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Preparation and characteristics of monostearin nanostructured lipid carriers

Fu-Qiang Hu *, Sai-Ping Jiang, Yong-Zhong Du, Hong Yuan, Yi-Qing Ye [1], Su Zeng

School of Pharmaceutical Science, Zhejiang University, 353 Yanan Road, Hangzhou 310031, PR China

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Abstract

Nanostuctured lipid carriers (NLC) consisted of solid lipid and liquid lipid are a new type of lipid nanoparticles, which offer the advantage of improved drug loading capacity and release properties. In this study, solvent diffusion method was employed to produce NLC. Monostearin (MS) and caprylic/capric triglycerides (CT) were chosen as the solid lipid and liquid lipid. Clobetasol propionate used as a model drug was incorporated into the NLC. The influences of preparation temperature and CT content on physicochemical properties of the NLC were characterized. As a result, monostearin solid lipid nanoparticles (without CT content, SLN) obtained at higher temperature (70 °C) exhibited slightly higher drug loading capacity than that of 0 °C ($P < 0.05$). In contrast, the production temperature made little effect on NLC drug loading capacity ($P > 0.05$). The improved drug loading capacity was observed for NLC and it enhanced with increasing the CT content in NLC. The results were explained by differential scanning calorimetry (DSC) measurement for NLC. The incorporation of CT to NLC led to crystal order disturbance and thus left more space to accommodate drug molecules. NLC displayed a good ability to reduce the drug expulsion in storage compared to SLN. The in vitro release behaviors of NLC were dependent on the production temperature and CT content. NLC obtained at 70 °C exhibited biphasic drug release pattern with burst release at the initial 8 h and prolonged release afterwards, whereas NLC obtained at 0 °C showed basically sustained drug release throughout the release time. The drug release rates were increased with increasing the CT content. These results indicated that the NLC produced by solvent diffusion method could potentially be exploited as a carrier with improved drug loading capacity and controlled drug release.

Keywords: Nanostructured lipid carriers; Monostearin; Caprylic/capric triglycerides; Entrapment efficiency; In vitro release; Preparation temperature

1. Introduction

Solid lipid nanoparticles (SLN) are developed at the beginning of 1990s as an alternative colloidal carrier system for controlled drug delivery. Compared with polymeric nanoparticles, SLN have more advantages for drug delivery system, such as a good tolerability due to the use of physiological lipids (Müller et al., 1996a; Maaßen et al., 1993), larger scale production by high pressure homogenization (Müller and Lucks, 1996b), and also a targeting effect on brain (Yang et al., 1999). Common disadvantages of SLN included limited drug loading capacity, drug expulsion during storage, etc (Müller et al., 2002a). To overcome the limitations of SLN, nanostructured lipid carriers (NLC) are developed in recent years (Müller et al., 2002a).

Nanostructured lipid carriers (NLC) composed of a solid lipid matrix with a certain content of liquid lipid are a new generation of solid lipid nanoparticles (Müller et al., 2002a). Up to now, its special features, such as the improved drug entrapment efficiency (Jenning et al., 2000a; Jenning and Gohla, 2001; Souto et al., 2004a; Hu et al., 2005), the morphological characterization (Jores et al., 2004), the possibility of topical use (Souto et al., 2004a,b), the crystal order by differential scanning calorimetry (DSC) (Jenning et al., 2000a; Castelli et al., 2005) and ^{1}H NMR (Jenning et al., 2000b) were studied. Besides, NLC remain their solid state by controlling the liquid lipid content added to the formulation, therefore, the controlled drug release properties for NLC can be achieved (Müller et al., 2002b).

High pressure homogenization is the main method for the NLC preparation (Jenning et al., 2000b). The major advantage of high pressure homogenization is that can be large scale production (Müller and Lucks, 1996b). However, the high temperatures used in the process may increase the degradation rate of the drug and the carriers (Mehnert and Mader, 2001), and the conformational modifications of proteins were found by using

* Corresponding author. Tel.: +86 571 87217327; fax: +86 571 87217327.
E-mail address: hufq@zju.edu.cn (F.-Q. Hu).
[1] Present address: Women's Hospital School of Medicine, Zhejiang University, PR China.

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high pressure homogenization (Vannini et al., 2004). The high homognization pressures often resulted into the coalescence of particles (Mehnert and Mader, 2001). Moreover, the lipid might remain as supercooled melt for several months due to the small particle size and the presence of emulsifiers (Bunjes et al., 1998), the high emulsifiers concentration were also believed to produce burst drug release (Mühlen and Mehnert, 1998a).

In present study, the solvent diffusion method was employed as an alternative production method for NLC. This method was the first reported about the preparation of nanoparticles with synthetic polymers (Kawashima et al., 1998). Under this method, the nanoparticles can be obtained in mild conditions according to one step, being very easy, do not require any special equipment and also can achieved the sustained drug release (Hu et al., 2002, 2005), but the use of organic solvent and lack of large scale production were the main drawbacks for this method. To prepare NLC, monostearin (MS) was used as solid lipid, caprylic/capric triglycerides (CT) was chosen as the liquid lipid. The physicochemical properties of obtained NLC, such as drug loading capacity, stability in storage, in vitro release behavior and crystallinity, were investigated and compared with those of SLN.

2. Materials and methods

2.1. Materials

Monostearin (Shanghai Chemical Reagent Co. Ltd., China) was used as solid lipid material of NLC. Caprylic/capric triglycerides (Zhejiang Lanxi Wumei Chemical Industry Co. Ltd., China) were chosen as liquid lipid material for NLC. Clobetasol propionate was kindly donated by Hangzhou Huadong Pharmaceutical Co. Ltd., China. Polyvinyl alcohol (PVA 0486, Beijing Chemicals Co. Ltd., China) was used as a dispersant in water phase. Poloxamer 188 (Jiqi Pharmaceutical Industry of Shen Yang Pharmaceutical University Co. Ltd., China) and mannitol (Zhejiang Wenzhou Dongsheng Chemical Industry Reagent Co. Ltd., China) were chosen as cryoprotectants. The surfactant, sodium dodecyl sulfate was provided by Guangzhou Chemical Reagent Co. Ltd., China. Ethanol, acetone and other chemicals were analytical reagent grade.

2.2. Preparation of SLN and NLC

The NLC with or without drug were prepared by solvent diffusion method in an aqueous system reported in our previous study (Hu et al., 2002, 2005). Briefly, 228 mg mixture of CT and MS (CT–MS) with 12.5, 25 wt.% CT content, which were prepared by adding CT to MS, and 12 mg drug (clobetasol propionate, 5 wt.% compared to the total number of lipid and drug) were completely dissolved into a mixture of acetone (6 ml) and ethanol (6 ml) in water bath at 50 °C. The resultant organic solution was quickly dispersed into 120 ml of 0.2% PVA (w/v) aqueous solution, under mechanical agitate (DC-40, Hangzhou Electrical Engineering Instruments, China) with 400 rpm in water bath at 70 °C or ice bath at 0 °C for 5 min. The temperature of resulted dispersion was then returned to room temperature for about 60 min. The drug-free NLC dispersion was prepared exactly the same manner only replacing 12 mg drugs by CT–MS. For the case of SLN, only MS was used as lipid. The concentration of the resultant nanoparticles in dispersions was 0.5% (w/v).

The pH value of the above obtained SLN or NLC dispersion was adjusted to 1.20 by addition of 0.1 M hydrochloric acid to form aggregation of nanoparticles. The aggregate of nanoparticle dispersion was then centrifuged (25,000 rpm for 30 min, 3K30, Sigma, Germany) and received the SLN or NLC precipitate. The precipitate of SLN or NLC was collected for drug entrapment efficiency determination.

The SLN or NLC precipitate that produced at 0 and 70 °C was re-dispersed in distilled water or in the aqueous solution containing 0.3% poloxamer 188 (w/v) and 2% mannitol (w/v) (1.0% of lipid content, (w/v)), and the resultant dispersion was fast frozen under −75 °C in a deep-freezer (Sanyo Ultra Low Temperature Freezer MDF-192, Japan) for 5 h and then the sample was moved to the freeze-drier (Freezone 2.5L, LABCONCO, USA). The drying time was controlled in 72 h and then the SLN or NLC powders were collected for DSC, storage stability and in vitro release experiments.

2.3. Particle size and zeta potential measurement

The volume average diameter and zeta potential of drug-free or drug-loaded nanoparticles in dispersion with 0.1 mg/ml concentration were determined with Zetasizer (3000HS, Malvern Instruments, UK).

2.4. Drug entrapment efficiency determination

The precipitate of drug-loaded nanoparticles were dispersed in 80 ml of 1 wt.% sodium dodecyl sulfate solution and surged by vortexing (XW-80A, Instruments factory of Shanghai Medical University, China) for 3 min to dissolve the free drugs. The resulting dispersions were centrifuged for 20 min at 25,000 rpm (3K30, Sigma, Germany). The drug content in the supernatant after centrifugation was measured by HPLC method (Hu et al., 2002) using an Agilent G1310A pump (1100 Series) unit control, an Agilent G1314A Variable Wavelength Detector (1100 Series) set at 240 nm. An Hypersil C18 column (150 mm × 3.9 mm) was used. The mobile phase was consisted of methanol and water (74:26, (v/v)). The calibration curve of peak area against concentration of clobetasol propionate was $y = 39.191x + 18.1114$ under the concentration of clobetasol propionate 0.1–100 μg/ml ($R^2 = 0.9997$, where y = peak area and x = clobetasol propionate concentration), the limit of detection was 0.04 μg/ml.

The drug entrapment efficiency (E_e) and drug loading (L) of nanoparticles were calculated from Eqs. (1) and (2)

$$E_e = \frac{W_a - W_s}{W_a} \times 100\% \quad (1)$$

$$L = \frac{W_a - W_s}{W_a - W_s + W_L} \times 100\% \quad (2)$$

where W_a, W_s and W_L were the weight of drug added in system, analyzed weight of drug in supernatant and weight of lipid added in system, respectively.

2.5. Stability test of SLN and NLC

The storage stabilities of drug-loaded SLN and NLC with 25% CT content obtained at 0 °C were determined as follows. Briefly, a volume of 5 ml of nanoparticles dispersion with 2 mg/ml concentration were filled into glass vials, and stored at 25 and 4 °C in the dark for 1 month, the changes of particle size and zeta potential against storage time were investigated.

Additionally, lyophilized SLN and NLC with 25% CT content (drug-loaded) obtained at 0 °C were stored at 4 °C in the dark for 6 months. Before the measurement of particle size and zeta potential, the nanoparticles powders were re-dispersed in distilled water with 0.1 mg/ml concentration by vortexing (XW-80A, Instruments factory of Shanghai Medical University) for 3 min. The drug loading in the nanoparticles was determined by the method as described above.

2.6. DSC analysis

Differential scanning calorimetry (DSC) analysis was performed using Delta Series DSC7 (PE, USA). For DSC measurement, 10 mg of powdered drug-free nanoparticles were put in the aluminum pans. A scan rate of 10 °C/min was employed in the 10–80 °C temperature range.

2.7. In vitro release study

The drug release profiles from nanoparticles were measured in vitro 15 mg of powdered SLN or NLC (without cryoprotectants) were dispersed in 30 ml sodium dodecyl sulfate solution (1 wt.%) in 50 ml appropriate glass test-tube. The resulting samples were surged by vortexing (XW-80A, Instruments factory of Shanghai Medical University) for 3 min, and then shaken horizontally (SHELLAB1227-2E, SHELLAB, USA) at 37 °C and 60 strokes/min. One millilitre of the dispersion was withdrawn from the system at definite time interval and filtrated with 100 nm filter. The filtrate was determined by HPLC method as described above.

3. Results and discussion

3.1. Preparation of SLN and NLC by solvent diffusion method in an aqueous system

The SLN and NLC with different amounts of CT content were prepared by solvent diffusion method in an aqueous system. Volume average diameters, zeta potential and the polydispersity indexes of resulted SLN and NLC are listed in Table 1. It was found that the nanoparticles obtained at 0 °C exhibited bimodal particle size distribution (the polydispersity indexes were about 0.35), when the production temperature increased up to 70 °C, the mono-modal size distribution were obtained, and the polydispersity indexes decreased markedly ($P < 0.05$). However, the mean particle size affected by the production temperature was slight ($P > 0.05$). No special trend was found on particle size for the nanoparticles with different CT content. This was basically consistent with the result reported by Jores et al. The liquid lipid content did not influence the particle size of NLC as the liquid lipid content below 25 wt.% (Jores et al., 2004).

3.2. Storage stability of SLN and NLC

To assess the effect of the storage temperature on the stability, the SLN and NLC dispersion were stored at 4 and 25 °C in the dark over a period of 30 days. Fig. 1 shows the changes of particle size and zeta potential against storage time. For the case of 25 °C, the particle sizes of both NLC and SLN were increased significantly ($P < 0.001$, during the storage period (Fig. 1(A))). In contrast, the particle growth was slower ($P > 0.05$) when nanoparticles were stored at 4 °C. In addition, the visible flocculation of NLC and SLN (stored at 25 °C) was found at the 15th and 30th day, respectively. The high temperature (25 °C) increased the kinetic energy of system, which could accelerate the collision of particles (Freitas and Müller, 1998), and consequently increased the possibility of aggregation for nanoparticles. Moreover, from Fig. 1(A), it can be seen that the rate of particle growth for NLC was higher than that for SLN during storage period at 25 °C. This was probably due to the increased viscosity of NLC surface when higher amounts of liquid lipid was added to the formulation. Notice the zeta potential of SLN and NLC decreased during storage at 25 °C, especially for the case of NLC (Fig. 1(B)).

Table 1
Particle size, polydispersity index (PI) and zeta potential of drug-loaded monostearin SLN (0 wt.% CT) and NLC with 12.5 and 25 wt.% CT content

Temperature (°C)	Liquid lipid content (wt.% CT)	Volume average (nm)				PI	PI average	Zeta potential (mV)
		Area	Mean	Width	Average (nm)			
0	0	84.3, 15.7	468.2, 118.4	196.5, 66.9	413.3 ± 175.1[a]	0.346		−27.6 ± 3.8
	12.5	93.5, 6.5	414.2, 178.0	242.2, 65.6	398.8 ± 230.6[a]	0.353	0.369 ± 0.011[b]	−25.1 ± 4.2
	25	97.4, 2.6	409.4, 124.9	199.5, 64.2	402.0 ± 196.0[a]	0.369		−21.2 ± 2.9
70	0	100	360.7	273.4	360.7 ± 273.4[a]	0.071		−20.5 ± 2.8
	12.5	100	328.4	177.6	328.4 ± 177.6[a]	0.107	0.065 ± 0.045[b]	−20.7 ± 3.7
	25	100	374.2	122.9	374.2 ± 122.9[a]	0.017		−21.8 ± 1.9

[a] Indicates no significant difference ($P > 0.05$).
[b] Indicates significant difference ($P < 0.05$).

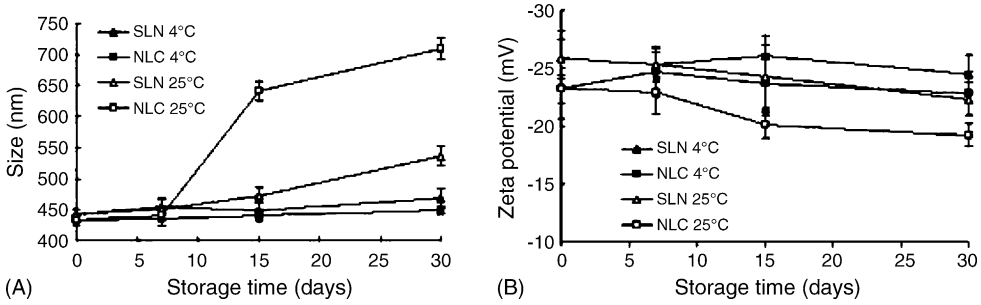

Fig. 1. The particle size (A) and zeta potential (B) of SLN and NLC (25% CT content) dispersion against storage time at 4 and 25 °C.

Due to the instabilities of the SLN and NLC dispersions, the freeze-dried SLN and NLC formulations were employed to improve the storage stability. Poloxamer 188 and mannitol were chosen as the cryoprotectants to decrease the aggregation of nanoparticles during the freeze-drying process. Based on the results of storage stability for SLN and NLC dispersion, the lyophilized nanoparticles were stored at 0 °C in the dark. Fig. 2 shows the particle size and zeta potential of nanoparticles against storage time. Even the lyophilized powders of SLN and NLC were stored for 6 months, the particle sizes only slightly increased ($P > 0.05$). For the case of NLC, the particle size increased from 528 to 558 nm ($P > 0.05$).

Table 2
Drug entrapment efficiency (EE) and drug loading (DL) of monostearin SLN (0 wt.% CT content) and NLC with 12.5 and 25 wt.% CT content

Temperature (°C)		Liquid lipid content (wt.% CT)		
		0	12.5	25
0	EE	45.15 ± 1.23[a]	60.12 ± 1.07[b]	67.17 ± 2.46[a,b]
	DL	2.26 ± 0.06	3.01 ± 0.05	3.35 ± 0.12
70	EE	52.71 ± 2.31[a]	59.24 ± 1.78[b]	69.61 ± 2.54[a,b]
	DL	2.63 ± 0.12	2.96 ± 0.09	3.48 ± 0.13

Data are represented with mean ± S.D. ($n = 3$).
[a] Indicates significant difference ($P < 0.05$).
[b] Indicates no significant difference ($P > 0.05$).

3.3. Drug entrapment efficiency and loading capacity

The effects of CT content and production temperature on drug entrapment efficiency and drug loading of SLN and NLC were investigated. The data of drug entrapment efficiency and drug loading of SLN and NLC prepared by 0 and 70 °C are given in Table 2. It is clear that the drug entrapment efficiencies and drug loadings of SLN and NLC were enhanced with increasing the content of CT ($P < 0.05$). It was reported that the incorporation of liquid lipid to solid lipid can lead to massive crystal order disturbance, and the resulting matrix of lipid particles indicates great imperfections in the crystal lattice and leaves enough space to accommodate drug molecules, thus leading to improved drug entrapment efficiency and drug loading capacity (Jenning et al., 2000a; Jenning and Gohla, 2001; Souto et al., 2004a).

Table 2 shows the influence of production temperature on drug entrapment efficiency and drug loading of SLN and NLC. For the case of SLN, higher production temperature (70 °C) induced higher drug loading capacity ($P < 0.05$), and the drug entrapment efficiency of SLN increased from 45.12% to 52.71%. On the other hand, the production temperature played a small role in NLC drug entrapment efficiency ($P > 0.05$).

These results could be explained by the degrees of crystallinity of nanoparticles. DSC was employed to study the crystallinity of nanoparticles. Fig. 3 shows the DSC curves of SLN and NLC. It can be seen that the melting point depressed with increasing of CT content. The difference between onset and melting point can be taken as a measure for the width of the peak (Jenning et al., 2000a). Table 3 shows the related data of peaks in Fig. 3. It is clear that the difference between onset and melting point of nanoparticles was increased with enhancing the CT content. This is an indicative for massive crystal order disturbance (lattice defects) of monostearin NLC (Jenning et al., 2000a), and formed less ordered modification of NLC. The less ordered modification could allow more space to accommodate drug molecules, thus leading to total drug loading capacity

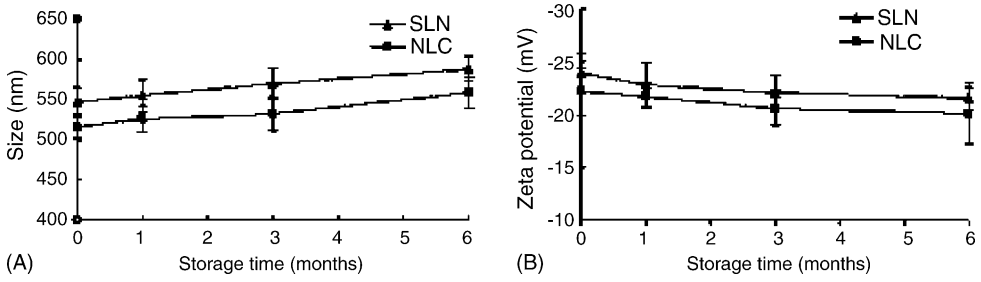

Fig. 2. The particle size (A) and zeta potential (B) of SLN and NLC (25% CT content) lyophilized powder (with 0.3% poloxamer 188 (w/v) and 2% mannitol (w/v) as cryoprotectants) against storage time at 4 °C.

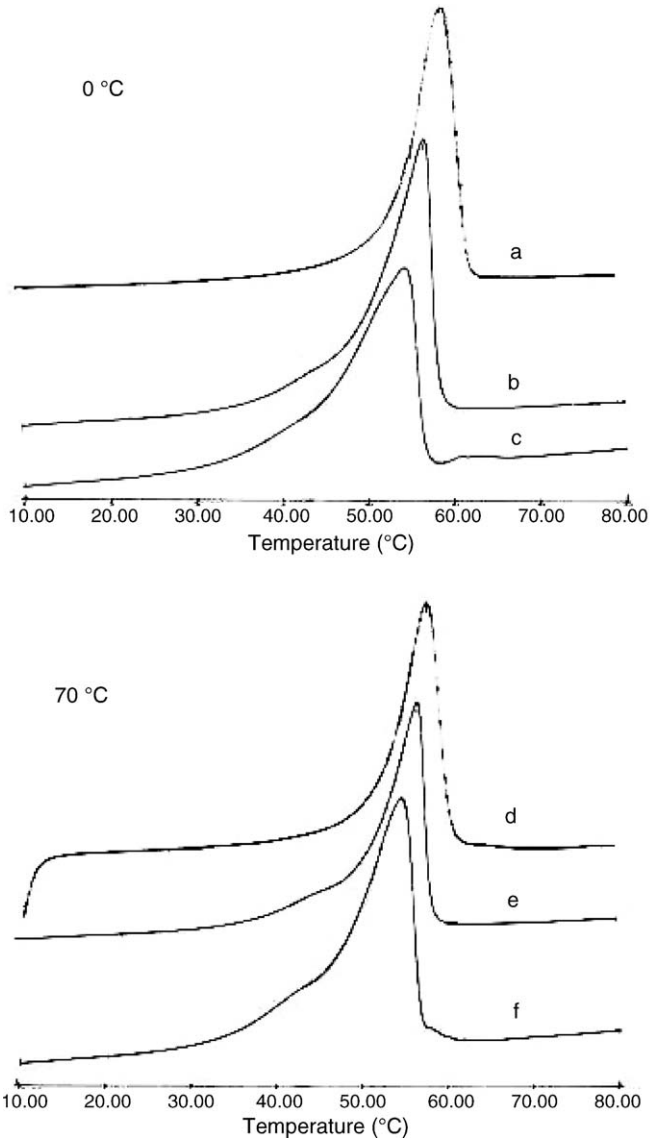

Fig. 3. Differential scanning calorimetry curves of drug-free monostearin SLN and NLC, nanoparticles prepared at 0 °C: (a) monostearin SLN (0 wt.% CT); (b) monostearin NLC with 12.5 wt.% CT content; (c) monostearin NLC with 25 wt.% CT content; nanoparticles prepared at 70 °C: (d) monostearin SLN (0 wt.% CT); (e) monostearin NLC with 12.5 wt.% CT content; (f) monostearin NLC with 25 wt.% CT content.

improvement. Moreover, it was interesting to notice that the difference between melting point and onset data of NLC obtained at 0 °C was higher than that of 70 °C. This was probably related with the different mixture behaviors of liquid lipid and solid lipid

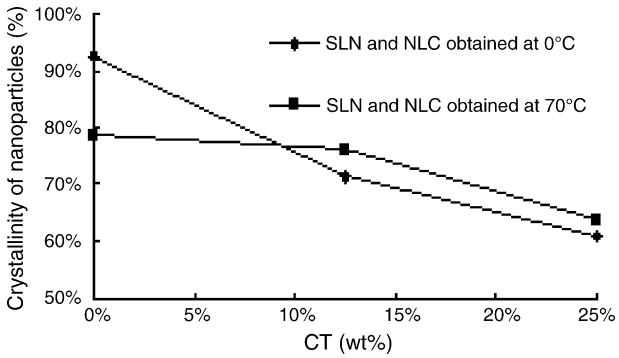

Fig. 4. The relationship between degree of crystallinity and caprylic/capric triglycerides (CT) content in monostearin SLN and NLC.

in nanoparticles produced at 70 or 0 °C, and will be discussed in Section 3.5.

Degrees of crystallinity of SLN and NLC were calculated from the ratio of SLN and NLC enthalpy to bulk lipid enthalpy (Mühlen et al., 1998b) and the enthalpies of SLN and NLC were calculated on the basis of total weight taken. Considering the enthalpy of bulk monostearin at 133.3 J/g as 100%, then the degrees of crystallinity of SLN and NLC were shown in Fig. 4. It revealed that SLN obtained at 70 °C had much lower degree of crystallinity than that of 0 °C (about 13.8% less), which meant higher imperfection in the crystal lattice of nanoparticles, and thus allowed more space for accommodating drug molecule. NLC with the same CT content, however, displayed smaller difference in degree of crystallinity between the two production temperatures that could be applied to support the similarity in their drug loading capacity. On the other hand, it is clear that the degree of crystallinity of nanoparticles decreased with increasing the CT content in nanoparticles. This result presented further evidence that the CT was the main reason for decreased crystallinity and increased less ordered modification of monostearin NLC.

3.4. Effect of storage time on the drug loading

Fig. 5 shows the relationships between drug loading and storage time of SLN and NLC. The NLC exhibited a good ability to reduce the drug expulsion during storage. After 6 months of storage, the drug loading of SLN was reduced from 2.27% to 1.24% ($P < 0.01$, about 45.37% drug was expulsed). In contrast, the drug loading of NLC only reduced about 7.65% under the same storage condition ($P > 0.05$). One disadvantage for SLN was crystallization of particles during storage, which could lead

Table 3
Melting parameters of monostearin SLN (0 wt.% CT content) and NLC with 12.5 and 25 wt.% caprylic/capric triglycerides (CT) content

Temperature (°C)	CT content (wt.% CT)	Onset (°C)	Melting point (°C)	Melting point − onset (°C)	Enthalpy (J/g)
0	0	56.1	62.3	6.2	123.3
	12.5	48.7	56.8	8.1	95.0
	25	42.3	54.0	11.7	81.4
70	0	53.0	59.1	6.1	104.9
	12.5	50.3	56.7	6.4	101.5
	25	45.7	54.3	8.6	84.8

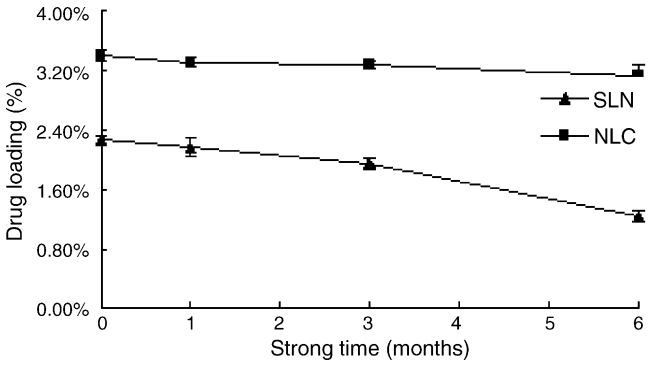

Fig. 5. The drug loading of SLN and NLC lyophilized powder (with 0.3% poloxamer 188 (w/v) and 2% mannitol (w/v) as cryoprotectants) against storage time at 4 °C.

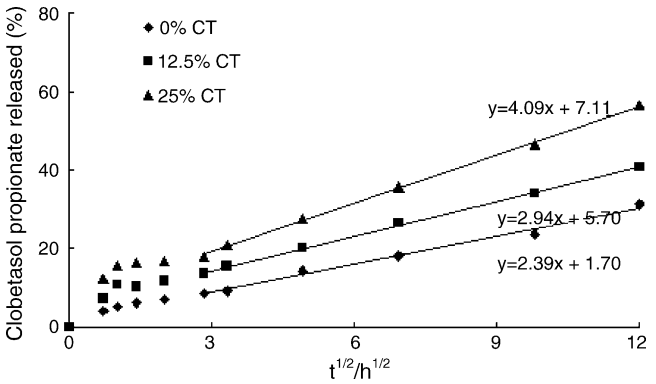

Fig. 7. In vitro release profile of clobetasol propionate from monostearin SLN (0 wt.% CT) and NLC with 12.5 and 25 wt.% CT content prepared at 0 °C ($n = 3$).

to the expulsion of drug. The incorporation of liquid lipid to solid lipid matrix, could increase the imperfection in crystal order of matrix and reduce the crystallization process in the storage, and thus improve the drug expulsion phenomenon (Müller et al., 2002a).

3.5. Drug in vitro release

The drug release profiles from the SLN and NLC prepared by the solvent diffusion method at 70 °C were shown in Fig. 6. For all formulations, a biphasic drug release pattern was observed. The relative burst drug release was found at the initial 8 h, the drug was then released slowly with a linear relationship for Higuchi plotting (the trend line equations were listed in Fig. 6). Obviously, at the initial 8 h, the drug release rate from nanoparticles was enhanced with increasing the CT content. After 8 h, the release profiles of three formulations were almost parallel, which indicated that CT gave little influence on drug release rate after initial 8 h.

This drug release patterns were probably related with the CT distribution in nanoparticles. As reported in our previous study, when solvent diffusion method at 70 °C was applied to produce NLC, liquid lipid was not homogenously distributed in nanoparticles matrix. Instead, most of liquid lipid was located at the shell of nanoparticles and left little or no liquid lipid entrapped into the core during the cool process from melted lipid droplet to solid nanoparticles (Hu et al., 2005). The liquid lipid enriched shell possessed soft and considerable higher solubility for lipophilic drugs character (Mühlen et al., 1996), in which the drug was easily loaded to higher amount, and the drug could be easily released as well by the drug diffusion or the matrix erosion manners. Therefore, the NLC obtained at 70 °C exhibited the burst release at the initial 8 h and sustained release subsequently.

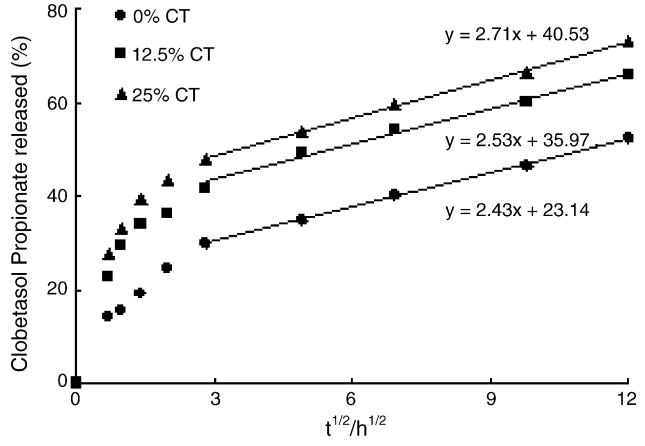

Fig. 6. In vitro release profile of clobetasol propionate from monostearin SLN (0 wt.% CT) and NLC with 12.5 and 25 wt.% CT content prepared at 70 °C ($n = 3$).

Fig. 7 gives the release curves of SLN and NLC obtained at 0 °C. Obviously, the ratio of drug burst release (at the initial 8 h) was reduced. After the initial 8 h, the drug release rate was slow and fitted to Higuchi equation (listed in Fig. 7) as well. But the most important result was that the drug release rate was still affected by the CT content after initial 8 h. As shown in Fig. 7, the slopes of three release profiles after the initial 8 h were enhanced with increasing the CT content, while those of nanoparticles obtained at 70 °C were almost parallel with each other (Fig. 6).

The NLC obtained by high pressure homogenization technique, the liquid lipid inside was homogenously distributed, and the drug release rate of NLC was affected by liquid lipid throughout the drug release time (Jenning et al., 2000a). Therefore, one possible explanation for release curves of NLC obtained at 0 °C was that the liquid lipid was homogenously distributed in NLC matrix when 0 °C production temperature was used to produce NLC. As described in this section, the difference between melting point and onset data of NLC obtained at 0 °C was higher than that of 70 °C (Table 3). This was probably related with the different distributed behaviors of liquid lipid and solid lipid in nanoparticles produced at 70 or 0 °C. Furthermore, the incorporation of liquid lipid into solid lipid matrix caused the NLC became more imperfect and allowed loaded drugs easier to release, thus increased the drug release rate when liquid lipid was included in NLC matrix. For the above reasons, it achieved to the results of sustained release and increased drug release rate (compared to SLN) of NLC obtained by solvent diffusion method at 0 °C.

4. Conclusion

A solvent diffusion method in aqueous system was successfully employed to prepare the monostearin NLC. Compared to SLN, the NLC showed improved drug loading capacity and a good ability to reduce the drug expulsion in storage. The NLC obtained by solvent diffusion method at 70 °C exhibited a biphasic release pattern with burst release at the initial 8 h and followed by sustained release fitted to Higuchi equation. The NLC obtained by solvent diffusion method at 0 °C, however, could reduce the ratio of drug burst release at the initial 8 h, and showed sustained drug release fitted to Higuchi equation as well after the initial 8 h. The drug release rates of NLC were enhanced with increasing the content of liquid lipid (CT). These results indicated that the NLC obtained in this study could potentially be exploited as a carrier with improved drug loading capacity and controlled drug release properties by controlling the production temperature of solvent diffusion method and liquid lipid content in nanoparticles.

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