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Development of solid dispersion lipid nanoparticles for improving skin delivery

Duong T.T. Pham [a], Phuong H.L. Tran [b], Thao T.D. Tran [c,d,*]

[a] Chung-Ang University, Seoul, Republic of Korea
[b] Deakin University, Geelong Australia, School of Medicine, Australia
[c] Department for Management of Science and Technology Development, Ton Duc Thang University, Ho Chi Minh City, Vietnam
[d] Faculty of Pharmacy, Ton Duc Thang University, Ho Chi Minh City, Vietnam

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ABSTRACT

Applications of poorly water-soluble drugs in skin delivery pose several challenges to pharmaceutical formulation. This research originally developed solid lipid nanoparticles (SLNs) packaging a modified core of a solid dispersion (SD) in the lipid matrix to modulate the skin release patterns. Curcumin (CUR) was selected as the poorly water-soluble drug applied in the formulation. The designed system, so-called solid dispersion lipid nanoparticles (SD-SLNs), was fabricated by incorporating a solidifying SD or a non-solidifying SD into the core of the SLNs by ultrasonication. Release studies illustrated an important enhancement in the drug release of the proposed system compared to pure CUR and SLN formulations without the presence of SD as the modified core, which indicated the positive effect of the combined colloidal method of SD and SLNs. The physicochemical properties of the SD-SLN systems were also elucidated using powder X-ray diffraction, Fourier transform infrared spectroscopy, and particle size analysis. The drug was found to change to an amorphous state without any molecular interactions along with a marked particle size reduction. This work demonstrated the strong potential of applying a novel SD-SLN system for the skin delivery of a drug with poor water solubility.

1. Introduction

The feasibility of administering a drug via a topical or transdermal route may incur several difficulties that may result in unwanted side effects (Choi and Maibach, 2005). Colloidal drug delivery systems have arisen as popular approaches that can overcome these obstacles, thereby enhancing the drug accumulation, absorption, and delivery to targeted sites (Dinh et al., 2017; Maia et al., 2000; Tran and Tran, 2019; Tuong et al., 2017).

Solid lipid nanoparticles (SLNs) have been recognized as alternative colloidal carriers that can substitute for conventional ones such as polymer nanoparticles, liposomes, nanoemulsions and microemulsions. SLNs possess noticeable advantages, including skin occlusion, modulation of drug/cosmetic release, increased skin hydration and elasticity, UV blocking effects, drug targeting, and enhanced stability of chemically labile drug/actives (Müller et al., 2002; Schäfer-Korting et al., 2007; Teeranachaideekul et al., 2007; Üner et al., 2005; Wissing et al., 2000; Wissing and Müller, 2003). The preparation technique of SLNs is also advantageous compared to that of other techniques, due to the absence of organic solvents, the use of basic equipment, and the ability of the manufacturing processes to be easily scaled up to large-scale production (Fricker et al., 2010). SLNs provide an increased surface area of drug particles in a compatible lipid matrix, which favours the drug's penetration into the skin in a controlled manner (Jenning et al., 2000; Le et al., 2019).

Another effective colloidal formulation that can be applied in skin delivery is a solid dispersion (SD), in which the drug is dispersed in inert carriers (Huang and Dai, 2014; Yousaf et al., 2019). An SD has the ability to reduce the dispersed particle size, convert the drug from the crystalline to the amorphous state, and augment its wetting capability, which greatly contribute to the solubility improvement of poorly water-soluble drugs (Moes et al., 2013; Yousaf et al., 2015).

* Corresponding author at: Ton Duc Thang University, Ho Chi Minh City, Vietnam.
E-mail address: trantruongdinhthao@tdt.edu.vn (T.T.D. Tran).
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In this study, we developed a dual system that combines SLNs and SD (SD-SLNs) to modulate the skin release patterns of poorly water-soluble drugs. Curcumin (CUR) was selected as the model drug due to its poor water solubility and well-known properties for potential applications in skin products (Tran et al., 2015). The low oral bioavailability due to poor aqueous solubility and extensive first pass metabolism of curcumin would be overcome by transdermal delivery (Patel et al., 2009). In addition, this route of administration showed the advantage of the drug sustained release pattern in the blood circulation rather than the oral and intravenous dosage forms (Ghanghoria et al., 2013). We hypothesized that the poorly water-soluble drugs entrapped in a solid lipid core may exhibit a very low drug permeability. The proposed system would be expected to overcome the existing limitations and enable highly efficient treatments. Specifically, the solid lipid matrix is more hydrophilic due to the incorporation of the SD in the solid lipid core of the SLN, leading to a high penetration of drug into the skin, which is further facilitated by the SLN carrier. The SLN plays a role of the nanoparticulate system that can carry the drug highly soluble in the SD. The highly specific surface area of the nano-sized SLNs facilitates the contact of drug with the stratum corneum and may favour accumulation for sustained drug release. Generally, the combination of these systems can facilitate the bioavailability enhancement of poorly water-soluble drugs through skin absorption and protects the drug molecules from degradation.

2. Materials and methods

2.1. Materials

Curcumin (98%, CUR) was provided by Merck KGaA (Germany). Sodium hydroxide (97%) was purchased from Guanghua Sci-Tech Company (China). Stearic acid (95%, SA) and Tween 80 (97%) were obtained from Guangzhou Jinhuada Chemical Reagent. The methanol used for the HPLC was purchased from Fisher Scientific International, Inc. (99.9%, US). Monopotassium phosphate (95%) was provided by Wako Pure Chemical Industries (Japan). Polyethylene glycol 6000 (95%, PEG 6000) was purchased from Sino-Japan Chemical Co., Ltd. (Taiwan). Liquid paraffin (97%) and ethanol absolute (100%) were purchased from XiLong Chemical (China). Isopropyl microstate (98%, IPM) was kindly supported from Korea United Pharma Company.

2.2. Methods

2.2.1. Preparation of CUR-loaded SLNs (CUR-SLNs)

The CUR and stearic acid (SA) were completely melted at 75 °C and then mixed with aqueous solutions containing Tween 80 on a digital stirring hot plate (Thermo Scientific™ Cimarec™, USA) at 12,000 rpm for 30 min. After agitation, the pre-emulsion was converted into a hot oil-in-water nanoemulsion using an ultrasonicator at 19 W for 5 min (Q700, Qsonica – USA). The mixture was cooled in an ice-water bath over 15 min to allow the formation of SLNs. The detailed formulations are shown in Table 1. The CUR-SLN samples were subjected to freeze-drying (EYLA, Tokyo, Japan) for physicochemical characterization.

2.2.2. Preparation of CUR SD-SLNs

A pre-determined amount of hydrophilic polymer (PEG 6000) was melted at 190 °C (Nguyen et al., 2015), and CUR was then incorporated into the melted polymer until a molten liquid (drug polymer ratios 1:2, 1:5 and 1:9, as presented in Table 1) was obtained. Two methods for embedding the system of the SD and SLNs were investigated. In method 1 (M1), the SD was cooled at room temperature for solidification prior to being dissolved in SA at 75 °C. In contrast, for method 2 (M2), a weighed amount of SA was immediately incorporated into the SD at the drug melting temperature without the SD solidification process. Then, the aqueous phase containing Tween 80 as a surfactant was kept above the solid lipid melting point before being emulsified into the lipid phase under continuous magnetic stirring (Thermo Scientific™ Cimarec™, USA) at 12,000 rpm for 30 min. The resulting binary mixtures were subjected to ultrasonication at 19 W for 5 min (Q700 sonicator – USA) and then cooled in an ice bath for 15 min and stored at room temperature.

Encapsulation efficiency and drug loading were determined according to a previous report (Cho et al., 2014). Briefly, a 100 μL aliquot of SLNs was mixed with 900 μL water. The mixture was then centrifuged to separate the undissolved components, and the drug from SLN was then extracted with methanol and analysed using the HPLC method.

2.2.3. Preparation of plain creams loaded with CUR-SLNs or CUR SD-SLNs

In the plain cream formulations, the oil phase containing beeswax (16.65%), liquid paraffin (41%), emulsifying wax (1%), and Span 80 (0.8%) were melted at 75 °C. The aqueous phase consisted of Tween 80 (7.5%) and distilled water (33%). The mixture of two phases was crushed continuously for 20–30 min by mortar and pestle until the temperature decreased to 45–50 °C. The successfully formed plain cream was exposed to gentle stirring until cool and uniform. The CUR-SLNs or CUR SD-SLNs were physically blended into the plain cream at a ratio of 1:1, with a concentration of 0.03% CUR by total weight.

2.2.4. Particle morphology and size analysis

The particle size and zeta potential of the SLNs were analysed by the Zetasizer Nano ZS (Malvern Instruments Ltd, UK). The samples were diluted to 1 mg/mL at 37 °C before analysis. In addition, scanning electron microscope (SEM – JEOL/EO, Japan) was used to characterize morphology of the particles.

2.2.5. In vitro release test

The *in vitro* release of the CUR cream and SLN cream were measured using Franz cells at 37 ± 0.5 °C. The receptor chamber volume was 20 mL. The cellulose acetate membrane (Sartorius Biolab Products Germany, 0.45 μm, D = 25 mm), used to fit between the donor and receptor compartments, was activated by drenching in IPM for 24 h prior to testing. The receptor medium

Table 1
Formulation compositions of CUR-SLNs and CUR SD-SLNs with different ratios of CUR to PEG 6000 (1:2, 1:5 and 1:9).

Formulation	SD-SLNs 1:2	SD-SLNs 1:5	SD-SLNs 1:9	SLNs
SA (g)	2.4	2.4	2.4	2.4
Tween 80 (g)	1.5	1.5	1.5	1.5
Distilled water (g)	26.1	26.1	26.1	26.1
CUR (g)	0.009	0.009	0.009	0.009
PEG 6000 (g)	0.018	0.045	0.081	0

consisting of 20 mL of an ethanol: distilled water (50:50 v/v) (Montenegro et al., 2012; Tiyaboonchai et al., 2007) mixture was continuously stirred by a digital stirring hot plate (Thermo Scientific™ Cimarec™, USA) at a speed of 7500 rpm. An amount of cream (0.4 g) was evenly spread on the membrane surface covering 0.5 mL of the receptor medium and was taken at predetermined time intervals of 30, 60, 90, 120, 150, and 180 min. The amount of CUR release was determined by high-performance liquid chromatography (HPLC) analysis.

2.2.6. HPLC analysis

The quantification of the CUR was conducted using an Ultimate 3000 HPLC (Thermoscientific, Inc., USA) with a Luna 5μ C18 analytical column (150 × 4.6 mm). The mobile phase consisted of methanol and water in a ratio of 80:20 with a flow rate of 1.2 mL/min and a detection wavelength of 425 nm. Then, 20 μL of each sample was injected into the HPLC system for analysis for 5 min.

2.2.7. Powder X-ray diffraction (PXRD)

PXRD patterns of the pure CUR, SLNs, SD-SLNs, and physical mixture (PM) were recorded using a Cu Kα X-ray generator with a 40 kV voltage and 50 mA of current and the D2 PHARSER diffractometer (Bruker, Germany). The scanning rate was 1 s/step in increments of 0.02° from 5° to 70° (diffraction angle 2θ), using a zero background sample holder.

2.2.8. Fourier transform infrared spectroscopy (FTIR)

Fourier transform infrared spectrophotometer (Model Excalibur Series UMA-500, Bio-Rad, USA) was employed to analyse the spectra of the pure CUR, SLNs, SD-SLNs, and PM. The KBr discs were prepared by mixing 1 mg of the sample with 200 mg KBr. The wavelength was scanned from 500 to 4000 cm^{-1} with a resolution of 2 cm^{-1}.

2.2.9. Statistical analysis

All experiments were analysed using SigmaPlot. The data were evaluated at least in triplicate as the mean value ± SD and analysed by a one-way analysis of variance (ANOVA). A P value of 0.05 was considered significant.

3. Results and discussion

3.1. Effect of SD-SLN preparation method on drug release

To fabricate the SD-SLNs, the SD must be included into the SLNs to form modified cores using a suitable manufacturing process. Thus, various factors that may affect the drug release including the temperature, solidification process and polymer content were investigated. The CUR dissolution profiles of the two methods. M1 and M2, applied to study the effect of SD solidification on the drug release from the SD-SLNs with drug to polymer ratios of 1:2 and 1:9 are illustrated in Figs. 1 and 2. The drug release from the SD-SLNs prepared by M1 was higher than that for M2 at both ratios ($p < 0.05$). Specifically, the drug releases of the SD-SLNs obtained from M1 at the ratios of 1:2 and 1:9 were approximately 28 μg and 25 μg, respectively, whereas in M2, they were 25 μg and 13 μg. Dissolution enhancement using SD principally depends on drug crystal modifications or drug-polymer molecular interactions (Nguyen et al., 2015; Tran et al., 2013, 2016). SD has the ability to alter the drug crystallinity to a lower energy state known as amorphous (Tran et al., 2010, 2009). However, the drug exhibits a thermodynamic instability in the amorphous state, leading to the tendency of recrystallization into a more stable form. The act of solubilizing the lipid phase containing SA under continuous magnetic stirring at the drug melting temperature causes a spontaneous recrystallization of the drug owing to the thermal, chemical and mechanical stresses applied. Moreover, it is interesting to note that the increasing amount of polymer in the formulation is accompanied by a lower drug release rate, which contradicts the dominant dissolution results of the drug in SD. Generally, a higher polymer content in the SD leads to a higher dissolution rate due to the better dispersion of the drug (Tran and Tran, 2013). Further development of the SD-SLN formulation to optimize the results of the CUR release by adjusting the drug to polymer ratio was conducted as follows.

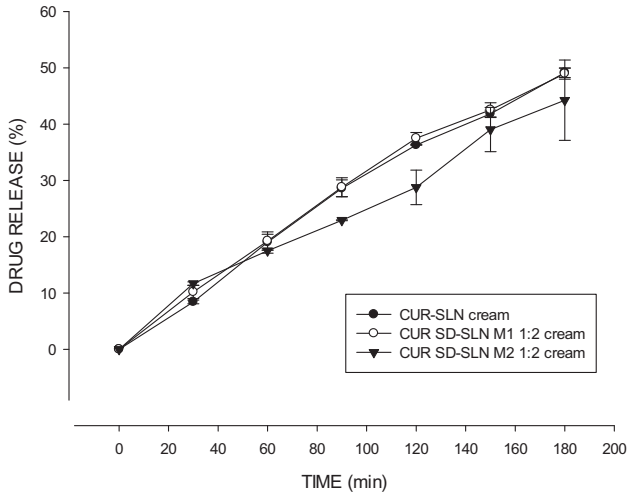

Fig. 1. Drug release profiles of CUR from SLN and SD-SLN cream prepared by M1 and M2 with a drug to polymer ratio of 1:2.

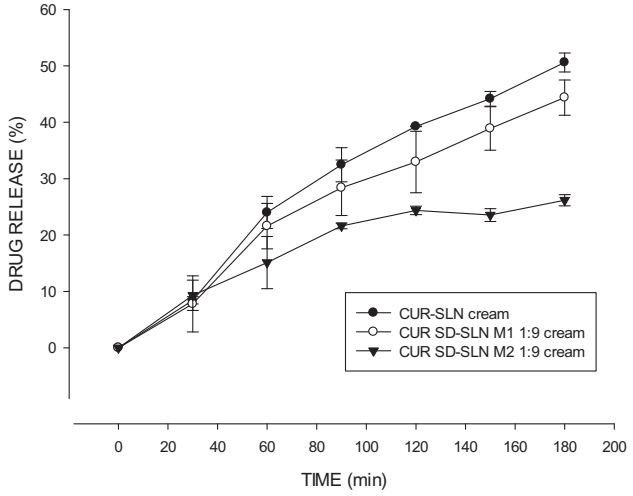

Fig. 2. Drug release profiles of CUR from SLN and SD-SLN creams prepared by M1 and M2 with a drug to polymer ratio of 1:9.

3.2. Effect of polymer-drug ratio in SD-SLNs on drug release

To achieve the best ratio between the drug and polymer for the drug dissolution improvement, the SDs were further prepared at a ratio of 1:5 by M1. Fig. 3 shows the drug release profiles of the SD-SLNs with ratios of 1:2, 1:5, and 1:9 compared to the SLN formulation and SD in cream (without encapsulation in SLN). After 180 min, the drug release rate from the CUR SD-SLN cream at the ratio of 1:5 was the highest ($p < 0.05$), while the slowest release was observed with the SD incorporation in cream. The amount of released CUR was approximately 25 μg, 30 μg and 37 μg after

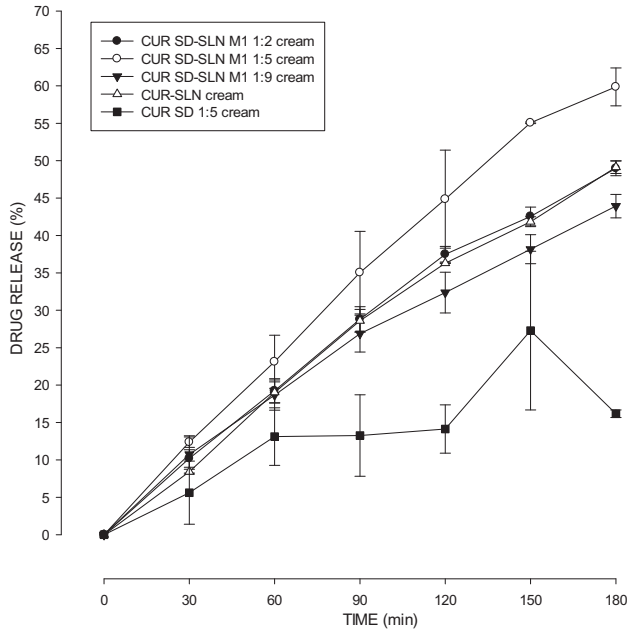

Fig. 3. Drug release profiles of CUR from SLN and SD-SLN creams by M1 with drug to polymer ratios of 1:9, 1:5, and 1:2.

180 min for the CUR SD-SLN cream at ratios of 1:9, 1:2 and 1:5, respectively. After the first 30 min, all three formulations showed similar amounts of CUR release. Then, whereas the drug release patterns from the CUR SLN and CUR SD-SLN creams at the ratio of 1:2 showed no significant difference, the CUR SD-SLN cream at the ratio of 1:9 displayed a significantly lower drug release. The varying content of PEG 6000 in the formulations was probably the critical factor in the SD-SLN fabrication that led to this drug dissolution performance. Because PEG is a hydrophilic polymer, the higher the concentration of PEG 6000 present in the vicinity of the drug particles, the higher the drug release rate from the SDs was. The drug particles were assumed to be covered by the PEG film, which could reduce the hydrophobicity of the drug surfaces, thereby improving the drug wettability. As a result, the increase in wettability due to the high content of the hydrophilic polymer could lead to an increased dissolution rate (Sekiguchi et al., 1964). Interestingly, SD-SLNs with a higher concentration of hydrophilic polymer resulted in a lower drug release, which is in accordance with a previous report of SD containing PEG 6000 and Tween 80 whereby Tween 80 may affect the dissolution rate by increasing PEG 6000 concentration (Modasiya and Patel, 2012). This phenomenon could be explained by the increased particle size.

First of all, it could be seen although all SLN and SD-SLNs had a similar morphology with spherical shape (see supplementary information), the formulation of SD-SLN M2 1:5 was more uniform than the others (Table 2). In addition, for method 1 (M1), Table 2 shows that an appropriate amount of PEG 6000 (at the ratio 1:5) could reduce the size of the SD-SLNs from 380 nm to 320 nm; whereas, a smaller amount and an excess amount of PEG (ratios of 1:2 and 1:9) increased the SD-SLN size from 380 nm to 539 nm and 476 nm, respectively. To compare method 1 (M1) and method 2 (M2), the particle size of CUR SD-SLN M2 was larger than that of M1 at the same ratio of PEG 6000. The ratio 1:9 having a size of 662 nm indicated that the larger size compared to M1 led to the lower drug release rate. In contrast, at the ratio of 1:2, the amount of polymer was considered to be insufficient for modulating the drug release patterns, so there was little dissolution improvement.

Concerning the surface charge of the SD-SLNs (Table 2), the encapsulation of the SD in the SLNs resulted in small changes in the zeta potential (approximately −21 to −31 mV), which is expected to affect the dissolution rate of the SLNs and SD-SLNs insignificantly. Further investigations were performed to explain the different release behaviours between the formulations and the mechanisms of drug release.

It is also noted that a higher amount of the polymer could enhance a little encapsulation efficiency and drug loading, while the preparation method did not affect encapsulation efficiency and drug loading significantly (Table 2).

3.3. Physicochemical characterizations

3.3.1. PXRD analysis

PXRD was performed on pure CUR, the physical mixture (PM), CUR-SLNs and SD-SLNs of CUR prepared by the different methods at various ratios (Fig. 4). The PXRD diffractogram of pure CUR exhibits numerous characteristic peaks, thus emphasizing its poor

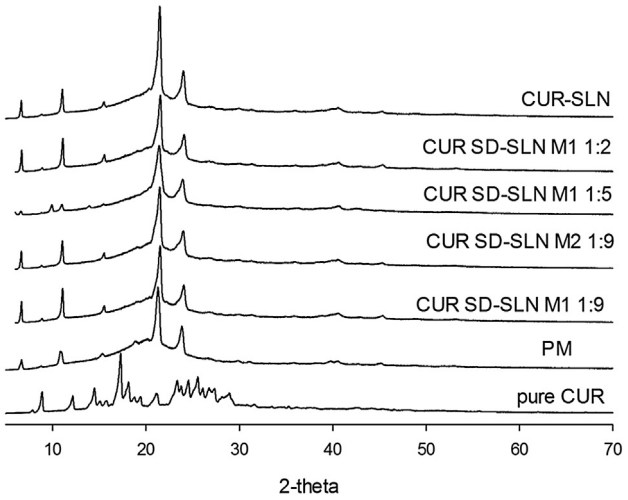

Fig. 4. PXRD patterns of pure CUR, SLNs, physical mixture (PM), SD-SLNs M1 1:2, SDSLs M1 1:5, SD-SLNs M1 1:9, and SD-SLNs M2 1:9.

Table 2
Average particle size and zeta potential of CUR SLN and SD-SLN formulations prepared by M1 and M2.

Formulation		SD-SLNs 1:2	SD-SLNs 1:5	SD-SLNs 1:9	SLNs
Particle size (nm)	Method 1 (M1)	539	320	476	380
	Method 2 (M2)	554.9	376.4	662	
Zeta potential (mV)	Method 1 (M1)	−29.6	−23.9	−26.6	−21.1
	Method 2 (M2)	−27.6	−23.3	−31.1	
Encapsulation efficiency (%)	Method 1 (M1)	64.22	69.50	72.62	78
	Method 2 (M2)	67.71	70.16	72.43	
Drug loading (%)	Method 1 (M1)	0.0193	0.0209	0.0218	0.0235
	Method 2 (M2)	0.0203	0.0210	0.0217	
Polydispersity index (PDI)	Method 1 (M1)	0.591	0.359	0.520	0.621
	Method 2 (M2)	0.651	0.623	0.630	

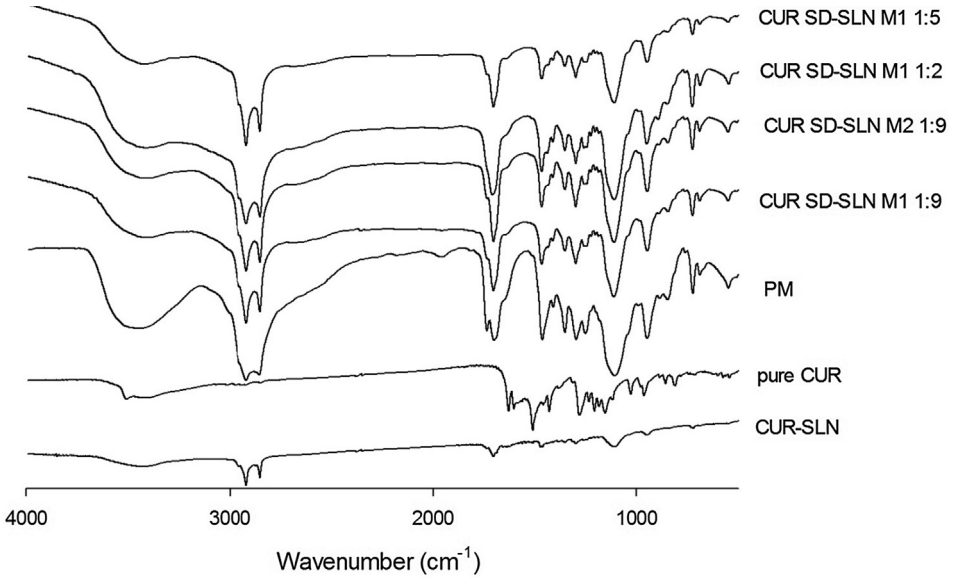

Fig. 5. FTIR of pure CUR, SLNs, physical mixture (PM), SD-SLNs M1 1:2, SD-SLNs M1 1:5, SD-SLNs M1 1:9, and SD-SLNs M2 1:9.

water solubility and confirming that CUR is a naturally crystalline drug. A comparison between the pure CUR and PM patterns indicates a significant reduction of the various characteristic peaks for the latter, which could be explained by the overlapping of the crystalline peaks of the pure drug and other ingredients. However, some distinct peaks of the drug were still observed at 8.75°, 15.1°, 21.1°, and 23.8°, proving the presence of the drug in the mixture. The diffractogram of the PM was extremely similar to those of both the CUR SLN and SD-SLN formulations. However, small peaks at the 9.8° and 14° positions existed in the pattern of the CUR SD-SLN cream prepared by M1 at the ratio of 1:5, which is remarkably different from the case of the other patterns. This may be attributed to the recrystallization of CUR during the SD-SLN preparation, which could convert the high-energy crystallinity of the pure drug into a lower-energy crystal. As a result, a higher drug release was obtained for the CUR SD-SLNs M1 1:5 compared to those of CUR SD-SLNs M1 1:2 and 1:9 and the CUR SLNs.

3.3.2. FTIR analysis

To support the mechanism elucidation of the drug release behaviours, Fig. 5 presents the FTIR spectra of the pure CUR, physical mixture (PM), CUR-SLN and CUR SD-SLNs formulations. The performance provides evidence of the change in molecular interactions between the therapeutic drug and other ingredients, which may lead to improved drug release. Li et al attributed the sharp band at approximately 3500 cm^{-1} and the broad peak centred at approximately 3300 cm^{-1} in the crystalline spectrum to phenolic (OH) stretching vibrations (Li et al., 2013). The presence of a strong band at 1626 cm^{-1} can be assigned to a predominantly mixed (C=C) and (C=O) character (Mohan et al., 2012). Moreover, the appearance of peaks at 714 cm^{-1} (Mohan et al., 2012) and 1450 cm^{-1} presented cis C-H and C=C out of plane vibrations and those of the aromatic ring, respectively (Wang et al., 2008; Yallapu et al., 2010). It was recognized that there was no significant difference among the spectra of the PM, SLN, and SD-SLN formulations. Therefore, the lack of molecular interaction between the drug and the other components could be the reason for the drug release enhancement.

4. Conclusions

This work successfully developed a novel method in which SD was incorporated into the core of SLNs for improving the CUR penetration into the skin for topical treatment. Two methods in the study that differed by a solidification step in the SD preparation revealed that the formation of CUR SD by the melting of the drug with PEG 6000 followed by cooling to room temperature before being embedded in the SLN system was the best method for enhancing the drug release rate. The polymer-drug ratio was also an important factor affecting the particle size of the SLN and the drug release rate. Elucidation of drug release mechanism using PXRD, FTIR, and particle size measurement showed the effectiveness of the established formulations in enhancing the skin absorption of CUR by altering the drug particle size and drug crystallinity without any molecular interaction changes. The study introduced a new technique by modifying the SLN structure using an SD formulation to combine the advantages of SD and SLNs to promote potential applications of poorly water-soluble drugs in skin products.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jsps.2019.08.004.

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