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Original Research Paper

Development of a topical ointment of betamethasone dipropionate loaded nanostructured lipid carrier

Xin Kong, Yuan Zhao, Peng Quan, Liang Fang *

Department of Pharmaceutical Sciences, Shenyang Pharmaceutical University, 103 Wenhua Road, Shenyang 110016, China

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ABSTRACT

The purpose of this study was to design an innovative topical ointment containing betamethasone dipropionate loaded nanostructured lipid carrier (BD-NLC) for the treatment of atopic dermatitis (AD). BD-loaded NLC was produced with precirol ATO 5 and oleic oil (OA) by melt emulsification method. Effects of surfactant concentration, amount of solid lipid and liquid lipid on skin retention and skin penetration were investigated by *in vitro* percutaneous permeation experiment. The optimized BD-NLC showed a homogeneous particle size of 169.1 nm (with PI = 0.195), negatively charged surface (–23.4 mV) and high encapsulation efficiency (85%). Particle morphology assessed by TEM revealed a spherical shape. *In vitro* skin permeation study was carried out to investigate the percutaneous behaviors of W/O ointment with BD-NLC and Carbopol emulgel ointment with BD-NLC. W/O ointment with BD-NLC showed high skin retention (35.43 μg/g) and low penetration (0.87 μg/ml). *In vitro* drug release studies were carried out to demonstrate the drug releasing properties of the two ointments. W/O ointment with BD-NLC showed an advantage for skin retention as it was better for drug release. The tissue distribution test suggested that BD distribution was skin > muscle > blood. Self-made topical ointment in mice showed no skin irritation. The animal experiments indicated that BD-loaded NLC ointment was effective and safe for topical use.

1. Introduction

The nature of skin, especially the bulk of stratum corneum (SC) is the main physical barrier of transdermal drug delivery system (TDDS) [1]. The approaches to enhance drug permeation include chemical techniques based on chemical penetration enhancers (CPEs) [2], and physical techniques such as ultrasound [3], iontophoresis [4], and microneedles [5,6]. CPEs can enhance skin permeability of drugs. Though CPEs are commonly used in enhancing drug penetration, they are limited by safety concerns, such as skin irritation [7]. The overall effectiveness of

* *Corresponding author.* Shenyang Pharmaceutical University, No. 103 Wenhua Road, Shenyang 110016, China. Tel.: +86 24 23986330; fax: +86 24 23986330.
E-mail address: fangliang2003@yahoo.com (L. Fang).
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physical strategies is as strong as that of CPEs, but their inconvenient use and high cost limit their use. Recently, lipid nanoparticles have been introduced into topical application to improve skin drug delivery. Many researches have been conducted on this novel strategy, indicating remarkable results [8–10].

Nanostructured lipid carrier (NLC) is new generation of lipid nanoparticles, which is an aqueous colloidal dispersion composed of blended solid lipids and liquid lipids (oils) [11]. It was recognized as a promising drug carrier system for topical application because of its improving skin penetration properties [12]. The applications of NLC in the treatments of skin diseases such as skin dermatitis, psoriasis and inflammations were reported in the literature [12,13]. For TDDS, molecular properties of active compound are crucial for transdermal potential. For example, when the molecular weight is >500 Da, it is considered that the drug cannot go through skin. So far, the mechanism of the improved skin penetration of NLC is not yet clear. Compared with other vehicles such as creams, tinctures, and emulsions, NLCs possess such advantages as controlled drug release, protection of active compounds and negligible skin irritation. Moreover, the small particle sizes ensure that the nanoparticles are in close contact with the stratum corneum (SC), thus promoting the amount of active compound which penetrates into the skin [11]. Lipid nanoparticles used as a carrier system for topical delivery of several drugs including clotrimazole, prednicarbate, betamethasone 17-valerate and podophyllotoxin were investigated and they were reported to have a skin targeting potential [14,15].

Atopic dermatitis (AD) is a kind of skin dermatitis. Topical glucocorticoids are recommended for acute exacerbations of atopic dermatitis [16]. Betamethasone Dipropionate (BD), a kind of glucocorticoid, is mainly used for the treatment of AD [17,18]. As we know, glucocorticoids can bring many side effects. Normally, short-term treatment, and reducing the amount of drug are recommended in the clinic [17]. Hence, it is necessary to improve the drug skin retention and reduce the penetrating amount into systemic circulation in topical application, which will decrease the risk of a systemic side effect.

In the present study, NLC was investigated as a drug delivery system for BD. Particle size, zeta potential, morphology and the entrapment efficiency of NLC dispersions were characterized. It would be convenient for topical use when NLC dispersions are combined with ointment. Therefore, W/O ointment and Carbopol emulgel ointment were prepared as topical ointment matrix, respectively. Meanwhile, *in vitro* drug release studies were carried out to demonstrate drug release properties of the two ointments. Tissue distribution experiment in mice was conducted finally to evaluate the skin retention effect for reducing the penetration amount into systemic circulation. Skin irritation test was carried out to demonstrate whether NLC could reduce the risk of skin irritation.

2. Materials and methods

2.1. Chemistry and materials

Betamethasone Dipropionate (BD) (purity >99%) was provided by Wuhan Dahua Pharmaccutical Co., Ltd. (Wuhan, China). Oleic oil (OA), Tween 80, Span 80, liquid paraffin and stearyl alcohol were obtained by Tianjin Bodi Chemical Co., Ltd. (Tianjin, China). Carbopol 971 was from Lubrizol Co. Ltd. (Ohio, USA). White vaseline, iso-propyl alcohol and isopropyl palmitate (IPP) were provided by Shandong Damao Chemical Reagent Factory (Shandong, China), Shandong Yuwang Industrial Co., Ltd. (Shandong, China), and International Specialty Products Inc. (New Jersey, USA), respectively. Transparent cellophane membrane and sephadex G-50 were from Shangyu cellophane Co., Ltd. (Zhejiang, China) and Pharmacia & Upjohn Company (New Jersey, United States), respectively. Precirol ATO 5 was a generous gift from Gattefossé (Lyon, France). All other chemicals used were of analytical grade and commercially available.

2.2. Animals

Rabbits (male, 1.5–2.0 kg) and KM mice (male, 20 ± 2.0 g) used in the experiments were purchased from the Experimental Animal Center of Shenyang Pharmaceutical University (Shenyang, China). The experiments were performed in accordance with the guidelines for animal use published by the Life Science Research Center of Shenyang Pharmaceutical University.

2.3. Preparation and characterization of BD loaded NLC

2.3.1. Preparation of BD loaded NLC

BD-loaded NLC was produced using melt emulsification combined with ultra-sonication technique as reported previously [19]. In brief, Precirol ATO 5 and OA (3% in total, w/v) were blended under gentle stirring in water bath at 85 °C to form the lipid phase. Successively, BD (0.05%, w/v) was added in the lipid phase until completely dissolved. Meanwhile, Tween 80 was dissolved into distilled water corresponding to 10 ml at 85 °C and added dropwise to the lipid phase, with moderate magnetic stirring for 7 minutes. The coarse emulsion was further subjected to an ultrasonication procedure through a probe-type sonicator (Scientz-II D, NingBoXinZhi, Ningbo, China) for 72 s under 400 W ultrasonic output power to reduce the particle sizes of emulsions to nano range. The obtained nanoemulsions were cooled down in an ice-water bath to form the NLC rapidly. The total volume of BD-NLC suspensions were supplemented by adding distilled water to 10 ml.

2.3.2. Characterization of the NLC dispersion

Mean particle size (Z-average), dispersity index (PI) and zeta potential of BD-NLC suspensions were determined by photon correlation spectroscopy (PCS) (Malvern Nanosizer ZS90, Worcestershire, UK) for characterizing the width of distribution and the stability of the product under 25 °C. For particle size and PI detection, the PCS was performed at a detection angle 90 °C. Before the detection, each sample was diluted 100 folds with distilled water. Each value was measured in triplicate.

The shape and surface morphology of BD loaded NLC was observed by transmission electron microscopy (TEM, JEM-1200EX, Tokyo, Japan). A drop of NLC suspensions diluted 5 folds was dispersed on a 200-mesh copper grid. After the excessive water was removed with filter paper, the sample was negatively stained with 2.5% phosphotungstic acid for 4 min for observing.