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International Journal of Pharmaceutics 298 (2005) 55–67
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Preparation and characterisation of liposomes encapsulating ketoprofen–cyclodextrin complexes for transdermal drug delivery

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Received 4 November 2004; received in revised form 21 March 2005; accepted 25 March 2005
Available online 6 June 2005

Abstract

Multilamellar vesicle (MLV) liposomes containing ketoprofen–cyclodextrin complexes intended for drug topical delivery were prepared, with the aim of simultaneously exploiting the favourable properties of both carriers. Drug complexes with β-cyclodextrin (βCyd) and hydroxypropyl-βCyd (HPβCyd), prepared by coevaporation and sealed-heating methods, were characterised by differential scanning calorimetry, hot stage microscopy, scanning electron microscopy and tested for dissolution properties. The coevaporated system with HPβCyd was the most effective, enabling an about 11-fold increase in drug dissolution. Drug and drug-Cyd systems were incorporated in MLV liposomes prepared by the thin layer evaporation technique. All liposomal formulations were characterised for encapsulation efficiency, particle size and morphology, using dialysis, light scattering and transmission electron microscopy techniques, respectively. MLV formation was negatively influenced by the presence of Cyd; nevertheless, it was possible to prepare stable MLVs containing ketoprofen-Cyd complexes. The presence of the Cyd complex affected MLV dimensions but not their lamellar structure. The complex with HPβCyd, in virtue of its greater stability than the βCyd one, allowed higher percentages of encapsulation and gave rise to more stable MLV systems. Permeability studies of drug and drug-Cyd complexes, as such or incorporated in liposomes, performed both across artificial membranes and rat skin, highlighted a favourable effect of Cyd on drug permeation rate, due to its solubilizing action; by contrast, unexpectedly, no skin-permeation enhancer property of liposomes has been evidenced. Confocal laser scanning microscopy studies carried out with the rhodamine-Cyd complex as fluorescent marker, confirmed such results, showing that the label permeated deeper across rat skin layers when it was in solution than when entrapped in liposomes.

Keywords: Ketoprofen; Cyclodextrins; Liposomes; Skin permeation studies

1. Introduction

Ketoprofen is a non-steroidal anti-inflammatory drug, scarcely soluble in water, which is widely used

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doi:10.1016/j.ijpharm.2005.03.033

as analgesic and for the acute and long-term treatment of rheumatoid arthritis and osteoarthritis. Its short elimination half-life and adverse effects, like gastrointestinal mucosa ulceration, restrict its oral use and make it a good candidate for transdermal administration (Cordero et al., 1997, 2001; Hadgraft et al., 2000). However, due to the excellent barrier function of the skin, the need to use safe and effective enhancers for improving transdermal absorption of drugs is well recognized (Irion et al., 1995; Sinh et al., 1996; Cho and Choi, 1998; Sridevi and Diwan, 2002).

Liposomes have been widely used as safe and effective vehicles for topical drug delivery systems since, in spite of the controversial literature about possible vehicle-mediated phenomena of skin uptake (Alvarez-RománNaik et al., 2004), in several cases they allowed effective drug penetration and enhanced clinical efficacy (Gregoriadis, 2000; Verma et al., 2003a,b). However, the entrapment of poorly water soluble drugs in the lipid bilayers of liposomal membranes is often limited in terms of drug-to-lipid mass ratio and requires the use of organic solvents (McCormack and Gregoriadis, 1994; Gregoriadis, 2000). Furthermore, the carrier functions of liposomes through the skin layers often cannot actually be achieved for lipophilic drugs that, when incorporated in the membrane bilayers rather than entrapped in the aqueous core of the vesicles, are rapidly released from the carriers after administration (Takino et al., 1994).

Cyclodextrins have been widely used to improve solubility and dissolution rate of a number of lipophilic drugs by inclusion complexation in their hydrophobic cavity (Uekama and Otagiri, 1987). The role of cyclodextrins as possible enhancers of percutaneous absorption of drugs has also been investigated (Loftsson et al., 1998; Loftsson and Masson, 2001). It seems that cyclodextrins may improve dermal absorption of drugs mainly by increasing their thermodynamic activity in the vehicles, and favouring their delivery to the skin surface (Loftsson et al., 1998; Matsuda and Arima, 1999; Masson et al., 1999), whereas no carrier functions of cyclodextrins across the skin layers have been clearly demonstrated.

Recently, the entrapment into the aqueous phase of liposomes of lipophilic drugs in the form of water-soluble cyclodextrin inclusion complexes has been proposed as a possible approach for circumventing the problems associated with both systems and combines their relative advantages in a single system. This concept establishes a novel system in drug delivery, by joining liposomes and cyclodextrin complexes of lipophilic drugs and forming drugs-in-cyclodextrins-in-liposomes formulations. (McCormack and Gregoriadis, 1994, 1998; Loukas et al., 1995, 1998).

Therefore, the aim of this work was to prepare liposomes, intended for topical drug delivery, containing ketoprofen–cyclodextrin complexes in the aqueous core, with the purpose of increasing both drug encapsulation stability into the vesicles and its clinical efficacy, by simultaneously exploiting the cyclodextrin solubilizing power towards the drug and the liposome carrier function through the skin layers.

The effectiveness of cyclodextrins in improving solubility and dissolution rate of ketoprofen has already been demonstrated (Funk et al., 1993; Mura et al., 1998). In the present paper, in order to select the most effective cyclodextrin and preparation method for ketoprofen complexation, drug-cyclodextrin complexes with both natural β-cyclodextrin and its hydroxypropyl derivative, prepared by coevaporation and sealed-heating methods, were investigated by differential scanning calorimetry, hot stage microscopy, scanning electron microscopy and tested for dissolution properties. Drug alone and selected drug-cyclodextrin complexes were then incorporated in liposomes prepared by the thin layer evaporation technique. All liposomal formulations were characterised for encapsulation efficiency, particle size and morphology, using, respectively, dialysis, light scattering and Transmission electron microscopy techniques. Permeability properties of these systems were evaluated through both excised rat skin and artificial lipophilic membranes. The liposomal membrane structure and integrity as well as the capacity of the vesicles to penetrate into the rat skin were investigated by confocal laser scanning microscopy using liposomes encapsulating a cyclodextrin complex with rhodamine 6G as fluorescent marker.

2. Materials and methods

2.1. Materials

Ketoprofen (keto), l-α-phosphatidylcholine (PC), cholesterol (CH) and rhodamine 6G (Rho) were provided by Sigma-Aldrich (Italy), β-cyclodextrin (βCyd)