Solid−Liquid−Gas Equilibrium of the Ternaries Ibuprofen + Myristic Acid + CO_2 and Ibuprofen + Tripalmitin + CO_2

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A method via the observation of the first and last melting points (FLMP) of solids is proposed to measure solid−liquid−gas (SLG) equilibrium for the ibuprofen + myristic acid + CO_2 and ibuprofen + tripalmitin + CO_2 ternary systems. The temperature−composition (*T*, *w*) data as well as the eutectic compositions at different pressures (0.1, 6.0, 10.0, and 15.0) MPa were determined. Results indicate that the two systems are both simple eutectic at (0.1 and 6.0) MPa, while the phase diagrams transform into the solid solution as the pressure increases. The eutectic composition of the ibuprofen + myristic acid + CO_2 system is nearly constant (about 0.5 mass fraction of ibuprofen), while that of the ibuprofen + tripalmitin + CO_2 system increases from 0.4 (mass fraction of ibuprofen) at 0.1 MPa to 0.6 at 15.0 MPa. *T*, *w* data at 0.1 MPa from FLMP are in good agreement with those determined by differential scanning calorimetry (DSC) and also with predictions from the ideal solubility equation.

Introduction

The particle formation technology by using supercritical fluids (SCFs) has been extensively studied in recent years.[1] The phase equilibria for systems involving SCFs are crucial for the thorough understanding and further development of the technology. In particular, the solid−liquid−gas (SLG) equilibrium of solute-SCF binary systems has attracted much attention of many researchers with respect to its role in the rapid expansion of supercritical solutions (RESS) and particle from gas-saturated solution (PGSS) processes.[2−5] On the other hand, the SLG equilibrium for ternary systems (containing two solid solutes and a SCF) have potential applications in drug/carrier composite particles by using either PGSS or RESS techniques. This is because the particle size, morphology, and drug release are affected by the SLG phase behavior, and the initial load of drug and carrier may be determined by the eutectic composition which appears to have an effect on the crystallization route. A previous study[6] shows that ibuprofen has different release profiles from the ibuprofen/myristic acid and ibuprofen/tripalmitin composite particles, which drives us to study the SLG phase behavior of these two systems.

Many papers were published on the solid−liquid phase equilibrium, giving temperature−composition (*T*, *w* or *T*, *x*) curves for drug/carrier systems[7−9] with no high pressure gases. On the other hand, for systems involving a high pressure gas and a solid solute, several methods have been proposed in the literature for determining the SLG coexisting lines. Among them are the static solubility measurement,[10] the first melting point (FMP) method,[11−14] the first freezing point (FFP) method,[13,15,16] the high-pressure differential scanning calorimetry (HP-DSC),[17,18] and the scanning transitiometry.[19,20] Yet, only a few works deal with ternary systems, in particular drug/carrier systems that involve two solid solutes and a high pressure gas, relevant to the SCF technology, for example, PGSS. Van Gunst et al.[11] measured the S_1-S_2-L-G four-phase line for ethylene + naphthalene + hexachloroethane system by FMP. Later, Zhang et al.[16] presented the S_1-S_2-L-G four-phase line for the naphthalene + biphenyl + CO_2 system and the naphthalene + phenanthrene + CO_2 system using FFP. Wilken et al.[19] used the transitiometer method to determine the melting diagram of naphthalene + benzoic acid with a high pressure gas. Very recently, Vezzu et al.[18] measured and modeled solid−liquid equilibria of binary lipids in CO_2. However, they limited the pressure to 6 MPa because of the limitation of the HP-DSC technique.

On the basis of the FMP method,[4] we propose in this work a method via the observation of the first and last melting points (FLMP) of solid solutes to measure the phase equilibrium data (*T*, *w* phase diagram) of ternary systems. The initial appearance of a liquid phase and the ultimate disappearance of the solid phase are taken respectively as the FMP and the last melting point for defining the boundary lines of the system's SLG equilibrium region. The ternaries ibuprofen + myristic acid + CO_2 and ibuprofen + tripalmitin + CO_2 were studied by the FLMP method. The change observed in the phase diagram as well as the dependence of the eutectic compositions with pressure is discussed. Finally, DSC measurements at atmospheric pressure were performed, and results are compared with those from FLMP and with predictions by the ideal solubility equation.[21]

Experimental Section

Materials. Myristic acid (purity ≥ 98.0 %) was purchased from Sinopharm Chemical Reagent Co., Ltd., Shanghai, China. Ibuprofen (purity ≥ 99.8 %) was supplied by BeiKe HengDi Co., Ltd., Hubei, China. Finally, tripalmitin (purity ≥ 95 %, Fluka) and CO_2 (purity ≥ 99.9 %, Linde Gas) were used as received.

Apparatus and Experimental Procedure. Figure 1 shows a schematic diagram of the experimental apparatus. The main components of the apparatus are a high-pressure view cell (with

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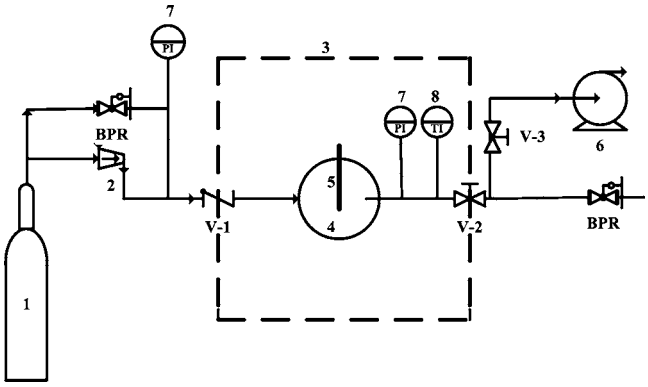

Figure 1. Schematic diagram of the experimental apparatus: BPR, back-pressure regulator; V-1, check valve; V-2, exhaust valve; 1, CO_2 cylinder; 2, compressor; 3, thermostatted air bath; 4, view cell; 5, capillary; 6, vacuum pump; 7, pressure indicator; 8, temperature indicator.

an inner volume of about 11 cm^3), a compressor (G447−400, Beijing HuiZhi M&E Facilities Co., Ltd., Beijing, China), a vacuum pump (2XZ-2, Linhai Tanshi Vacuum Equipment Co., Ltd., Zhejiang, China), a pressure transducer (HT-C4000-GK, Hitek I&M Industry Co., Ltd., Taiwan), and a thermostatted air bath. The pressure is controlled by a back-pressure regulator (modified from BY-3, Yantang Equipment Co., Ltd., Beijing, China). This apparatus can operate at pressures to 30 MPa and at temperatures to 363 K.

Solid mixtures with different mass fraction (w) were prepared by weighing (two solids were mixed and heated to melt, then the melt was allowed to cool to room temperature to form homogeneous solid mixture, and finally the mixture was grounded), and about 4 mg of the mixture was loaded into a capillary. The capillary was placed inside the view cell, which was then sealed and vacuumed, followed by a flush with pure carbon dioxide. Carbon dioxide was supplied from a gas cylinder and slowly charged into the system by the compressor until the pressure reached a desired value. Then the temperature was slowly raised by the air bath, with the initial heating rate of 1.0 $K \cdot min^{-1}$. When the temperature was close to the expected first melting temperature, the heating rate was reduced to less than 0.1 $K \cdot min^{-1}$ until the initial appearance of a liquid phase; the temperature at this point was taken as the first melting temperature (a magnifier was used for better visualization). After that, the temperature was kept constant for 30 min or more, and then the view cell was heated continuously and slowly (less than 0.1 $K \cdot min^{-1}$) until all of the solid phase disappears. The temperature of this state was taken as the last melting temperature.

The temperature was measured with a calibrated thermocouple. Repeated melting temperature measurements (typically three times) were performed to reduce the uncertainty of the experimental data. The uncertainties are less than (0.4 and 0.8) K for the first and last melting temperatures, respectively; this difference is attributed to the more difficult observation of the last melting points. The pressure was measured with a transducer with an uncertainty of less than 0.1 MPa. The mass of solutes was weighed with a precise balance (± 0.1 mg); therefore, the uncertainty of the calculated mass fraction w (see Tables 1 and 2) is less than 0.001. To reduce errors associated to the solute solubility in CO_2 at high pressure (solutes may appreciably dissolve in the gas phase), a small quantity of the mixture (e.g., about 70 mg for ibuprofen + myristic acid and 50 mg for ibuprofen + tripalmitin) according to pure compound solubility data[22−24] were loaded at the CO_2 entrance (a tube with filters) of the cell and in the cell for the presaturation of the CO_2.

Table 1. Temperature−Composition (T, w) Data for the Ibuprofen + Myristic Acid + CO_2 System

P/MPa	0.1		6.0		10.0		15.0	
w^a	$T_F{}^b$/K	$T_L{}^c$/K	T_F/K	T_L/K	T_F/K	T_L/K	T_F/K	T_L/K
0.00	326.7	327.4	315.2	316.2	310.6	311.3	310.2	310.9
0.50	317.7	326.1	303.5	316.2				
0.20	320.4	324.6	302.1	311.9	308.7	310.9	309.0	310.2
0.40	318.7	320.4	302.3	308.4	301.5	303.0	302.1	304.2
0.50	318.2	319.2	302.2	303.3	300.0	302.2	300.1	302.4
0.55	318.4	329.0	302.3	305.3	300.5	302.0		
0.60	318.7	330.6	302.6	309.5	300.3	302.2	300.6	302.9
0.65	320.5	336.2			300.2	308.3	300.5	306.2
0.80	320.1	340.0	303.1	320.4	300.6	314.6	300.9	311.5
0.90	318.6	340.2	303.3	330.4	301.4	321.0	301.6	319.6
1.00	346.2	347.0	331.4	332.0	321.4	322.3	320.5	321.1

[a] Initial mass fraction of ibuprofen in the samples. [b] First melting temperature (T_F). [c] Last melting temperature (T_L).

Table 2. Temperature−Composition (T, w) Data for the Ibuprofen + Tripalmitin + CO_2 System

P/MPa	0.1		6.0		10.0		15.0	
w^a	$T_F{}^b$/K	$T_L{}^c$/K	T_F/K	T_L/K	T_F/K	T_L/K	T_F/K	T_L/K
0.00	337.4	338.2	328.1	328.9	323.5	324.3	322.7	323.6
0.05	332.7	336.2						
0.20	332.6	334.7	321.7	326.5	319.9	322.5	319.5	321.8
0.40	331.3	333.2	320.4	323.2	315.5	320.2	314.8	320.0
0.50	331.2	340.4	320.2	322.4	315.3	318.1	314.5	316.9
0.60	332.5	341.8	320.7	325.9	315.2	316.7	314.6	316.5
0.80	331.5	344.4	321.4	329.8	315.4	320.2	314.9	317.5
0.90	332.1	345.1	321.6	330.7	315.3	320.8	314.6	319.0
1.00	346.2	347.0	331.4	332.0	321.4	322.3	320.5	321.1

[a] Initial mass fraction of ibuprofen in the samples. [b] First melting temperature (T_F). [c] Last melting temperature (T_L).

For a comparison, thermal analysis was carried out by a differential scanning calorimeter (DSC, STA 449 C, NETZSCH, Germany) to measure the melting points of ibuprofen + myristic acid and ibuprofen + tripalmitin solid systems at atmospheric pressure. Scanning temperatures ranged from (295.2 to 373.2) K at a heating rate of 5 $K \cdot min^{-1}$.

Results and Discussion

FLMP Results. The SLG equilibrium data determined by FLMP for the three pure compounds (ibuprofen, myristic acid, and tripalmitin) were measured and shown in Figure 2 and Tables 1 and 2. As the figure shows, the data from FLMP are in good agreement with those from published works, indicating that this technique is applicable for binary systems containing one solute and a dense gas.

The experimental T, w data at four different pressures (0.1, 6.0, 10.0, and 15.0) MPa for ibuprofen + myristic acid + CO_2 and ibuprofen + tripalmitin + CO_2 by the FLMP method are presented in Tables 1 and 2, respectively. The changes in the phase diagram and in the eutectic composition as well as the eutectic temperature with pressure are shown in Figures 3 and 4.

Figure 3a shows that the phase diagram of ibuprofen + myristic acid + CO_2 at atmospheric pressure (0.1 MPa) is simple eutectic. When the pressure reaches 6.0 MPa, the T, w phase diagram evidences the melting point depression under high pressure CO_2, and the phase diagram profile is similar to that at atmospheric pressure. When the pressure is raised to 10.0 MPa, the phase diagram changes dramatically: the FMPs at the left of the diagram rises up, indicating that the system transforms into a solid solution. The phase diagram at 15.0 MPa is similar and only slightly lower than that at 10.0 MPa. Figure 3 shows

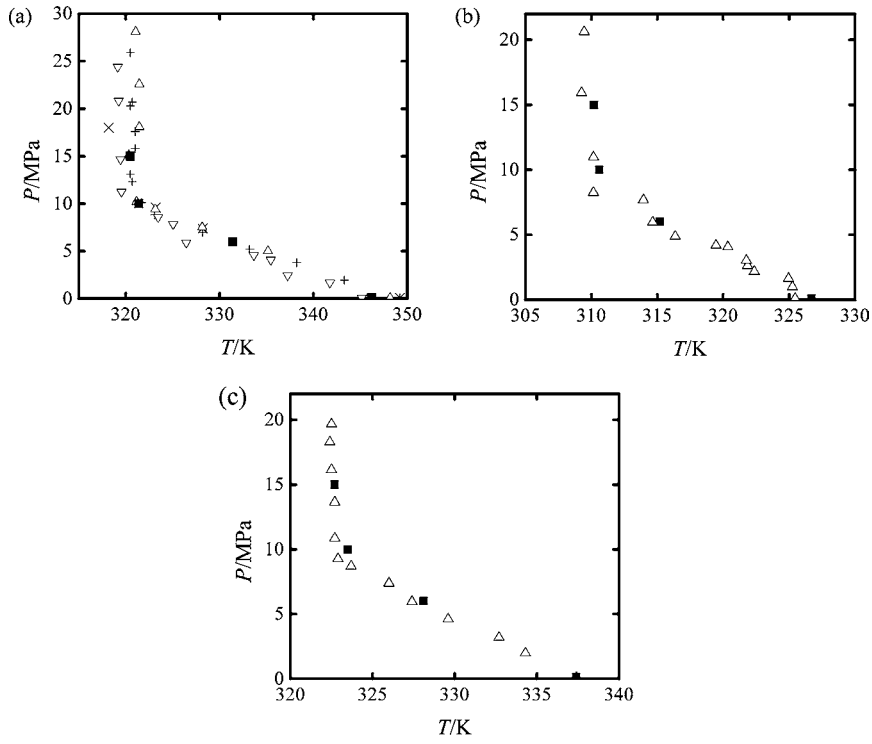

Figure 2. *P*, *T* projection of the SLG equilibrium: (a) ibuprofen + CO_2; ■, this work; Δ, ref 25; □, ref 26; +, ref 14; ×, ref 22. (b) Myristic acid + CO_2; ■, this work; □, ref 26. (c) Tripalmitin + CO_2; ■, this work; Δ, ref 4.

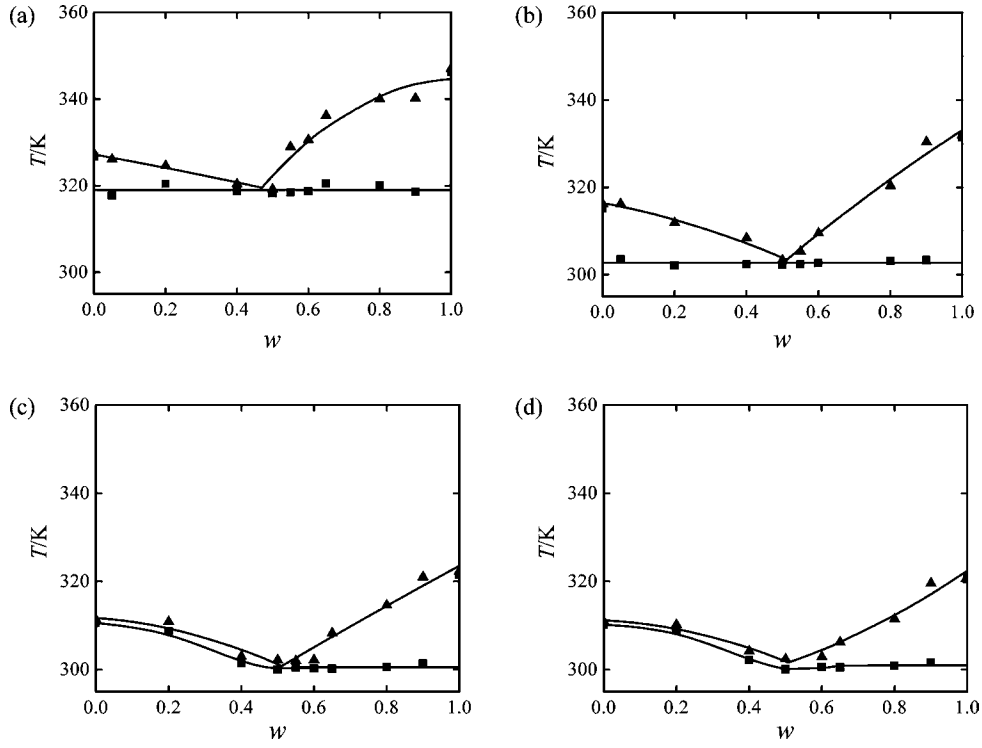

Figure 3. *T*, *w* phase diagram of the ibuprofen + myristic acid + CO_2 system at different pressures: (a) 0.1 MPa; (b) 6.0 MPa; (c) 10.0 MPa; (d) 15.0 MPa. ■, first melting temperature; ▲, last melting temperature.

clearly that the eutectic composition is nearly constant (w_E = 0.5, where the subscript E denotes eutectic) with pressure. In addition, when pressure is either (10.0 or 15.0) MPa, some FMPs are below the critical temperature of CO_2 (304.3 K), indicating that the CO_2 is in the liquid state, and therefore the system behaves like a solid−liquid−liquid equilibrium instead of solid−liquid−gas equilibrium (SLGE). At 6.0 MPa, the system is still in SLGE because CO_2's saturated temperature is about 295 K at this pressure.

As Figure 4 shows, the ibuprofen + tripalmitin + CO_2 system phase diagram behaves similarly: the phase diagrams at (0.1 and 6.0) MPa are typically simple eutectic, while those at (10.0 and 15.0) MPa transform into the solid solution. However, the simple eutectic composition of the ibuprofen

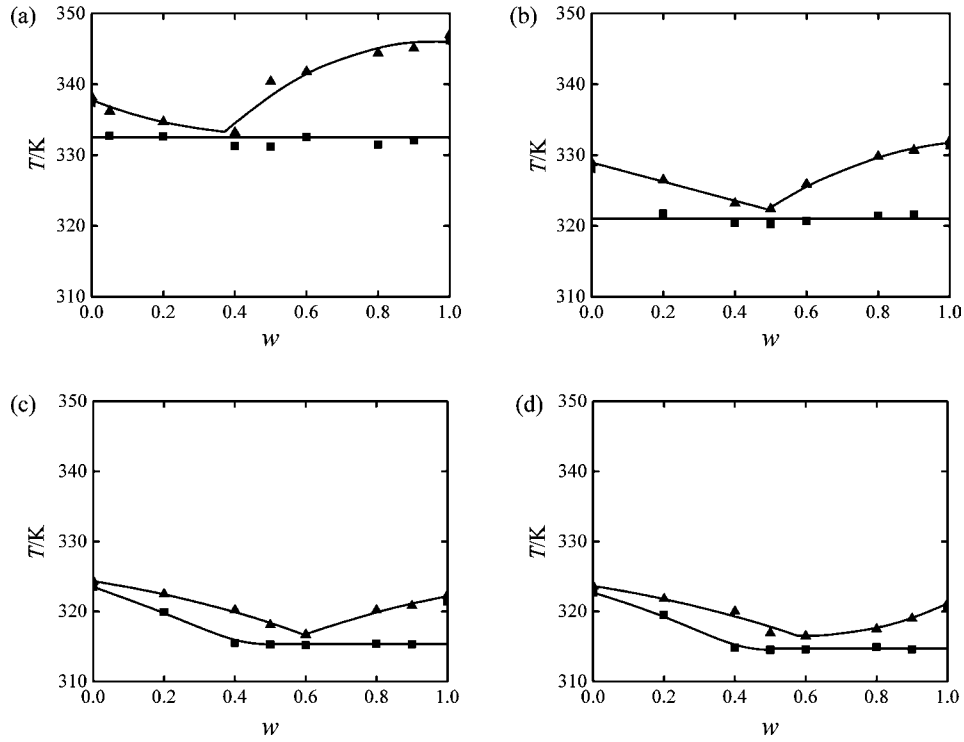

Figure 4. *T*, *w* phase diagram of the ibuprofen + tripalmitin + CO_2 system at different pressures: (a) 0.1 MPa; (b) 6.0 MPa; (c) 10.0 MPa; (d) 15.0 MPa. ■, first melting temperature; ▲, last melting temperature.

Table 3. Temperature−Composition (*T*, *w*) Data from DSC at 0.1 MPa

ibuprofen + myristic acid			ibuprofen + tripalmitin		
w	T_F[a]/K	T_L[b]/K	*w*	T_F/K	T_L/K
0.00	326.2		0.00	340.5	
0.05	314.4	327.2	0.17	330.3	337.5
0.20	316.4	322.8	0.30	330.7	335.6
0.50	316.9	316.9	0.40	330.8	330.8
0.90	315.7	344.9	0.60	329.6	342.9
0.95	314.3	347.2	0.80	328.6	345.2
1.00	347.6		1.00	347.6	

[a] First melting temperature (T_F). [b] Last melting temperature (T_L).

Table 4. Melting Enthalpy and Melting Temperature for Pure Compounds from DSC at 0.1 MPa

solute	ibuprofen	myristic acid	tripalmitin
$\Delta_{fus}H_i$/kJ·mol^{-1}	27.94[a]	45.75[a]; 45.29[f]	162.6[a]
	25.47[b]	45.100 ± 0.098[g]; 4.700 ± 1.800[g]	121.0[i]
	25.5[c]	39.750 ± 0.800[g]; 2.260 ± 0.423[g]	163.176[j]
		44.940[g]; 45.10[h]	177.2[k]
$T_{m,i}$/K	347.6[a]; 348.6[b] 347.2[c]; 349.2[d] 349.2[e]	326.2[a] 327.37[h]	340.5[a]; 339.5[j] 337.4[i]; 339.01[k]

[a] This work. [b] From ref 25. [c] From ref 27. [d] From ref 14. [e] From ref 22. [f] From ref 28. [g] From ref 29. [h] From ref 30. [i] From ref 4. [j] From ref 31. [k] From ref 32.

+ tripalmitin + CO_2 system increases with pressure: the eutectic composition w_E is 0.4 at 0.1 MPa, 0.5 at 6.0 MPa, and 0.6 at (10.0 and 15.0) MPa. This difference from the ibuprofen + myristic acid + CO_2 system may be attributed to the different solubilities of CO_2 into the solutes.[19]

DSC Results and Predictions. From the DSC measurements, the onset temperatures of pure compounds were determined by extrapolation of the endothermic peak as the melting temperature. For binary eutectic systems, the temperature from the extrapolation of the first endothermic peak was taken as the first melting temperature, and the peak temperature of a secondary endothermic was taken as the last melting temperature.[7] Table 3 presents the *T*, *w* data obtained from DSC at atmospheric pressure.

Predictions were also implemented for the melting points of ibuprofen + myristic acid and ibuprofen + tripalmitin solid systems at atmospheric pressure by the ideal solubility equation.[21]

$$x_i = \exp\left[\frac{\Delta_{fus}H_i}{R}\left(\frac{1}{T_{m,i}} - \frac{1}{T}\right)\right]$$

where x_i is the mol fraction of solute *i* in the mixture, *R* is the gas constant, and $\Delta_{fus}H_i$ and $T_{m,i}$ are the melting enthalpy and melting temperature respectively for the pure component *i*. From the DSC measurements, $\Delta_{fus}H_i$ and $T_{m,i}$ can be obtained and compared with literature values for the three solutes as shown in Table 4.

Figure 5 compares the *T*, *w* data from FLMP and DSC with the predictions from the ideal solubility equation. Table 5 provides the eutectic compositions and eutectic temperatures determined from FLMP, DSC, and the ideal solubility equation.

As Figure 5, Tables 1 to 3, and Table 5 show, the data measured from FLMP are in good agreement with those from DSC: the average absolute deviations (AADs) for ibuprofen + myristic acid's first melting temperatures and last melting temperatures are (2.2 and 2.0) K (calculated from data at w = 0, 0.050, 0.200, 0.500, 0.900, and 1 in Tables 1 and 3), respectively, and the AADs for ibuprofen + tripalmitin's first melting temperatures and last melting temperatures are (2.0 and 1.6) K (calculated from data at w = 0, 0.400, 0.600, 0.800, and 1 in Tables 2 and 3), respectively. The slight difference of the melting temperatures from FLMP and DSC can be attributed to the different definitions of melting temperature: FLMP defines it by either the liquid appearance or the solid disappearance of the solute (most pure organics melt over a narrow temperature

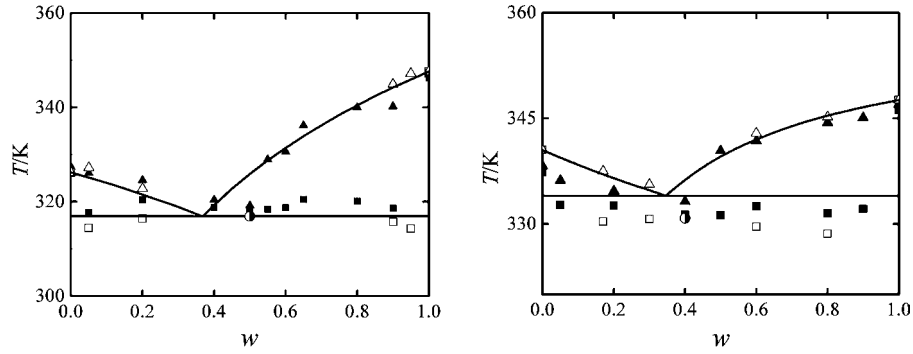

Figure 5. Comparison of the *T*, *w* data from FLMP and DSC at 0.1 MPa: (a) ibuprofen + myristic acid; (b) ibuprofen + tripalmitin; ■, first melting temperatures by FLMP; ▲, last melting temperatures by FLMP; □, first melting temperatures by DSC; △, last melting temperatures by DSC; ◑, eutectic point determined by DSC; solid lines, calculated from the ideal solubility equation.

Table 5. Comparison of Eutectic Compositions (w_E) and Eutectic Temperatures (T_E) at 0.1 MPa from Different Methods

system	ibuprofen + myristic acid		ibuprofen + tripalmitin	
method	w_E	T_E/K	w_E	T_E/K
FLMP	0.50	318.2	0.40	331.3
DSC	0.50	316.9	0.40	330.8
prediction[a]	0.37	316.9	0.35	334.0

[a] From the ideal solubility equation.

range, typically (1 to 2) K),[33] and DSC defines it by the extrapolation of the endothermic peaks or the peak temperature. Figure 5 and Table 5 also show that the measured melting temperatures can be qualitatively described by the ideal solubility equation; nevertheless, the eutectic compositions predicted are less than those from FLMP or DSC. The comparison of the results from FLMP and DSC with the predictions indicates the robustness of the proposed FLMP method.

Comments on FLMP and HP-DSC. In another work,[34] we have shown that results from FLMP for naphthalene + biphenyl + CO_2 at 3 MPa were in good agreement with that from a HP-DSC. From solubility calculation,[5] we can obtain the solute's mass dissolved in CO_2 in the visual cell (11 cm^3) under certain conditions: 40.3 mg of ibuprofen at 10 MPa and 318.2 K, 25.1 mg of myristic acid at 10 MPa and 318.2 K, 4.7 mg of tripalmitin at 10 MPa and 313.2 K,[24] 63.5 mg of naphthalene at 8 MPa and 308.2 K (0.7 mg at 6 MPa and 308.2 K; 0.07 mg at 3 MPa and 308.2 K), and 54.0 mg of biphenyl at 8 MPa and 308.2 K (0.2 mg at 6 MPa and 308.2 K; 0.02 mg at 3 MPa and 308.2 K). Therefore, HP-DSC at higher pressures cannot be directly applied to a system with high solubility in CO_2 because the flow of CO_2 will appreciably change the composition of the system's solid phase (and sometimes will dissolve all of the solid mixture in the sample pan); this serves as the reason that HP-DSC fails for our investigated systems at higher pressures of (6.0 and 10.0) MPa.

For the proposed FLMP, the above problem can be solved by the presaturation of CO_2 as described. Except for the use of presaturated CO_2, similar to other melting observation methods, FLMP also needs to pay attention to the following: (1) loading the smallest amount of sample to see the melting process (4 mg in this work) because larger samples will lead to heat unevenly and (2) packing down the sample in the capillary as best as one can to avoid heating unevenly.

Conclusions

The FLMP technique was proposed to determine the SLG coexisting region for the ibuprofen + myristic acid + CO_2 and ibuprofen + tripalmitin + CO_2 systems. The effects of pressure on the change of the phase diagram as well as the eutectic composition were investigated. The data obtained at 0.1 MPa from FLMP were further compared with those from DSC and predictions from the ideal solubility equation. From this study, we conclude the following:

(1) The ibuprofen + myristic acid + CO_2 system is simple eutectic at (0.1 and 6.0) MPa; the phase diagram transforms into a solid solution at high pressures of (10.0 and 15.0) MPa with an almost constant eutectic composition (0.5).

(2) The ibuprofen + tripalmitin + CO_2 system is simple eutectic at (0.1 and 6.0) MPa; the phase diagram transforms into a solid solution at high pressures of (10.0 and 15.0) MPa with the eutectic composition increasing with pressure (0.4 to 0.6).

(3) The temperature−composition (*T*, *w*) data at 0.1 MPa from FLMP are in good agreement with those from DSC and predictions of the ideal solubility equation, indicating the availability of the proposed FLMP method.

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