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Skin delivery of nisoldipine from niosome proconcentrate

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ABSTRACT

Nisoldipine is used for treatment of hypertension and angina pectoris. However, it suffers from very low bioavailability due to its extensive pre-systemic metabolism. This together with its low dose made it excellent candidate for transdermal delivery. Accordingly, the aim of this study was to develop and evaluate transdermal delivery system for optimization of nisoldipine skin permeability. Proniosomes comprising cholesterol and span 60 with different ratios together with ethanol and minimal water were evaluated for such aim. The developed formulations were assessed with respect to drug entrapment efficiency, viscosity, in vitro drug release and transdermal permeability. All proniosomal formulations have significantly enhanced transdermal delivery of nisoldipine compared with saturated aqueous solution of the drug. Increasing cholesterol content resulted in reduced drug flux. The study was extended to compare the efficacy of such proniosomes to the corresponding niosomes. Proniosomes significantly optimized transdermal delivery of nisoldipine compared to their hydrated form. Such results contradict the hypothesis which claimed the necessity for niosome formation from proniosomes for efficient transdermal delivery with penetration enhancement being mainly responsible for improved delivery.

INTRODUCTION

Nisoldipine belongs to the second-generation dihydropyridine calcium channel blockers. It has been shown to induce potent peripheral and coronary vasodilatation. This drug has been approved in a number of countries as an immediate-release and Extended release formulations for treatment of hypertension and angina pectoris. In humans, the absorption of this drug occurs across the entire gastrointestinal tract with an increase in bioavailability in the colon due to lower concentrations of the metabolising enzymes. Despite of complete absorption the drug has very low bioavailability. This was attributed to the extensive first pass metabolism (Zannad, 1995; El Maghraby and Elsergany, 2013). This together with its low dose made the drug an excellent candidate for transdermal delivery. However, the barrier nature of the skin makes it difficult for most drugs to permeate through it reaching the systemic circulation (Barry, 1983). Many strategies have been used to overcome this barrier nature. These include the use of chemical penetration enhancers (Barry, 1987), adjusting the chemical potential (Megrab *et al*., 1995), formulating eutectic systems (Nyqvist-Mayer *et al*., 1986), employing physical enhancement techniques as iontophoresis, electroporation and sonophoresis (Menon *et al*., 1994; Banga *et al*., 1999). 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), Niosomes (Manosroi *et al*., 2008), 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 major stability problems of liposomes are loss of entrapped drug, change in the size upon storage and chemical degradation of the lipid components (Sharma and Sharma, 1997). Consequently, niosomes 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). Although niosomes exhibit more chemical stability during storage, there may be a physical stability problem upon storage of niosomal dispersion. Proniosomes were prepared as dry powder for reconstitution before use as a mean of preserving such vesicular chemical and physical integrity (Hu and Rhodes, 2000). For the transdermal delivery purpose proniosomes were prepared as a gel like concentrated niosomes suitable for topical application (El Maghraby and Williams, 2009). These gel like vesicles were claimed to deliver drugs across the skin after

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in-situ niosome formation (Vora *et al.*, 1998). Accordingly, the main aim of this study is to evaluate proniosomes as a promising alternative for optimization of the transdermal delivery of nisoldipine. Proniosomes with increasing cholesterol concentrations were evaluated. The efficacy of such proniosomes was compared to the corresponding niosomes with the goal of testing the hypothesis which necessitate niosome formation from proniosomes for efficient transdermal delivery.

MATERIALS AND METHODS

Materials

Nisoldipine was purchased from Jinan Jianfeng chemical CO. LTD, China. Span 60 and cholesterol were purchased from Sigma Chemical Co. (St. Louis, MO, USA). Methanol and acetonitrile (HPLC – grade) were obtained from BDH, England. Ethanol (96%) was from El-Nasr pharmaceutical Chemicals Company, Egypt.

Preparation of proniosomes and niosomes

The composition of the tested proniosomal formulations is presented in (Table 1). The surfactant mixture (Span 60 - cholesterol), the drug and ethanol were mixed and heated to 65 ± 1°C for 5 minutes in a stoppered vessel. This provided clear liquid system. The aqueous phase was added and the mixture was warmed on until clarity. This mixture was allowed to cool down with the aid of continuous mixing at room temperature till conversion to proniosome gel. The corresponding niosomes were prepared by hydrating the proniosomes gel (1 gram) using 10 ml distilled water. This involved mechanical stirring for 30 minutes. The resulting niosomal dispersions were subjected to 30 minutes of bath sonication.

Table. 1: The composition of the tested formulations.

Formulation	Cholesterol	Span 60	Ethanol	Aqueous phase*
L	0.5	4.5	5	4
M	1	4	5	4
H	1.5	3.5	5	4

*The aqueous phase is 0.1% w/w glycerol in water. The amount of the drug added to each formulation was 0.3 g.

Determination of entrapment efficiency

The entrapment efficiency was determined after separation of free drug by dialysis. Immediately after hydration of proniosomal gel, the noisome dispersion was incubated in dialysis sac (Cellulose tubing, Sigma diagnostics, St. Louis, MO, USA) and then dialysed against 100 ml of 40% v/v ethanol in water for 4 hours. Such dialysis fluid was selected to ensure sink condition. The amount of the drug found in the dialysate was taken as a measure for the free un-entrapped drug. The entrapment efficiency was calculated using the following equation (Trotta *et al.*, 2002; 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.

Viscosity measurements

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

Determination of drug release

Drug release from vesicles is temperature dependent, generally being greatest around the phase transition temperature of lipid (Papahadjopoulos *et al.*, 1973). According to our experimental condition the skin surface was maintained at 32 °C. Accordingly, the drug release studies were conducted at 32°C to provide a correlation between drug release and skin permeation data. The release study employed vertical glass Franz diffusion cells having a diffusional surface area of 2.27 cm^2 with a 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 carried out to ensure complete swelling of the membrane in order to provide constant pore diameter throughout the experiment. The membrane was 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 condition. The diffusion cells were incubated into a thermostatically controlled water bath to maintain the temperature of the membrane surface at 32±1°C to mimic in vivo conditions. Proniosomes (2.5 g) or niosomes (2 ml) were loaded into the donor compartments. Receptor samples were taken at different time intervals and replaced with fresh receptor. These samples were analysed for the drug by HPLC. The cumulative amount of drug released was calculated as a function of time (El Maghraby, 2010).

Preparation of skin samples

Skin permeation experiments should employ human skin. Unfortunately, it is difficult to obtain good human skin samples. Accordingly, the rabbit ear model which has been extensively used for investigation of transdermal delivery of a variety of lipophilic drugs like our drug was employed in this study (Corbo *et al.*, 1990; Touitou *et al.*, 2000; El Maghraby *et al.*, 2008). Full thickness skin obtained from the inner side of freshly excised ears of 6 male rabbits (weighing 2-3 Kg) was used. The skin was peeled from the underlying cartilage after cutting along the tips of the ears. The skin samples were mounted immediately on the diffusion cells (El Maghraby, 2010).

Skin permeation studies

As for the release studies, the vertical glass Franz diffusion cells were employed in the skin permeation experiments. The skin was mounted with the stratum corneal side uppermost on the diffusion cells. To ensure sink conditions, 40% v/v ethanol in water was used as receptor. The diffusion cells were incubated into a thermostatically controlled water bath with the temperature being

adjusted to maintain the temperature of the skin surface at 32±1°C to mimic in vivo conditions. After equilibration overnight of, the tested proniosomes (2.5 g) or niosomes (2 ml) were loaded into the donor compartments before occlusion with aluminium foil. Receptor samples were taken at different time intervals and analysed for the drug by HPLC. Such samples were replaced with fresh receptor. The study ensured that skin obtained from the same rabbit was used for the test and control (El Maghraby, 2010).

Chromatography

The drug concentrations in all samples were determined using HPLC. This employed a high pressure liquid chromatograph (Waters™ 600 controller, USA) equipped with a variable wavelength detector (Waters™ 486, Tuneable Absorbance Detector, USA) and an automatic sampling system (Waters™ 717 Plus Autosampler, USA). This was under computer control. Separation was accomplished on a reversed phase column 15 cm X 4.6 mm (i.d.) C_{18}, μ Bondapak™, Waters, with an average particle size of 10 μm. The mobile phase was a mixture of methanol, acetonitrile and water (35:30:35) flowing at 1.3 ml/min. The column effluent was monitored at 238 nm (El Maghraby and Elsergany, 2013). The chromatographic data analysis was performed with the Millinium™ Program (Waters, USA). The receptor samples (30 □l) were injected directly into the HPLC system.

Data analysis

The cumulative amounts of the drug permeated were plotted as a function of time to produce the permeation profiles. These plots were typical steady state profiles which are expected after occlusive application of formulations containing excess amounts of the drug (Fig. 1). The profiles were utilized to calculate the transdermal drug flux (J), which was obtained from the slope of the regression line fitted to the linear portion of the profile. Extrapolation of this line will intercept with the x axis at a time equal to the lag time.

RESULTS AND DISCUSSION

Entrapment efficiency

The recorded entrapment efficiency values ranged from 80.6 ± 0.1% to 84.1 ± 0.3% (Table 2). These values indicate that the amount of drug added to the formulations was enough to saturate the proniosome formulation. This will ensure equal thermodynamic activity among the tested proniosomes. This is important to ensure that any difference in transdermal drug delivery efficiency will be dependent only on the composition of the proniosomes. With regard to the entrapment efficiency of individual formulations the data indicated their dependence on the composition. Considering the effect of cholesterol content on the entrapment efficiency the results revealed a trend of reduced entrapment efficiency with increasing cholesterol content. This could be due to the fact that cholesterol beyond a certain level starts disrupting the regular bilayered structure leading to loss of drug entrapment (Mokhtar *et al*., 2008; Sengodan *et al*., 2009; Alam *et al*., 2010; Rita and Lakshmi, 2012). Reduction of entrapment efficiency with increase in cholesterol content may be also explained on the base of positioning of cholesterol between span molecules. This arrangement results in competition between cholesterol and lipophilic drug molecules for location within the vesicular structure with subsequent decrease in entrapment efficiency (El Maghraby *et al*., 2004).

Viscosity determinations

The flow behaviour of the tested proniosomes followed non-Newtonian system with a shear thinning behaviour. This can be considered advantageous as it allows easy application and spreading on the skin surface. Because of non-Newtonian flow, the viscosity values were calculated at a fixed rpm (50 rpm). The recorded viscosity values are presented in Table 2. Increasing cholesterol content reduced the viscosity. This was expected as higher cholesterol: span 60 ratio reduces span 60 content which have higher melting point than cholesterol with subsequent reduction of viscosity.

Drug release

The in vitro release of nisoldipine from various proniosomal formulations was studied at the same conditions of skin permeation experiments with an artificial semi-permeable membrane being used instead of the skin. This was conducted in order to correlate the release results with the skin permeation data (El Maghraby, 2010). The release profiles of nisoldipine obtained from different proniosomal formulations and their corresponding niosomes are shown in Fig. 2. The release profiles were linear with lag time in all cases. Similar pattern was previously reported for proniosomes containing tenoxicam which is also a lipophilic drug like nisoldipine (Ammar *et al*., 2011). The calculated release rates are presented in Table 3. All tested formulations showed significantly higher release rates compared with the saturated aqueous solution of drug. With respect to individual proniosomes, there was a trend of increased release rate with the decrease in viscosity. Comparing the release from proniosomes with that from the corresponding niosomes (Fig. 2) proniosomes presented higher rate of drug release than the corresponding niosomes. The reverse was expected as the amount of external water is an important factor in drug release from vesicular systems and reduction of water should reduce the release rate of drugs (Tsukada *et al*., 1984; Ozer and Talsma, 1989). Accordingly, proniosomes which contain minimal amount of water was expected to show lower release rate. The results obtained were explained on the basis of higher drug concentration in proniosomes compared to the corresponding niosomal dispersion resulting in higher concentration gradient which is the main driving force in passive diffusion process across semipermeable membrane.

Proniosomal and niosomal skin delivery of nisoldipine

The skin permeation studies employed full thickness skin obtained from the inner side of freshly excised rabbit ears. This

skin has been successfully used to study skin permeation of a variety of drugs from various vehicles (Touitou *et al*., 2000, El Maghraby *et al*., 2009). To ensure sink conditions 40% (v/v) ethanol in water was utilized as receptor fluid. Such receptor has been successfully used as a receptor to monitor skin delivery of a lipophilic drug from vesicular delivery systems (El Maghraby *et al*., 1999). Fig. 1 presents the permeation profiles obtained after application of proniosomes with increasing cholesterol content and their corresponding niosomal formulations with the permeation parameters being showed in Table 3. The control was saturated aqueous solution of the drug. Generally in all formulations proniosomes produced the greatest delivery relative to the corresponding niosomes and drug control. Correlating the composition of each formulation with the recorded transdermal permeation, it was found that increasing cholesterol concentration resulted in reduced flux (Table 3). Reduced drug permeation with increasing cholesterol concentration can be better explained on the basis that the presence of cholesterol produces a more rigid membrane structure and it is believed that more rigid vesicles are less successful in transdermal delivery. Similar reports about comparing flexible and rigid vesicles have recorded similar findings (Scherier and Bouwstra, 1994; El Maghraby *et al*., 1999). Correlating the skin permeation data with the release data it could be concluded that the drug release is not the limiting factor for enhanced drug delivery. This is because the amount of drug released at any time was more than the total flux obtained at this time. Comparing the transdermal delivery of the drug from proniosomes with that from the corresponding niosomes, proniosomes were better in all cases (Fig. 1). The superiority of proniosomes over niosomes can be explained on the basis that the former contained high ethanol content which was diluted in case niosomes. Accordingly, ethanol can be considered as the main reason for the obtained enhancement. Thus disruption of skin structure can be taken as a possible mechanism of action of proniosomes. This consideration was further evidenced by the reduced lag time. Reduced lag time indicated increased diffusivity which suggested a reduction in the barrier nature of skin. Ehosomes (liposomes with high ethanol content) enhanced transdermal delivery and this was explained also on the basis of high ethanol content (Touitou *et al*., 2000). These results contradict the hypothesis which was reported by (Vora *et al*., 1998) and claimed that proniosomes should transform into niosomes before delivering the entrapped drug. If this hypothesis is true we should have similar delivery from proniosomes and the corresponding niosomes. Also the lag time of proniosomes must be longer than that of niosomes in all cases. However in our case the reverse was true in all cases where better delivery and sometimes shorter lag time was obtained with proniosomes. Previous reports comparing proniosomes with the corresponding niosomes have recorded the drug in the receptor in the first 30 minutes after application. The authors considered this as a short time for niosomes formation and subsequent drug transfer. In addition the hydrated proniosomes (niosomes) were less efficient compared to the corresponding proniosomes. The authors suggested direct drug transfer from proniosomes with a role for the penetration enhancing effect of the non-ionic surfactant component of such system (Fang *et al*., 2001).

CONCLUSION

Proniosomes can be considered as a promising transdermal delivery system for nisoldipine with their efficacy being dependent on their composition. An optimum concentration of cholesterol is required for optimum vesicular drug delivery. High cholesterol affects the vesicular membrane structure and produces more rigid vesicles which are less successful in transdermal delivery. Regarding the mechanism of proniosomal drug delivery, direct drug transfer from proniosomes is possible without hydration to niosomes with penetration enhancement being mainly responsible for the improved delivery.

Table. 2: Characteristics of the tested formulations.

Drug formulation	Entrapment efficiency	Viscosity (cp) At 50 RPM
L	84.1 (0.3)	51800 (1633)
M	81.9 (0.2)	47416 (1495)
H	80.6 (0.1)	42600 (1343)

Values between brackets are S.D. (n = 3)., Formulation details are in Table 1.

Table. 3: Transdermal permeation parameters and release rate of nisoldipine obtained after application of nisoldipine in the form of proniosome formulations with different cholesterol content and their corresponding niosomes.

Drug formulation	Release rate ($\mu g\ cm^{-2}\ h^{-1}$)	Flux ($\mu g\ cm^{-2}\ h^{-1}$)	Lag time (h)
L	15.3 (1.12)	12.18 (2.32)	0.99 (0.11)
M	15.9 (2.83)	7.74 (1.2)	1.03 (0.36)
H	19.2 (1.92)	5.97 (0.73)	1.77 (0.06)
NL	11.3 (0.48)	1.61 (0.31)	1.06 (0.21)
NM	12.0 (0.49)	1.38 (0.19)	1.22 (0.19)
NH	12.3 (1.13)	1.09 (0.36)	1.14 (0.14)
Control*	9.7 (0.8)	0.46 (0.03)	1.9 (0.1)

Values between brackets are S.D. (n = 3).
Formulation details are in Table 1. NL, NM and NH are the hydrated niosomes of the corresponding L, M and H formulations respectively.
* Control was saturated aqueous solution of the drug.

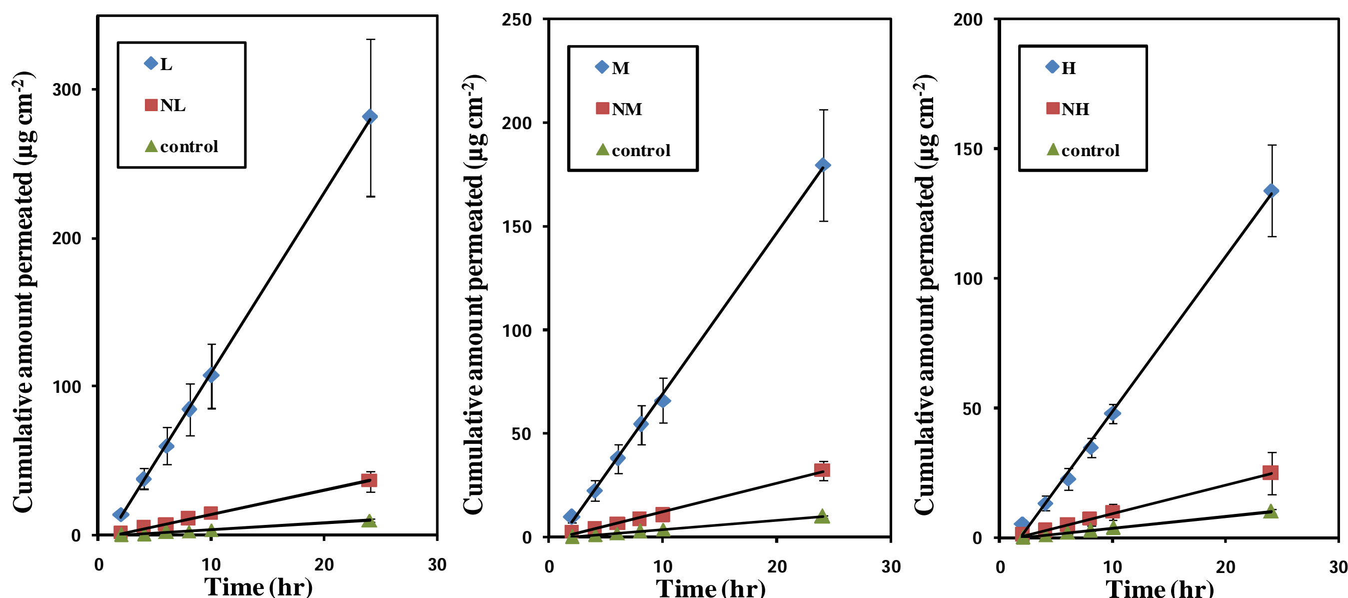

Fig. 1: The transdermal permeation profiles of nisoldipine after its application in the form of proniosomes and their corresponding niosomes. Formulation details are in Table 1.

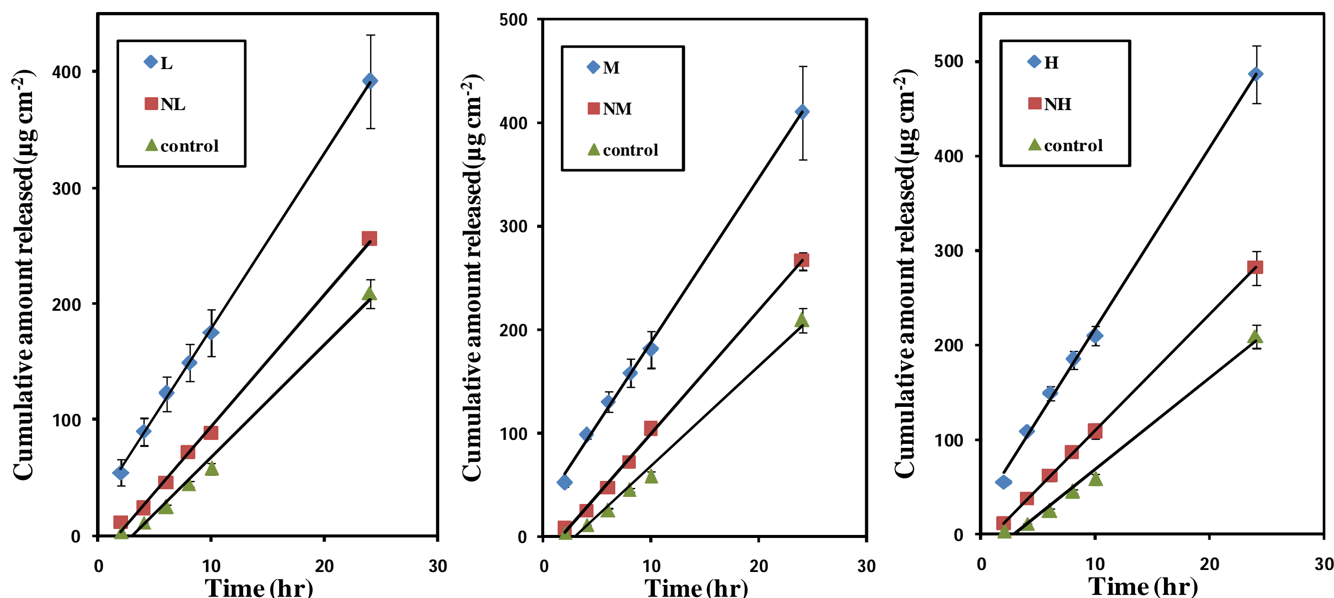

Fig. 2: The in vitro release profiles of nisoldipine from proniosomal formulations and their corresponding niosomes. Formulation details are in Table 1. NL, NM and NH are the hydrated niosomes of the corresponding L, M and H formulations respectively. Control was saturated aqueous solution of the drug.

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