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Nanostructured lipid carrier (NLC) based gel of celecoxib

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Abstract

Nanostructured lipid carriers (NLC) based topical gel of celecoxib was formulated for the treatment of inflammation and allied conditions. NLC prepared by the microemulsion template technique were characterized by photon correlation spectroscopy for size and scanning electron micrograph (SEM) studies. Drug encapsulation efficiency was determined using Nanosep® centrifugal device. The nanoparticulate dispersion was suitably gelled and assessed for *in vitro* release and *in vitro* skin permeation using rat skin. Efficacy of the NLC gel was established using a pharmacodynamic study, i.e., aerosil-induced rat paw edema model. The skin permeation and rat paw edema pharmacodynamic studies were carried out in comparison with a micellar gel which had the same composition as that of the NLC gel except for the solid lipid and oil. The NLC based gel described in this study showed faster onset and elicited prolonged activity until 24 h.

Keywords: Celecoxib; Nanosturctured lipid carriers (NLC); Topical gels; Micellar; Anti-inflammatory; Prolonged action

1. Introduction

In the last decade, solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) have been looked upon as promising carriers for presenting several attractive features for transdermal drug delivery. SLN are identical to an oil-in-water emulsion, except that the liquid lipid (oil) portion of the emulsion is replaced by a solid lipid having a mean photon correlation diameter (PCS) ranging between 80 and 1000 nm (Müller et al., 2000a). SLN are particles made from solid lipids or lipid blends and are produced by one of the following techniques, namely, high pressure homogenization (Müller and Lucks, 1996), microemulsion template technique (Gasco, 1993), solvent emulsification evaporation technique (Sjöström and Bergenståhl, 1992), solvent displacement technique (Hu et al., 2002; Schubert and Müller-Goymann, 2003), solvent emulsification diffusion method (Trotta et al., 2003; Quintanar-Guerrero et al., 2005), phase inversion (Heurtault et al., 2002) and a very recently introduced membrane contractor technique (Charcosset et al., 2005; Ahmed El-Harati et al., 2006). NLC, the new generation of lipid nanoparticles, overcome the limitations associated with the SLN, namely, limited drug loading, risk of gelation and drug leakage during storage caused by lipid polymorphism (Müller et al., 2000b). NLC consists of a mixture of spacially very different lipid molecules, i.e., solid lipid(s) is blended with liquid lipid(s) (oils) (Müller et al., 2004). The resulting matrix of the lipid particles shows a melting point depression compared to the original solid lipid; however, the matrix remains solid at body temperature (Müller et al., 2002a).

Both SLN and NLC possess numerous features that are advantageous for topical route of application (Müller et al., 2000c, 2002a,b; Mehnert and Mäder, 2001). SLN and NLC are colloidal carrier systems providing controlled release profiles for many substances (Müller et al., 1995; Zur Muhlen et al., 1998; Souto et al., 2004; Souto and Müller, 2005). These carriers are composed of physiological and biodegradable lipids exhibiting low systemic toxicity and low cytotoxicity (Müller et al., 1997). Most of the used lipids have an approved status or are excipients used in commercially available topical cosmetic or pharmaceutical preparations. The small size of the lipid particles ensures close contact to stratum corneum and can increase the amount of drug penetrating into mucosa or skin. Due to their solid lipid matrix, a controlled release from these carriers is possible. This becomes an important tool when it is necessary to supply the drug over prolonged period of time, to reduce systemic absorption, and when drug produces irritation in high concentrations. As a result of film formation after topical application, occlusive

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properties have also been reported for SLN (Wissing and Müller, 2001, 2002a,b).

Celecoxib (CXB), a selective COX-2 inhibitor, has been approved for the treatment of rheumatoid arthritis, osteoarthritis, acute pain, familial adenomatous polyposis and primary dysmenorrhea (Krishnan et al., 2003; Marshall, 1999; Simon et al., 1998). An arthritic condition demands a controlled release drug delivery system for a prolonged period so that can satisfy the goals of the treatment like reduction of pain and inflammation, maintenance of functional ability, slowing of disease progression and prevention of adverse effects of drugs. Moreover, topical formulations of COX-2 inhibitors are being developed as a novel pharmacologic approach for the treatment of COX-2 mediated skin diseases like inflammation, pain and nociception, skin tumors, injury and wounds (Lee et al., 2003). The development of a novel delivery system for a particular drug for topical application is complex due to the wide diversity of the drug solubility in the vehicle components and the vast range in cutaneous fluxes. In the majority of the pharmaceutical formulations intended for topical and dermatological therapy, the drug molecules are totally dissolved in a liquid phase of oil-in-water (o/w) or water-in-oil (w/o) emulsions. However, due to the low viscosity of the inner phase of the afore-mentioned systems, it is difficult to achieve a prolonged or controlled release of a model drug (Siekmann and Westesen, 1998). The need of the hour is design of a topical drug delivery system of CXB that could not only increase the presence of the drug locally and for a prolonged period, but also reduce the risk of systemic toxicity as a result of the reduced dose. SLN and NLC have been shown to exhibit a controlled release behavior for various active ingredients such as ascorbyl palmitate (Üner et al., 2005), clotrimazole (Souto et al., 2004), ketoconazole (Souto et al., 2005), suncreens (Müller et al., 2002a,b) and other antifungal agents (Souto and Müller, 2006).

Hence, in the present investigation, the feasibility of NLC as a novel carrier system for topical application of CXB, with regard to the modulation of the release of CXB, was checked. The role played by the oily phase component of the NLC was also judged by comparing the *in vitro* release, permeation, and *in vitro* pharmacodynamic activity with a micellar gel. The micellar gel was prepared using the excipients as that in the NLC gel, except the solid lipid and the oil. NLC were prepared from microemulsion templates and the procedure is as described in our previous publication (Joshi and Patravale, 2006).

The developed topical gel could also have implications in chemoprevention of skin cancer as the topical application of COX-2 inhibitors is known to inhibit ultraviolet-B (UVB) mediated cutaneous inflammation. Various topical drug delivery systems have been suggested for the same (Subramanian et al., 2005; Yener et al., 2003).

2. Materials and methods

2.1. Materials

Celecoxib (CXB) was obtained as a gift from Cadila Pharmaceuticals Ltd., Ahmedabad, India; Emulsynt Glyceryl dilaurate (GDL) was a kind gift from ISP through Anshul Agencies, Mumbai, India; Capmul MCM (glyceryl mono-dicaprylate) from Abitech Corporation through Indchem International, Mumbai, India; Capryol 90 (propylene glycol monocaprylate, containing 90% monoesters), Gelucires (glycerol esters of saturated fatty esters), Apifil pastils (PEG-8 Beeswax), Transcutol (purified diethylene glycol monoethyl ether), Labrasol (caprylocaproyl macrogol-8 glycerides) from Gattefosse France through Colorcon Asia Pvt. Ltd., Mumbai, India; Cremophor RH 40 (PEG 35 Castor oil), Solutol HS 15 (poly-oxyethylene esters of 12-hydroxystearic acid) from BASF India Ltd., Mumbai, India; Glyceryl monostearate from Fine Organics Pvt. Ltd., Mumbai, India; Miglyol 812 (caprylic/capric triglyceride) and Softigen 767 (PEG-6 caprylic/capric glycerides) from Sasol GmBH through S. Zhaveri and Co., Mumbai, India. While PEG 400, Tween 20, Tween 80 were purchased from SD Fine Chemicals, Mumbai, India. The gelling agent Carbopol Ultrez 10 was obtained as a gift sample from Noveon, India. All the other chemicals were of the analytical grade.

2.2. Screening of components (solubility studies)

The solubility of CXB was determined in different solid lipids, oils, surfactants and solubilizers (Shen and Zhong, 2006). An excess of drug was added individually to oil, surfactant and solubilizer (5 ml each) in screw capped tubes. After 24 h, each sample was centrifuged and 0.5 ml of the clear supernatant layer was diluted suitably with methanol, and analyzed by high performance liquid chromatography (HPLC). One of the most important factors that determines the loading capacity of the drug in the lipid is the solubility of drug in melted lipid. However, equilibrium solubility studies can not be carried out in this case. Hence, we used a modified method (Joshi and Patravale, 2006) to identify the solid lipid having better solubilization potential for CXB. For studying the solubility in solid lipids, 100 mg of the CXB was taken in a test tube, the solid lipid was added in increments of 0.5 g, and the test tube was heated in a controlled temperature water bath kept at 80 °C. The amount of lipid required to solubilize the CXB

Table 1
Solubility of celecoxib in different oils, surfactants and solubilizers

	Solubility
Oils (mg/g)	
Miglyol 812	10.73 ± 2
Capmul MCM	53.02 ± 5
Capryol 90	84.23 ± 8
Surfactants (mg/g)	
Tween 20	307.38 ± 30
Tween 80	381.12 ± 40
Labrasol	397.91 ± 40
Cremophor RH 40	239.74 ± 20
Softigen 767	378.73 ± 30
Solutol HS 15	404.33 ± 40
Solubilizers (mg/ml)	
PEG 400	301.66 ± 30
Transcutol	554.16 ± 50