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Influence of state and crystallinity of lipid matrix on physicochemical properties and permeation of capsaicin-loaded lipid nanoparticles for topical delivery

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ABSTRACT

The purpose of this study was to evaluate the influence of crystallinity and state of lipid matrix on the physicochemical properties and *in vitro* skin permeation of capsaicin-loaded lipid nanoparticles. Capsaicin-loaded SLN were prepared from Dynasan 116 and Softisan 378 and their physicochemical properties were investigated and compared with a nanoemulsion prepared from Miglyol 812. The mean particle sizes of all lipid nanoparticles were in the range of 160–340 nm with the PDI between 0.10 and 0.25. From DSC data, capsaicin was dissolved or molecularly dispersed in lipid matrix of nanoparticles and Dynasan 116 SLN was in the crystalline state whereas Softisan 378 SLN remained in supercooled melts. The occlusion factor was influenced by crystallinity and state of lipid matrix. The physical stability of capsaicin-loaded SLN and NE hydrogel strongly depended on storage temperature and emulsifiers. The percentage of capsaicin after stored for 6 months was in the range of 90–110%, regardless of studies storage temperature. The *in vitro* skin permeation revealed that the amount of capsaicin permeated through epidermis related to the state of lipid matrix and crystallinity. The solid state with high crystallinity and occlusion factor provided the greater skin permeation whereas the supercooled melts behaved like the nanoemulsions.

1. Introduction

Capsaicin is an active compound found in chilli peppers which are plants belonging to the genus *Capsicum* family. It is abundant in a placental region of chilli where the seeds are attached. For topical application, the physicochemical properties of drugs are almost important for skin penetration. Regarding the physicochemical properties of capsaicin, it is considerably suitable for skin delivery because it has a molecular weight (MW) of 305.42 g/mol, a melting point between 62 °C and 65 °C, partition coefficient (Log P) of 3.6 and the topological polar surface area of approximately 58.6 A^2. In practical, it has been widely used in many topical formulations, e.g. cream, gel, and ointment to help relieve pain in diabetic neuropathy which is common complication found in diabetic patients with poor control. The concentration of capsaicin in topical formulations is ranging between 0.025% and 0.1% by weight [1] which can be sold without the requirement of a prescription. It is intended for daily skin application about 3–5 times per day for a period of 2–6 weeks. Recently, a high-concentration 8% capsaicin transdermal patch (Qutenza™) have been approved in the EU for the management of peripheral neuropathic pain in non-diabetic neuropathy patients and in the US for management of neuropathic pain associated with post-herpetic neuralgia (PHN) [2]. A single 60-min application can be used to manage pain relief for up to 12 weeks. However, the use of such transdermal formulation should be under the supervision of a health care professional. The major drawbacks for topical administration of capsaicin have been reported including burning or itching sensation, poor patient compliance and cross contamination to the environment (e.g. clothing) [2] which may limit the use of topical capsaicin.

Lipid nanoparticles such as solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) are a novel colloidal delivery

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system for cosmetic and pharmaceutical products [3–7]. SLN and NLC are, in general, prepared from physiological and well-tolerated lipids which are generally recognized as safe (GRAS) status [4,8]. Several advantages of SLN and NLC have been reported such as increase in skin hydration [9], modulation of drug release [10], enhancement of drug penetration [11], improvement of the chemical stability of sensitive compounds [12,13], potential to drug targeting [14–17], reduction of system uptake and skin irritation [18,19], etc. In previous studies, encapsulation of irritating drugs into SLN or NLC could reduce skin irritation, e.g. isotretinoin [20], celecoxib [21], capsaicin [18] and adapalene [19,22]. Raza et al. [18] successfully incorporated capsaicin into NLC which were prepared by microemulsification technique. Capsaicin-loaded stearic acid NLC showed good physicochemical properties in term of particle size (~290 nm), size distribution (~0.2), zeta potential (−22 mV), and drug entrapment efficiency (~70%). In addition, skin irritation was found to be minimized when evaluated by a radiant mouse tail-flick model.

Typically, types of lipids and production techniques have mainly an impact on the properties of SLN, e.g. encapsulation efficiency, release pattern, encapsulation model and crystallinity [23] which influence the performance of SLN for topical application. Therefore, selection of the suitable solid lipids may lead to the higher entrapment and higher skin penetration of capsaicin in SLN matrix. Thereby, the direct contact between capsaicin and skin surface would be reduced and skin irritation should be minimized.

The aim of this present study was to investigate an effect of three different triacylglycerols matrices on the properties of the lipid nanoparticles containing capsaicin, in terms of particle size, size distribution and drug entrapment efficiency (E.E.). The *in vitro* occlusion factor was also evaluated by means of the de Vringer method. Furthermore, the developed capsaicin-loaded SLN and NE were incorporated in hydrogels to obtain a desired topical application. The long-term physical and chemical stability of capsaicin-loaded SLN and NE hydrogels was evaluated. The *in vitro* skin permeation on human skin was performed in order to compare their delivery through the excised human skin.

2. Materials and methods

2.1. Materials

Capsaicin natural (65% capsaicin) was purchased from Sigma-Aldrich (Steinheim, Germany). Tripalmitin (Dynasan®116) was supplied by Hüls AG (Witten, Germany). Caprylic/Capric/Myristic/Stearic Triglyceride (Softisan® 378) was purchased from Sasol (Marl, Germany). Miglyol 812 was received from Beiersdorf (Hamburg, Germany). Poloxamer 188 was acquired from BASF (Ludwigshafen, Germany). Tween 80 was obtained from Uniqema (Everberg, Belgium). Xanthan gum was purchased from Sigma-Aldrich (Deisenhofen, Germany). Sterile water for injection was used throughout experiments from Thai Nakorn Patana (Nonthaburi, Thailand). All other solvents were of HPLC grade.

2.2. Method

2.2.1. Preparation of capsaicin-loaded SLN dispersions

The capsaicin-loaded SLN dispersions were produced using the hot high pressure homogenization technique as described in the literature [8,23]. Briefly, capsaicin was dispersed in the lipid and melted to approximately 5 °C above its melting point until the clear solution was obtained. Subsequently, it was dispersed in a hot aqueous surfactant (75–80 °C) and emulsified using an Ultra-turrax T25 (Janke & Kunkel GmbH, Staufen, Germany) stirred at 9000 rpm for 1 min. The obtained pre-emulsion was formed and further homogenized at 85 °C by high pressure homogenizer (HPH) for 3 cycles at 500 bar using an EmulsiFlex-C3 homogenizer (Avestin, Canada). The lipid dispersion was cooled down to room temperature under ambient condition. In the case of the nanoemulsion, it was produced in the same manner as the SLN dispersions. However, the solid lipid was replaced by Miglyol 812. In this experiment, SLN of 10% of capsaicin based on the lipid content were prepared with various solid lipids as given in Table 1.

2.2.2. Particle size analysis

The mean particle size was analyzed using dynamic light scattering (DLS) with a Malvern Zetasizer Nano ZS (Malvern Instrument, Malvern, UK). The hydrodynamic diameter (z-ave) was measured, and polydispersity index (PDI), a measurement of the width of the particle size distribution, was obtained. The PDI values of below 0.25 indicate a monodisperse or narrow distribution. Prior to the analysis, all samples were diluted with sterile water for injection to obtain a suitable concentration as noted by attenuation values.

2.2.3. Zeta potential analysis

The zeta potential [24] is a measure of the electric charge at the surface of the particles which indicates the physical stability of colloidal systems. Theoretically, the ZP values of higher than |30 mV| indicate electrostatic long-term stability of colloidal dispersion [23]. In this study, the ZP values were assessed by determining the particle electrophoretic mobility using the Malvern Zetasizer Nano ZS (Malvern Instruments, UK). The sample was diluted with sterile water for injection adjusted to a conductivity of 50 μS/cm with sodium chloride solution (0.9% w/v) in order to avoid changes in ZP values due to day-to-day variations. The ZP values were calculated using the Helmholtz-Smoluchowsky equation.

2.2.4. Scanning electron microscopy (SEM)

To evaluate the particle morphology of lipid nanoparticles, e.g. shape and surface structure, scanning electron microscopy (SEM) was applied. The samples were analyzed using the scanning electron microscope equipped with a field emission, a JSM 6301F (JEOL, Japan) after coating the samples with gold using a Gold coater JFC 1200 fine coater (JEOL, Japan). Prior to analysis, the samples were diluted with sterile water for injection, dropped on the amorphous carbon grid, and then air-dried at room temperature. The samples were kept in desiccators until the measurement.

2.2.5. Thermal analysis

To evaluate the degree of crystallinity and polymorphism of bulk lipids and SLN dispersions, differential scanning calorimetry (DSC) was performed using a Mettler Toledo STAR^e system. The test samples were accurately weighed between 2 and 5 mg related to lipid content into aluminum pans and hermetically sealed with an aluminum cap. The samples were heated from 20 °C to 85 °C and cooled down from 85 °C to 20 °C. The heating/cooling rate was set at 5 °C/min by flushing with nitrogen at the rate of 80 ml/min. The

Table 1
The composition of capsaicin-loaded SLN and NE dispersions.

Composition	Dynasan 116 SLN	Softisan 378 SLN	Miglyol 812 NE
Dynasan 116	9.0	–	–
Softisan 378	–	9.0	–
Miglyol 812	–	–	9.0
Capsaicin	1.0	1.0	1.0
Tween 80	2.0	–	2.0
Poloxamer 188		2.5	
Water q.s.	100.0	100.0	100.0