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ORIGINAL ARTICLE

Penetration enhancers in proniosomes as a new strategy for enhanced transdermal drug delivery

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Penetration enhancer

Abstract The aim of this work is to investigate penetration enhancers in proniosomes as a transdermal delivery system for nisoldipine. This was performed with the goal of optimising the composition of proniosomes as transdermal drug delivery systems. Plain proniosomes comprising sorbitan monostearate, cholesterol, ethanol and a small quantity of water were initially prepared. Subsequently, proniosomes containing lecithin or skin penetration enhancers were prepared and evaluated for transdermal delivery of nisoldipine. The plain proniosomes significantly enhanced the transdermal flux of nisoldipine to reach 12.18 μg cm^{-2} h^{-1} compared with a saturated aqueous drug solution which delivered the drug at a rate of 0.46 μg cm^{-2} h^{-1}. Incorporation of lecithin into such proniosomes increased the drug flux to reach a value of 28.51 μg cm^{-2} h^{-1}. This increase can be attributed to the penetration enhancing effect of lecithin fatty acid components. Replacing lecithin oleic acid (OA) produced proniosomes of comparable efficacy to the lecithin containing system. The transdermal drug flux increased further after incorporation of propylene glycol into the OA based proniosomes. Similarly, incorporation of isopropyl myristate into plain proniosomes increased drug flux. The study introduced enhanced proniosomes as a promising transdermal delivery carrier and highlighted the role of penetration enhancing mechanisms in enhanced proniosomal skin delivery. The study opened the way for another line of optimisation of niosome proconcentrates.

1. Introduction

The strategy of using lipid vesicles to improve drug delivery to and across the skin has gained interest. These vesicles included traditional liposomes (Mezei and Gulasekharam, 1980), transfersomes (ultradeformable vesicles), and ethosomes (Cevc and Blume, 1992; Touitou et al., 2000; El Maghraby et al., 2001). However, most of liposomes were reported to have stability problem and high cost. The stability problems of liposomes are in the form of loss of entrapped drug, change in the size upon storage as well as chemical degradation of the lipid components (Sharma and Sharma, 1997). Accordingly, niosomes

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which are surfactant based vesicles that are more stable (chemically) and less expensive than liposomes were introduced (Schreier and Bouwstra, 1994; Manosroi et al., 2008). However, although niosomes exhibit more chemical stability during storage, there may be a physical stability problem upon storage of niosome dispersion. Proniosomes were prepared as dry powder for reconstitution before use as a means of preserving the chemical and physical integrity of vesicles (Hu and Rhodes, 2000). For the transdermal delivery purpose proniosomes were prepared as gel like concentrated niosomes suitable for topical application (El Maghraby and Williams, 2009). These gel like structures have the advantage of being suitable for scaling up while maintaining the skin penetration enhancing abilities and better physicochemical stability. However, the published data on proniosomes are rare and are not systematic with many factors requiring further investigation. These factors include the effect of composition and the possibility of incorporating traditional skin penetration enhancers into proniosomes.

Accordingly, the main aim of this study is to investigate the effect of incorporation of skin penetration enhancers in proniosomes on the transdermal delivering ability of this system. To achieve this objective, nisoldipine a second-generation dihydropyridine calcium antagonist was selected as the test drug. This selection was based on the fact that the drug suffers from low and variable bioavailability after oral administration. This low bioavailability was attributed to the extensive first pass metabolism (Zannad, 1995; El Maghraby and Elsergany, 2014). This together with its high potency made the drug an excellent candidate for transdermal delivery. The physicochemical properties of nisoldipine were also considered in the selection of the drug candidate for this study. Nisoldipine has a molecular weight of 388.4 Daltons and is highly lipophilic as indicated from its high partition coefficient (log $P = 3.63$) (Marinkovic et al., 2003; El Maghraby and Elsergany, 2014). The molecular weight (below 500 Daltons) and lipophilicity provided nisoldipine with high potential for transdermal delivery. The lipophilic nature of the drug is another advantage for the current study due to expected high entrapment efficiency in proniosomes and other vesicular systems (El Maghraby et al., 2001). The study will thus provide dual functions as it will add a new factor in optimised transdermal delivery from provesicular systems and develop a method for enhanced nisoldipine transdermal delivery.

2. Materials and methods

2.1. Materials

Sorbitan monostearate (Span 60), cholesterol and lecithin were purchased from Sigma Chemical Co. (St. Louis, MO, USA). Nisoldipine was purchased from Jinan Jianfeng Chemical Co. Ltd., China. Methanol, acetonitrile (HPLC – grade) and propylene glycol were obtained from BDH, England. Ethanol (96%) and oleic acid were from El-Nasr Pharmaceutical Chemicals Company, Egypt. Isopropyl myristate (IPM) was a gift from Sigma for Pharmaceutical Industries, Egypt.

2.2. Preparation of proniosomes

Table 1 presents the composition of the tested proniosome formulations. The surfactant mixture (Span 60 – cholesterol), the drug, ethanol and penetration enhancer (if any) were mixed and heated to 65 + 1 °C for 5 min in a stoppered vessel. This provided a clear liquid system. The aqueous phase was added and the mixture was warmed upto clarity. The mixture was allowed to cool down by continuous mixing at room temperature till the formation of a proniosome gel (Vora et al., 1998).

2.3. Determination of entrapment efficiency

To determine the entrapment efficiency of the drug into proniosomes, the formulation was hydrated to develop the corresponding niosome. This was achieved by hydrating the proniosome gel (1 g) using 10 ml distilled water with the aid of mechanical stirring for 30 min. The resulting niosomes were subjected to 30 min of bath sonication. Immediately after hydration of proniosomes, the niosome dispersion was incubated in a dialysis sac (Cellulose tubing, cut off 12,000 Daltons, Sigma diagnostics, St. Louis, MO, USA) and dialysed against 100 ml of 40% v/v ethanol in water for 4 h. This dialysis fluid was selected to ensure sink conditions. The amount of the drug found in the dialysate was taken as a measure of the free drug. The entrapment efficiency was calculated by the following equation (Trotta et al., 2002; Foco et al., 2005; Maestrelli et al., 2005):

$$\text{Entrapment efficiency}(\%) = [(C_t - C_f)/C_t] \times 100.$$

where C_t is the total concentration of the drug and C_f is the concentration of the free drug.

2.4. Viscosity measurements

The flow behaviour and viscosity of the tested formulations were determined using a DV III rotating Brookfield viscometer using spindle RV-3 (Brookfield Engineering Laboratories Inc., Stoughton, MA, USA).

2.5. Determination of drug release

Drug release from vesicles is temperature dependent, generally being greatest around the phase transition temperature of the lipid (Papahadjopoulos et al., 1973). According to our experimental conditions the skin surface was maintained at 32 °C. Accordingly, the drug release studies were conducted at 32 °C to give a chance for correlation between drug release and skin permeation data.

The release study employed the vertical glass Franz diffusion cells which have a diffusional surface area of 2.27 cm^2 with the receptor compartment of 14.5 ml volume. The dialysis membrane (Cellulose tubing, Sigma diagnostics, St. Louis, MO, USA) was soaked in distilled water overnight before cutting into suitable pieces. This soaking was conducted to ensure complete swelling of the membrane to provide a constant pore diameter throughout the experiment. The membrane was then mounted between the donor and receptor compartments before filling the receptor compartment with 40% v/v ethanol in water. This receptor fluid was selected to maintain sink conditions which was confirmed by recording linear release profiles which did not tail off (see the results). The diffusion cells were incubated into a thermostatically controlled water bath with its temperature being adjusted to maintain the temperature of the membrane surface at 32 + 1 °C to mimic