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Preparation and Crystal Modification of Ibuprofen-Loaded Solid Lipid Microparticles*

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Abstract An emulsion-congealing technique is used to prepare solid lipid microparticles (SLM) containing ibuprofen with glyceryl behenate, tripalmitin and beewax as excipients. The difference of the solubility parameters between the excipients and ibuprofen are used to analyze their compatibility. Both the solubility parameter analysis and the experimental results show that glyceryl behenate is the best among the three excipients. The solid particles disperse well in aqueous phase when the drug loading reaches 10% (relative to lipid only). Glycerides exhibit marked polymorphism and their rapid rates of crystallization accelerate the formation of metastable crystal modification. The metastable crystal modification characterizes high drug loading capacity but less stability. Increasing the content of lipophilic drug in a lipid matrix facilitates the transformation of excipients to more stable polymorphic forms.

Keywords solid lipid microparticles, crystal modification, solubility parameter, drug loading capacity, ibuprofen

1 INTRODUCTION

Drug carriers of submicron sizes are attracting increasing attention in recent years. Because of their small sizes they exhibit distinctive properties which may enable drug release to be controlled and sustained. Solid lipid microparticles (SLM) are micro- and nano-scale drug carriers possessing matrix made from fatty acid, glyceride, fatty alcohol and solid wax with high melting points[1,2]. Compared to the polymer microparticles, SLM have the advantage of better bio-compatibility which minimizes the hazards of acute and chronic toxicity. Besides, as SLM possess solid cores, the mobility of incorporated drugs and drug leakage from the carriers are reduced. Therefore, it is believed that SLM combine the advantages of many colloidal carriers and also overcome some of their disadvantages[1,3].

There are several studies concerning the effects of production conditions, carrier materials and stabilizers on the morphological characterization, drug loading capacity, long-term stability as well as release performance of SLM[4—8]. However, the relationship between the behavior of SLM and their microstructure still lacks detailed analysis. SLM are complex multiphase systems and their properties are greatly influenced by their microstructures. For example, the solubility of a drug in an excipient affects the drug loading capacity and release performance[9]. Meanwhile, the crystallinity of the carrier material also influences the drug loading capacity, drug release performance, and the stability of a drug delivery system[10]. Hereby, it is important to investigate as to how the microstructure of a drug delivery system is affected, and then to relate the microstructure with its properties. The relationship between microstructure and properties can provide guidance in the drug delivery system design and the optimization of the operation conditions.

In this work, glyceryl behenate, tripalmitin and beewax are used as the excipients. A nonsteroidal anti-inflammatory drug, ibuprofen, is chosen as the lipophilic model drug. Ibuprofen has a low solubility and short half-life. Embedding ibuprofen in solid lipid matrices improves its physical stability and dissolution owing to reduced drug crystal particle size and highly dispersed amorphous state. The compatibility of ibuprofen with different carrier materials and their effects on drug loading capacity are investigated. Besides, the influences of cooling temperature and drug content on crystal modification of the excipients are studied; the drug loading capacity in different crystal modification is further discussed.

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2 EXPERIMENTAL

2.1 Materials

Compritol 888 ATO (glyceryl behenate) provided by Gattefossé (France) is a mixture of 13%—21% mono-, 40%—60% di- and 21%—35% triglycerides of behenic acid (C22). Other materials used in this work are tripalmitin (90% purity, Yihe Chemical Ltd., China), beewax (Shanghai Chemical Reagent Ltd.), bile salts (Guangdong Huankai Chemical Ltd.), soybean lecithin (Shanghai Boao Bio-Tech Ltd.), and ibuprofen (Shanghai Yuanji Chemical Ltd.).

2.2 Preparation of SLM

An emulsion-congealing technique is adopted to prepare SLM. The formulation consists of 5% lipid, 1.5% stabilizer (by mass), and other components including ibuprofen and water. Soybean lecithin and bile salts are mixed together in the ratio of 2∶1 and used as the stabilizer. The emulsion–congealing technique has been described in detail in literatures[1,11]. Briefly, the lipid with drug is first melted at 85℃, then emulsified into a 300ml aqueous phase containing the stabilizer. The emulsion is stirred at 300r·min^{-1} with a magnetic blender for 5min, and then treated with a high shear dispersing emulsifier (FM200, Fluko Equipment Shanghai Ltd.) at 8000r·min^{-1} for 10min. Finally, the emulsion is cooled in a cooling bath, which crystallizes the lipid. The cooling temperatures are 5, 10 and 25℃, respectively.

2.3 Measurement of particle size and drug entrapment efficiency

Particle size is analyzed by photo correlation spectroscopy (PCS, Malvern Zetasizer, Malvern Instruments, UK). All values are measured at an angle of 90° in 10mm-diameter cells. The SLM dispersion is diluted 100 times beforehand. All measurements are repeated thrice. The morphology of SLM is evaluated by optical microscopy (E200, Nikon, Japan).

The drug entrapment efficiency is determined by measuring the free drug concentration in the aqueous phase. SLM dispersion is separated using a refrigerated centrifuge that runs for 30min at 13000r·min^{-1}. The obtained aqueous phase is filtered through a 0.22μm membrane filter. Then the filtrate is measured spectrophotometrically (751-GW spectrophotometer, HP Analytical Apparatus Ltd., Shanghai) at a wave length of 222nm. The drug entrapment efficiency (*EE*) of the SLM is calculated from Eq.(1).

$$EE(\%) = \left(\frac{W_{\text{initial drug}} - W_{\text{free drug}}}{W_{\text{initial drug}}} \right) \times 100 \qquad (1)$$

where $W_{\text{initial drug}}$ is the mass of drug added to the system, while $W_{\text{free drug}}$ is the analyzed mass of the free drug in the aqueous phase.

2.4 Differential scanning calorimetry (DSC)

The degree of crystallinity is analyzed with a differential scanning calorimetry (DSC, STA4490, NETZSCH, Germany). SLM dispersion is thickened using a refrigerated centrifuge. About 10mg of thickened SLM dispersion is weighed in an aluminium pan using an empty pan as reference. The DSC scan is recorded at a heating rate of 2K·min^{-1}. The sample is heated from 5 to 90℃. Melting points correspond to the maximum point of the heating curve.

3 RESULTS AND DISCUSSION

3.1 Calculation of solubility parameters

Solubility parameter is widely used to describe the cohesive forces within materials. It has been used to describe many physical properties of a material and to predict interactions between materials[12,13]. The miscibility of some drugs and excipients has been successfully predicted using the solubility parameter, and an excipient for a desired drug may be screened with the property prediction based on the solubility parameter[14,15]. Hildebrand solubility parameter (δ) is defined as the square root of the cohesive energy density (*CED*).

$$\delta = (CED)^{1/2} = (\Delta E_{\text{v}} / V_{\text{m}})^{1/2} \qquad (2)$$

where ΔE_{v} is the energy of vaporization and V_{m} is the molar volume.

The solubility parameter is obtained by Hansen's approach[16] in this work, which uses partial solubility parameters to calculate the total solubility parameter as shown in Eq.(3).

$$\delta_{\text{t}} = (\delta_{\text{d}}^2 + \delta_{\text{p}}^2 + \delta_{\text{h}}^2)^{1/2} \qquad (3)$$

where δ_{t} is the total solubility parameter, and δ_{d}, δ_{p} and δ_{h} result from the contributions of van der Waals dispersion forces, dipole interactions and hydrogen bonding. The partial solubility parameters are calculated by the group contribution method using Eqs.(4—6)[17]:

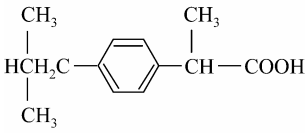
$$\delta_{\text{d}} = \frac{\sum F_{\text{d}i}}{V} \qquad (4)$$

$$\delta_p = \frac{\sqrt{\sum F_{pi}^2}}{V} \quad (5)$$

$$\delta_h = \sqrt{\frac{\sum E_{hi}}{V}} \quad (6)$$

where F_{di}, F_{pi} and E_{hi} refer to the specific functional group contributions: van der Waals dispersion forces, dipole interactions and hydrogen bonding, respectively. The molecules are divided into small chemical groups and their partial and total solubility parameters are calculated using F_{di}, F_{pi} and E_{hi} values. As an example, the calculations of partial and total solubility parameters are carried out for ibuprofen. They are given below.

The molecular structure of ibuprofen is shown as follows:



Group contributions to the molar attraction constants and molar volumes are obtained from the work by Li *et al*.[18] and are shown in Table 1.

The partial and total solubility parameters of ibuprofen are calculated from Eqs.3—6.

Compounds with similar solubility parameters (δ) are likely to be miscible. The difference of the solubility parameters between an excipient and a drug ($\Delta\delta$) can be used to estimate their compatibility. Greenhalgh *et al*.[14] classified excipients based on the $\Delta\delta$. They demonstrated that compounds with $\Delta\delta$<7.0MPa$^{1/2}$ were likely to be miscible, and they were likely to be immiscible when $\Delta\delta$>10.0MPa$^{1/2}$. For the compounds with $\Delta\delta$ between 7.0 and 10.0MPa$^{1/2}$, the existence of the polar interaction and hydrogen bonding need further investigation. The partial and total solubility parameters of ibuprofen and three excipients are listed in Table 2. In calculating the solubility parameters of Compritol, 17% mono-, 54% bi- and 29% triglycerides of behenic acid (by mass) are considered. Converting the mass rate into molar rate, the total solubility parameter of the mixture is obtained by calculating the molar weighted average. The solubility parameter of each component is also given in Table 2. For beewax, the main constitution is triacontyl palmitate, and other free fatty acids with long chain are included. The solubility parameter of beewax is calculated by the chemical structure of its main constituent.

As shown in Table 2, the values of $\Delta\delta$ between the three excipients and ibuprofen are all lesser than 5MPa$^{1/2}$. It indicates that ibuprofen is miscible with all

Table 1 Calculation of the partial and total solubility parameters for ibuprofen

Group	$\sum V$ cm^3·mol^{-1}	$\sum F_{di}$ J$^{1/2}$·cm$^{3/2}$·mol^{-1}	$\sum F_{pi}^2$ J·cm^3·mol^{-2}	$\sum E_{hi}$ J·mol^{-1}
1 (—COOH)	28.5	530	176400	10000
1 (phenylene)	52.4	1270	12100	0
2 (—CH<)	−2.0	160	0	0
3(—CH$_3$)	100.5	1260	0	0
1 (—CH$_2$—)	16.1	270	0	0
total	195.5	3490	188500	10000

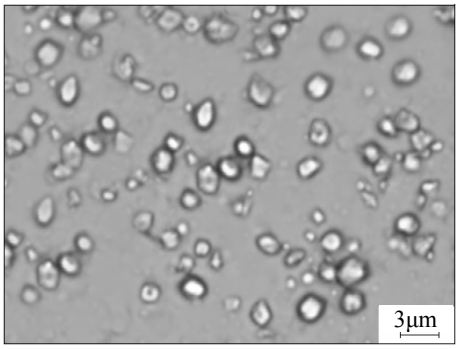
Table 2 The solubility parameters of the components

Compound	δ_d MPa$^{1/2}$	δ_p MPa$^{1/2}$	δ_h MPa$^{1/2}$	δ_t MPa$^{1/2}$	$\Delta\delta$ MPa$^{1/2}$
ibuprofen	17.85	2.22	7.15	19.36	—
beewax	16.52	0.63	3	16.80	2.56
tripalmitin	16.70	0.51	4.68	17.44	1.92
Compritol 888 ATO					
mono-	18.31	2.17	10.9	21.42	—
bi-	16.81	1.08	6.57	18.08	—
tri-	16.71	0.74	4.27	17.26	—
total	—	—	—	18.89	0.47

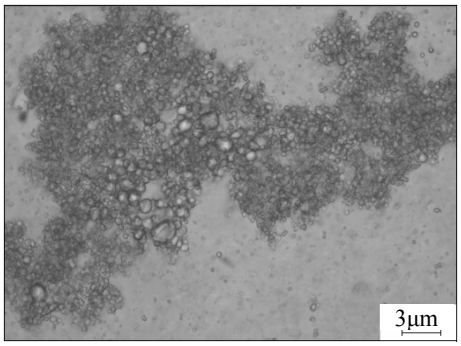
these three excipients. The value of $\Delta\delta$ between Compritol and ibuprofen is 0.47MPa$^{1/2}$ and it is much lesser than that between beewax and tripalmitin with ibuprofen. It suggests that stronger interaction exists between Compritol and ibuprofen.

3.2 Encapsulation of ibuprofen in different excipients

Ibuprofen is incorporated into Compritol, tripalmitin and beewax SLM. The cooling temperature is 5℃, and the drug content is 1%, 5%, 10% and 15% (relative to the lipid), respectively. The morphology of the SLM is observed using the optical microscopy. When the drug contents are 1% and 5%, the particles are well dispersed in the aqueous phase. The optical microscopy photographs of 5% ibuprofen-loaded beewax SLM and tripalmitin SLM are shown in Fig.1(a) and 2(a). As seen from Fig.1(b), for beewax SLM, when the drug content is up to 10%, no particles are observed, while the excipient sticks together. The particles in tripalmitin SLM begin to aggregate as the case shown in Fig.2(b). Meanwhile, the particles in Compritol SLM are still dispersed well, and they begin to aggregate when the drug content reaches 15%.

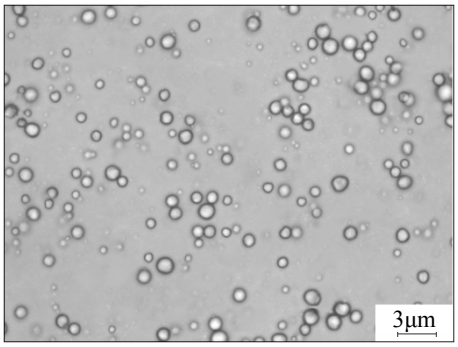


(a) 5%

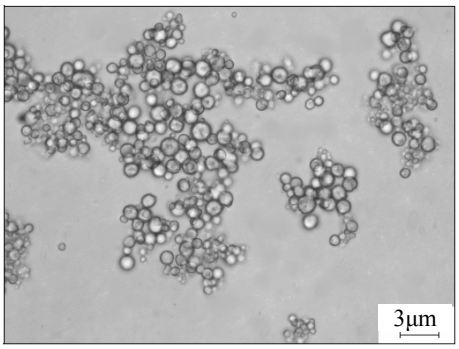


(b) 10%

Figure 1 Optical microscopy photographs of beewax SLM at different drug contents



(a) 5%



(b) 10%

Figure 2 Optical microscopy photographs of tripalmitin SLM at different drug contents

The entrapment efficiency of ibuprofen in different excipients and their mean diameters as well as polydispersity index are listed in Table 3.

As seen from Table 3, the entrapment efficiency of ibuprofen in Compritol is the highest, because of the stronger interaction between Compritol and ibuprofen. The difference of solubility parameter $\Delta\delta$ between tripalmitin and ibuprofen is similar to that of beewax. However, the entrapment efficiency of ibuprofen in tripalmitin is higher than that in beewax. This is probably due to the different microstructure of the subcells. Orthorhombic subcells prevail in beewax matrix. For freshly prepared tripalmitin SLM, however, it usually crystallizes in α modification (the DSC analysis will be discussed later), which is a hexagonal subcell. The less ordered crystal modification is beneficial to drug loading.

It is shown in Table 3 that the diameters of beewax SLM are much larger than that of Compritol SLM and tripalmitin SLM. Beewax is a liquid with low viscosity when melted at elevated temperatures, while it becomes a plastic solid at the room temperature[19]. When beewax crystallizes in a low temperature, it is easier to stick together. The diameters of Compritol SLM are smaller than that of tripalmitin

Table 3 The particle size and entrapment efficiency *vs.* drug content

Carrier material	Drug content %	Mean size nm	Polydispersity index	Entrapment efficiency %
Compritol 888 ATO	1%	603.3±12.5	0.335±0.025	93.2
	5%	651.8±8.3	0.313±0.017	88.6
	10%	626.5±9.1	0.408±0.022	89.3
	15%	813.7±15.7	0.443±0.031	82.1
tripalmitin	1%	913.3±19.5	0.441±0.021	85.7
	5%	921.6±15.3	0.381±0.013	80.1
	10%	1204.5±21.7	0.490±0.047	78.6
beewax	1%	1563.4±31.5	0.481±0.041	72.3
	5%	2130.4±35.8	0.550±0.032	65.5

SLM. It is because the mono- and diglycerides in Compritol possess the properties of a surfactant (HLB 2-5). These partial glycerides improve the surfactant film around the particles, thus preventing the aggregation of particles. More surfactant induces smaller particles to be formed. Comparing the three excipients, Compritol is the best excipient for ibuprofen.

3.3 Effect of cooling temperatures on the crystal modification of drug carriers

Crystallization behavior of a material is influenced by several factors, such as molecular structure, temperature, impurities and crystallization rate[20]. During the preparation of SLM, lipids and drugs are melted at a high temperature and then emulsified in a surfactant solution. The emulsion is then cooled in a cooling bath to crystallize the lipid. The formation of the solid microparticles and the degree of crystallinity are greatly affected by the cooling temperature, which need further investigation.

Glycerides crystallize in different subcell arrangements-hexagonal, orthorhombic and triclinic. They exhibit polymorphism with three or more individual forms, including α、β' and β modification[20]. For mixtures of glycerides, an intermediate form of β_i modification is also included. It is shown in Fig.3 that the melting point of Compritol bulk material is 71.6℃ (the curve of Co888). For pure tribehenate, it was reported that the melting point of α modification is 69℃, that of β' modification is 74.8℃ and β modification is 83℃, respectively[21]. As the content of diglycerides in Compritol is high (40%—60%), it is concluded that the crystal modification of Compritol bulk material is β'. The main modification of β′ and β_i in Compritol bulk material was reported[22,23]. Generally, β modification is prevailed in pure triglycerides. However, the existence of diglycerides results in a large number of lattice imperfections and prevents the transformation to β modification[8].

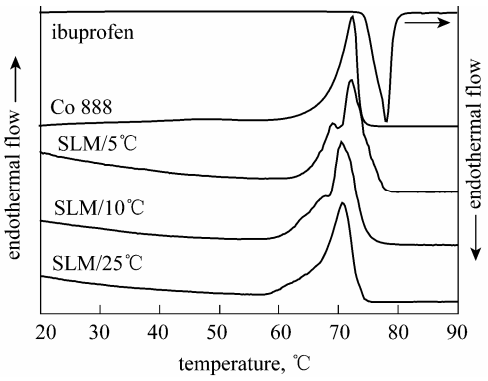


Figure 3 DSC thermograms of Compritol bulk material and SLM at different cooling temperatures

The melting point of α, β and β′ are reported as 44.7℃, 56.6℃ and 66.4℃ for tripalmitin[24]. Fig.4 (the curve of tripalmitin) shows that the melting point of tripalmitin bulk material is 63.4℃ and it is of β modification. The difference of the analyzed melting point with the literature is perhaps due to the different purity of the material and the environmental errors.

It is seen in Fig.3 and 4 that the crystallization behavior of SLM differs from that of the pure lipid. The DSC heating curves show that the melting peaks are broader, which indicates the reduction in melting points. One reason is that the drug existing in lipid matrices results in the increase of lattice defects. Meanwhile, the small particle size leads to a decrease of the crystallization point[22]. The drug contents in the SLM systems are 5%. The melting peaks of ibuprofen are not observed in all these DSC heating curves. It

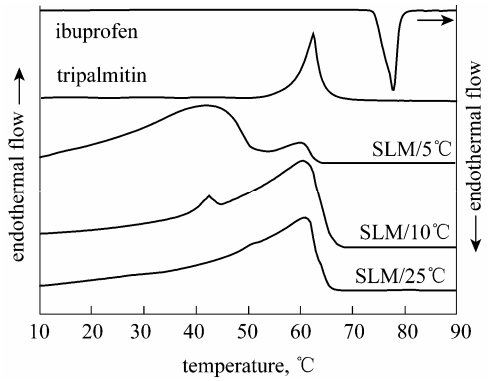


Figure 4 DSC thermograms of tripalmitin bulk material and SLM at different cooling temperatures

indicates that the incorporated drug is in an amorphous state.

As shown in Fig.3, when the cooling temperatures are 5℃ and 10℃, a melting peak at 66.5℃ appears besides the main melting peak at 70.38℃, which is attributed to β′ modification. The melting temperatures at 60℃ and 62℃ for α modification of Compritol were reported[22]. For pure tribehenate, it is reported that the melting point of α modification is 68℃[25]. It is believed that the melting point at 66.5℃ attributes to α modification of triglyceride in Compritol. When the cooling temperature is 25℃, the melting peak at 66.5℃ disappears. On the basis of the above analysis, it is found that the cooling temperature during SLM preparation greatly influences the crystallinity of the excipient. Lower cooling temperature induces the formation of less ordered crystal modification. When the crystallization rate is fast, the methylene groups of long chains in glycerides are not arranged in regular forms in time, hence a less ordered form appears.

The same phenomenon is observed in tripalmitin SLM. It is seen from Fig.4 that when the cooling temperature is 5℃ and 10℃, the DSC heating curves show two melting peaks. The melting point at about 42℃ is attributed to α modification and the other to β modification. The excipient crystallizes mainly in α modification when the cooling temperature is 5℃. α modification is much reduced when the cooling temperature is increased to 10℃ and it totally disappears when the emulsion is cooled at 25℃.

The drug entrapment efficiency varies with different cooling temperatures. As seen in Table 4, the lower the cooling temperature, the higher the drug entrapment efficiency. The crystal behavior of lipid modification has been determined for triglycerides as follows: α reveals a spherulic pattern, β′ is of loosely packed spherulite and β shows large coagulated platelets[25]. The microstructure of the subcell determines its drug loading capacity. The less stable crystal modification characterizes high drug loading. However, the less stable modification will transform to the more stable one during storage. The formation of a perfect crystal leads to drug expulsion from the matrix with no room for the guest molecules[3,26].

3.4 Effect of drug content on the crystal modification of excipients

The incorporated drug in a lipid matrix induces the increase of lattice defects, which broadens the melting peak and causes the melting point to decrease. On the other hand, the loaded lipophilic drug in a lipid matrix imposes another effect on the crystallization behavior of an excipient. In Figs.5 and 6, SLM are prepared at the cooling temperature of 5℃ and the drug contents are 1%, 5%, and 10%, respectively. It is seen that when the drug content increases, α modification decreases. A similar phenomenon is observed by Mühlen *et al.*[23]. In their case, prednisolone was loaded in Compritol 888 ATO. The DSC curve of the drug-free SLM was compared with that of 0.83% prednisolone-loaded SLM. Two melting peaks were observed in the cooling curve of drug free SLM, while only one melting peak appeared in both the heating and cooling curves of the drug-loaded SLM. It indi-

Table 4 The particle size and entrapment efficiency at different cooling temperatures

Carrier material	Cooling temperature ℃	Mean size nm	Polydispersity index	Entrapment efficiency %
Compritol 888 ATO	5	651.8±8.3	0.313±0.017	88.6
	10	631.1±10.2	0.341±0.023	85.8
	25	663.8±9.6	0.420±0.015	78.2
tripalmitin	5	921.6±15.3	0.381±0.013	80.1
	10	955.3±19.3	0.360±0.032	76.5
	25	868.4±22.8	0.410±0.031	70.8

cates that the presence of prednisolone prevents the formation of the unstable modification or facilitates the transition to a stable form. One possible explanation is that the drug-loaded SLM possess a higher amount of liquid lipids within the matrix. The content of liquid lipids accelerates the crystallization to stable modifications[27].

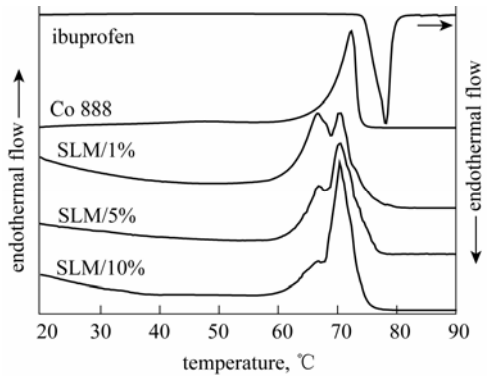


Figure 5 DSC thermograms of Compritol bulk material and SLM at different drug contents

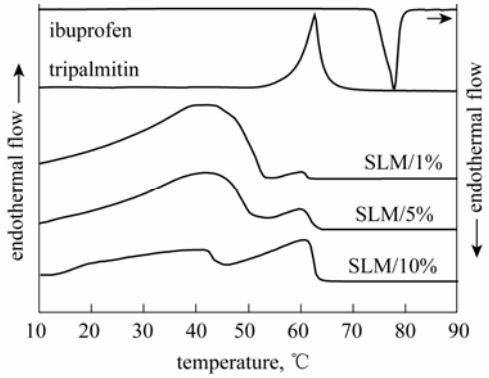


Figure 6 DSC thermograms of tripalmitin bulk material and SLM at different drug contents

4 CONCLUSIONS

The difference of solubility parameter $\Delta\delta$ between a drug and an excipient can be used to predict their miscibility and choose a proper excipient for a desired drug. The smaller the value of $\Delta\delta$ is, the stronger the interaction between the drug and the excipient, and the higher drug loading capacity is obtained. Glyceryl behenate is the best excipient for ibuprofen in this work, the entrapment efficiency for ibuprofen reaches 93.2%. The cooling temperature in the SLM preparation and the drug content in SLM greatly influence the formed crystal modifications of the excipients. Faster cooling rate facilitates the formation of more stable crystal modification which characterizes a higher drug loading capacity. To obtain a high drug loading capacity and better particle characters with long-term stability, choosing a proper excipient is required and the optimized preparation conditions should be investigated. Besides, the investigation is needed for a better understanding of the effects of the composition and concentration of the stabilizing surfactant mixture on drug entrapment efficiency.

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