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Development of curcumin loaded nanostructured lipid carrier based thermosensitive *in situ* gel for dermal delivery

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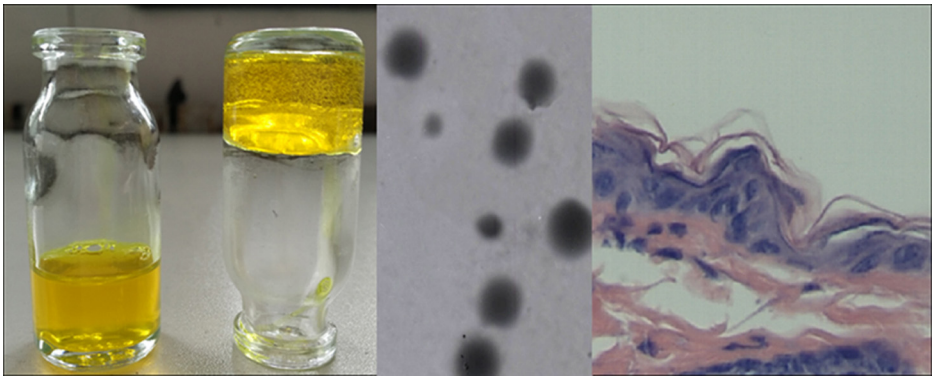
HIGHLIGHTS

- Novel Cur-NLCs and Cur-NLCs based thermosensitive *in situ* gel were prepared.
- Optimized Cur-LNCs had uniformly spherical shapes with a mean diameter of 263.9 nm.
- Cur-NLCs and the gel formulation showed the improved skin permeation *in vitro*.
- Cur-NLCs-Gel showed significant anti-inflammatory effect in auricle edemas mice.
- The permeation mechanism was researched by histopathology study.

GRAPHICAL ABSTRACT



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ABSTRACT

The objective of this research was to develop novel curcumin-loaded nanostructured lipid carriers (Cur-NLCs) and Cur-NLCs based thermo-sensitive *in situ* gel (Cur-NLCs-Gel) for topical delivery. Cur-NLCs were prepared using the method of emulsion evaporation- solidification at low temperature and optimized with orthogonal design. The permeation ability of Cur-LNCs and Cur-NLCs-Gel were characterized *in vitro*. The results showed that the optimized Cur-LNCs represented uniform nano-sized spherical shape with the mean diameter of 263.9 nm. The entrapment efficiency and drug loading were 91.76% and 2.19%, respectively. And there was no significant difference between Cur-NLCs-Gel and Cur-NLCs in morphology, entrapment efficiency and drug loading at the room temperature. The cumulative penetration amount of Cur-NLCs and Cur-NLCs-Gel *in vitro* were 3.02 times and 2.42 times than that of curcumin propylene glycol solution, respectively. Moreover, *in vivo* study demonstrated Cur-NLCs-Gel showed the significant anti-inflammatory effect in auricle edemas mice and no obvious irritation to the abdominal skin of rat. Histopathology study of skin showed that Cur-NLCs-Gel could weaken the barrier function of stratum corneum and enhance the permeation of drug into skin. All the evidence showed that NLCs-Gel could provide a promising tuning as a dermal delivery system of curcumin.

1. Introduction

Curcumin is a polyphenolic compound extracted from *curcuma* L. plants (such as turmeric, curcuma zedoary), which possesses a series of biological and pharmacological properties, such as anti-cancer [1], antioxidation [2] and anti-inflammatory [3] activities.

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These biological activities and pharmacological safety in large doses even at 12 g per day [4,5] make curcumin attractive to be used for disease treatment. However, curcumin has a poor bioavailability due to its low solubility and instability [6], which greatly limits its clinical application. The pharmacokinetic study of curcumin over past decades revealed that curcumin exhibited poor absorption, rapid metabolism and elimination [7]. The oral absorption rate of curcumin is only 25% of the administered dose [8], and little prototype drug is absorbed into blood due to the biotransformation of curcumin occurring in the course of intestinal absorption [9,10]. But curcumin shows good skin compatibility [11]. It can reduce inflammation and quench free radicals by inhibiting nuclear factor-kB to protect skin [11]. Besides, curcumin can enhance wound-healing through improving collagen deposition and increasing fibroblast and vascular growth.

Topical dermal delivery of curcumin to play its antioxidation or anti-inflammation role is very suitable, because the first pass metabolism can be avoided [12] and curcumin can be administrated directly to the target skin by topical dermal administration. However, as a main physiological barrier, stratum corneum restricts the absorption of foreign substances into body. To break the skin barrier, numerous methods have been developed, mainly including three classes as follows, chemical penetration enhancers, physical permeabilization (*e.g.* microneedles, sonophoresis, iontophoresis) and novel nanocarriers [13]. Nanostructured lipid carrier (NLC) is a novel drug delivery system based on solid lipid nanoparticles (SLN), which possesses higher drug loading and better stabilization than SLN [14]. Many studies have showed the potential of NLC for topical dermal application. For example, Khalil et al. [15] produced lutein loaded NLCs with a mean particle size in range of 200–250 nm. The *in vitro* penetration study demonstrated the preparation penetrated sufficiently deep but not entered blood circulation, so NLCs is suitable for dermal delivery. NLC can facilitate drug penetration through stratum corneum by breaking the skin barrier [16]. NLC can tightly adhere themselves to the skin surface, so the skin hydration degree can be improved and the lipid bilayers of SC become loose and fluidized. As a result, it makes skin delivery of drugs easier. Besides, since NLC has solubilization effect on insoluble drugs, the enhanced apparent solubility of the drugs can promote penetration by forming high concentration gradient on skin.

In this study, Cur-NLCs were prepared and their physicochemical properties were characterized. To make the preparation easy for administration, thermo-sensitive Cur-NLCs-Gel based on F127 was also developed, which will turn into a gel from a liquid form when applied to skin surface. The gelation temperature and *in vitro* penetration of Cur-NLCs-Gel were also investigated. The anti-inflammatory effect in auricle edemas mice and the irritation to the abnormal skin of rat *in vivo* were evaluated.

2. Material and methods

2.1. Materials

Curcumin (Cur) was purchased from Zhu'hai Fuxingyuan Food Industry Co. Ltd. (Zhu'hai, China). Glyceryl monostearate (GMS) was provided by Shanghai Chemical Reagents Co. Ltd. (Shanghai, China) and stearic acid (SA) by Beijing Chemical Reagents Co. Ltd. (Beijing, China). Caprylic/capric triglyceride (CT) was purchased from Tieling Beiya Medicinal Oil Co. (Tieling, China). Soya lecithin (including 65% phosphatidylcholine) was purchased from Shanghai Taiwei Medicine Co. Ltd. (Shanghai, China). Solutol HS 15 (polyethylene glycol monostearate) was obtained from BASF (Ludwigshafen, Germany) and Pluronic F127 was purchased from Sigma-Aldrich Chemical Co. (St. Louis, Missouri, USA). Methanol was of chromatographic grade. All other chemicals and solvents used in the study were of analytical reagent grade and available commercially.

2.2. Preparation of Cur-NLCs and Cur-NLCs-Gel

Cur-NLCs were prepared by the method of emulsion evaporation-solidification at low temperature according to previous reports [17–19]. In brief, curcumin and lipids were dissolved in chloroform/acetone (1:1) to form organic phase. The surfactant-dissolved water constituted the aqueous phase. After the two phases were heated to 70 °C, the oil phase was poured into aqueous phase (1:2, v/v) under mechanical stirring. Subsequently, the mixed system was stirred for 3 h at 70 °C to ensure the absolute evaporation of the organic solvent. After that, the resulting mixture was rapidly dispersed in ice water (1:2, v/v), stirred for 2 h at 800 rpm and centrifuged at 1500 rpm for 10 min to remove unencapsulated solid curcumin. The supernatant was homogeneous NLCs dispersion. Cur-NLCs-Gel was prepared by dissolving a certain amount of F127 in the NLCs suspension.

2.3. Drug encapsulation efficiency (EE) and drug loading (DL)

Based on previous reports [20,21], mini column centrifugation technique was used to separate free drug and prepared NLCs. The mini column was prepared by barreling well swelled Sephadex G-50 into 5 mL syringe. Briefly, 0.5 mL Cur-NLCs suspension was placed in the mini column and centrifuged at 500 rpm for 1 min. The column was subsequently eluted with 0.5 mL distilled water for six times under the same condition. Then, defined amount of methanol was added to the collected eluents containing drug-loaded NLCs to break their structure and completely dissolve the encapsulated curcumin. The curcumin dissolved in the solution was measured using an ultraviolet-visible spectrophotometer (UV-2102, Shanghai Instrument Ltd., China) at a wavelength of 425 nm. EE and DL of Cur-NLCs were calculated according to the following equations:

$$EE(\%) = \frac{W_{\text{entrapped}}}{W_{\text{total}}} \times 100\%$$

$$DL(\%) = \frac{W_{\text{entrapped}}}{W_{\text{NLCs}}} \times 100\%$$

In above equations, $W_{entrapped}$ was the amount of curcumin entrapped in Cur-NLCs, W_{total} presented the total amount of curcumin in Cur-NLCs, and W_{NLCs} showed the weight of QT-NLCs.

2.4. Morphology

The morphology of Cur-NLCs and Cur-NLCs-Gel was evaluated by using transmission electron microscope (TEM, JEM-1200EX, JEOL, Tokyo, Japan). Simply, samples were dropped onto a film-coated copper grid and then stained with 2% (w/v) phosphotungstic acid for 20 s. After staining finished, the phosphotungstic acid was wiped off by filer paper and the samples were examined after natural drying.

2.5. Particle size, zeta potential and pH value

Particle size and Zeta potential of the Cur-NLCs and Cur-NLCs-Gel were measured by a DelsaTM Nano C Particle Analyzer (Beckman Coulter. Inc., USA). The pH values were evaluated at 25 °C using a pH S-25 digital acidimeter (Shanghai Rex Instrument Factory, Shanghai, China).