scanning calorimetry (DSC) and hot stage microscopy (HSM)[1].

MATERIALS AND METHODS

Solubility parameter calculation

Group contribution methods (GCM) GCM was employed to calculate Hansen solubility parameters of BZC and PLLA using HSPiP program version 3. This method is based on structure fragmentation by Hoftyzer/Van Krevelen and Hoy approaches.

Molecular dynamics (MD) simulation 3D model of BZC and a unit of l-lactic acid (LA) were obtained from the Pubchem Substance Database. The MD simulation was carried out using Forcite molecular mechanics and dynamics simulation module of the Materials Studio version 5.5 software package (Accelrys, San Diego, CA, USA). The 30x30x30 $Å^3$ simulation box, with periodic boundary condition, containing bulk amorphous BZC of 81 molecules or PLLA of 25 unit chain length was created using Amorphous cell tool. Atomic charges and interactions between atom and molecules were assigned with COMPASS forcefield[5]. Electrostatic and van der Waals energies were calculated by Ewald summation and atom-based summation methods, respectively. The temperature was controlled by Nose thermostat; and the pressure was controlled by Berendsen barostat. Geometry of the system was first optimized and then its density was corrected under NPT ensemble at 298 K and 0.0001 GPa until the density was fluctuated around average value. After that, the simulation was carried out under NVT ensemble at 298 K for 500 ps until the system was equilibrated. The last 400 ps configurations were used for calculating solubility parameters. The difference between the solubility parameters of BZC and PLLA ($\Delta\delta$) was used as predictor for miscibility.

Thermal analysis

BZC ($\geq$ 99% purity) was purchased from Sigma-Aldrich. PLLA (Naturework®PLA2003D, 0.19% of residue lactide, 4.4% of d-isomer) was purchased from BC Polymer Co., Ltd. PLLA was cooled in liquid nitrogen for 5-10 min before grinding in a ultra-centrifugal mill (Model ZM200, Retsch, Germany) fitted with 0.5 mm sieve prior to use.

Differential scanning calorimetry (DSC) BZC-PLLA miscibility was evaluated using differential scanning calorimetry (DSC Model PB822e, Mettler Toledo, Columbus, USA) under nitrogen purge at 30 ml/min. BZC, PLLA and physical blends of BZC-PLLA at 10:90, 20:80, 30:70 and 50:50 ratios were examined by heat-cool-heat cycle. The cycle was started by heating the sample from 25 °C to 165 °C at 10 °C/min and holding it at 165 °C for 2 min, followed by cooling the melt to -60 °C at 20 °C/min and ended with reheating the cooled melt to 165 °C at 10 °C/min. Melting temperatures (T_m) and glass transition temperatures (T_g) were detected during heating and reheating step, respectively.

Hot stage microscopy (HSM) Thermal behavior of BZC, PLLA and their physical blends were examined using hot stage (Model FP82HT, Mettler Toledo, Columbus, USA) and light microscope (Model Eclipse E200, Nikon, Tokyo, Japan) connected to camera and adapters (Model EOS650D, Canon, Tokyo, Japan). The sample placed on slide glass and covered with cover glass was fixed on the hot stage. The sample

was heated from 30 °C to 165 °C at a heating rate of 10 °C/min.

RESULTS

Solubility parameter calculation

The solubility parameter of BZC and PLLA calculated by GCM using Hoftzyer/Van Krevelen and Hoy approaches, also MD simulation are presented in Table 1.The solubility parameter of BZC and that of PLLA was in the range of 20.7-23.3 $MPa^{0.5}$ and 17.4 - 21.3 $MPa^{0.5}$, respectively. The $\Delta\delta$ was quite small and slightly varied among calculation methods.

Table 2 Solubility parameters of BZCand PLLA

Method	Solubility parameter (δ) calculation $(MPa)^{0.5}$		Δδ
	BZC	PLLA	
Hoftyzer/Van Krevelen	20.7	17.4	3.3
Hoy	23.3	21.3	2
MD simulation	22.6	17.4	5.2

Thermal analysis

Differential scanning calorimetry (DSC) T_m peaks of BZC and PLLA were 91.83 °C and 151.49 °C, respectively (Table 2). T_m of the polymer was decreased as BZC proportion in the blends was increased (data not shown). T_g of PLLA was detected at 59.25 °C upon reheating the cool melt (Figure 1 (A)). However, determination of T_g of the drug was not possible due to recrystallization of BZC at 48.04 °C through cooling the molten drug.

Table 3 Thermal properties from DSC

Lists	BZC	PLLA
T_m (°C)	91.83	151.49
T_g (°C)	-	59.25

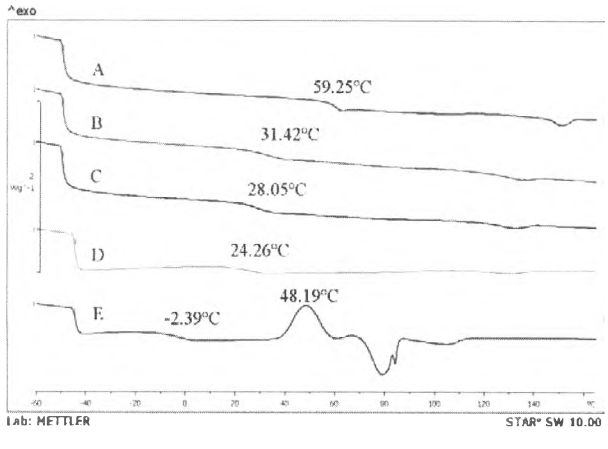

Figure 1 DSC thermograms of BZC:PLLA blends: (A) 0:100, (B) 10:90, (C) 20:80, (D) 30:70 and (E) 50:50 during reheating step of heat-cool-heat cycle.

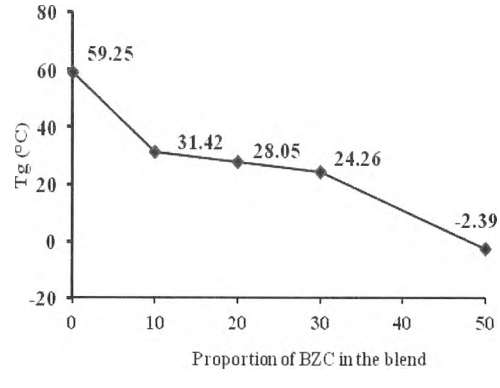

Figure 2 Effect of BZC on T_g of drug-polymer blend.

Single T_g of BZC-PLLA blends at the ratio of 10:90, 20:80, 30:70 and 50:50 were found at 31.42 °C, 28.05 °C, 24.26 °C and -2.39 °C, respectively (Figure 1(B-E)). The relationship between the proportion of BZC in the blends and their T_g is displayed in Figure 2. For the 50: 50 blend, above its T_g, recrystallization of amorphous BZC occurred at 48.19 °C (Figure 1(E)).

Hot stage microscopy (HSM) HSM allows thermal behaviors of the drug and polymer to be visualized. In the presence of the drug, PLLA was melted at the temperature below its T_m (Figure 3). Melting of the polymer occurred at lower temperatures with increasing BZC proportions. Dissolution of PLLA in molten BZC was clearly observed (Figure 3 (H, J)).

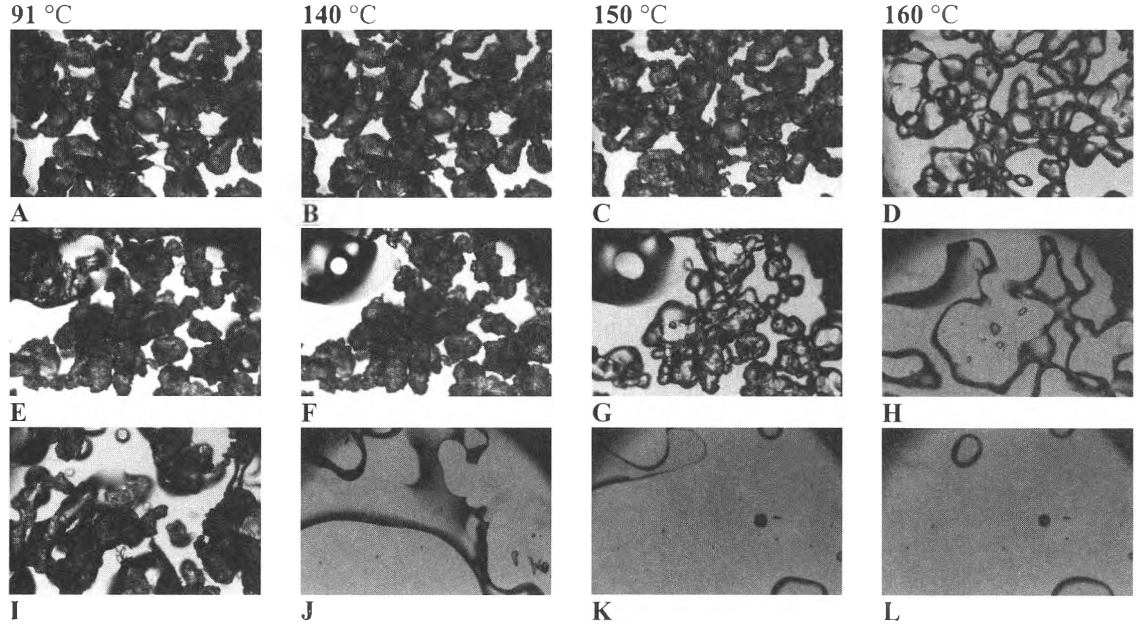

Figure 3 Hot-stage photomicrographs of BZC-PLLA blends at varied ratios: 0:100 (A-D), 10:90 (E-H) and 50:50 (I-L).

DISCUSSION

The calculated solubility parameters obtained from both methods were similar to the values reported earlier[6-7]. Greenlengh has been reported that if the $\Delta\delta$ was less than 7.0 $MPa^{0.5}$, the blend was likely to be miscible. If it was more than 10.0 $MPa^{0.5}$, the blend tended to be immiscible[2]. In the present study, the $\Delta\delta$ was less than 7.0 $MPa^{0.5}$, suggesting that BZC and PLLA were potentially miscible. Drug-polymer miscibility was confirmed by exhibiting of new single T_g of the blend between the individual T_g of the drug, which was reported in the literature at -31 °C[8] and of the polymer, 59.25 °C. The T_g values of the blends were decreased when the proportions of the drug in the blends were increased (Figure 2). This may be attributed to plasticizing effect of the drug like ibuprofen which was reported earlier[9]. Miscibility was also confirmed by melting behavior and dissolution of the polymer in the molten drug as visualized by HSM (Figure 3). Recrystallization of the drug during reheating the cooled melt in the DSC which was observed for the 50:50 blend may be explained by insufficient amount of the polymer to inhibit crystallization of the amorphous drug.

CONCLUSION

BZC and PLLA are miscible based on solubility parameter comparison and thermal analysis using DSC and HSM. The ratio of the drug and polymer may be an essential in formation of solid solution.

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