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Pharmaceutical versatility of cationic niosomes derived from amino acid-based surfactants: Skin penetration behavior and controlled drug release

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ABSTRACT

The natural capability shown by cationic vesicles in interacting with negatively charged surfaces or biomolecules has recently attracted increased interest. Important pharmacological advantages include the selective targeting of the tumour vasculature, the promotion of permeation across cell membranes, as well as the influence of cationic vesicles on drug delivery. Accordingly, cationic amphiphiles derived from amino acids may represent an alternative to traditional synthetic cationic surfactants due to their lower cytotoxicity. The importance of a synthesized lysine-based gemini surfactant (labelled $C_6(LL)_2$) was evaluated in drug delivery by designing cationic niosomes as usable pharmaceutical tools of chemotherapeutics and antibiotics, respectively like methotrexate and tetracycline. The influence of formulation factors on the vesicles' physical-chemical properties, drug entrapment efficiency, *in vitro* release and *ex-vivo* skin permeation were investigated. A niosomal gel containing the gemini surfactant was also tested as a viable multi-component topical formulation. Results indicate that in the presence of cholesterol, $C_6(LL)_2$ was able to form stable and nanosized niosomes, loading hydrophilic or hydrophobic molecules. Furthermore, *in vitro* release studies and *ex-vivo* permeation profiles showed that $C_6(LL)_2$-based vesicles behave as sustained and controlled delivery systems in the case of parenteral administration, and as drug percutaneous permeation enhancers after topical application. Finally, cationic $C_6(LL)_2$ acts as a carrier constituent, conferring peculiar and interesting functionality to the final formulation.

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1. Introduction

Niosomes are vesicular nanocarriers with a bilayered structure made of surfactants surrounding an internal aqueous compartment. They are able to encapsulate both lipophilic and hydrophilic substances respectively located in the lipophilic domain of the bilayers or encapsulated in the inner aqueous core (Uchegbu and Florence, 1995). Niosomes are applied in pharmacological treatments based on their similarity with natural membranes and on their possibility of acting as local depots for sustained drug release. The additional capabilities of modulating skin adsorption and ensuring specific drug release only at the desired site make niosomes one of the most studied drug delivery systems (Moghassemi and Hadjizadeh, 2014). Niosomes can be classified as cationic, anionic and non-ionic vesicles depending on the chemical nature of the surfactants. The recent increased interest in cationic vesicles is attributable to a certain natural capability, which they have in interacting with negatively charged surfaces or biomolecules. Resulting important pharmacological advantages can be seen, for instance, in the selective targeting of the tumour vasculature (Abu Lila et al., 2010) and in their influence on drug delivery (Mahale et al., 2012). Cationic vesicles have proved to be effective candidates for anticancer drug delivery to solid tumours due to their favourable electrostatic interactions with anionic molecules,such as proteoglycans, glycoproteins and anionic phospholipids in the tumour microvasculature. Together with the enhanced permeability and retention effect (EPR) and the sluggish and stunted blood flow in tumour vesselsthis improves their vascular targeting and accumulation efficiency (Abu Lila et al., 2009). Cationic niosomes are also able to complex anionic genetic molecules and to deliver them into the cells, thus promoting the permeation of genes across membranes and acting as successful

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transfer vehicles (Huang et al., 2011). Moreover, cationic niosomes have been found to enhance topical drug delivery; the skin surface also bears a net negative charge, which allows the positively charged vesicles to increase drug permeation rates (Dragicevic-Curic et al., 2010; Katahira et al., 1999).

All these features contribute to making cationic niosomes a unique and promising system, and have thus prompted researchers to develop and characterize additional pharmacological strategies based on these versatile carriers.

Traditional cationic surfactants (TCS) based on quaternary ammonium groups have revealed that the vesicles are able to transport drugs into the body and to generally show good antimicrobial activity. Unfortunately, however, TCS present hemolytic activity, whereby they are not suitable for medical applications. Despite improvements in their biodegradation, the second generation of quaternary ammonium derived cationic surfactantspresents stability problems and is still toxic to the aquatic environment. Furthermore, their use in medical fields is limited owing to the development of microbial resistance and to their high acute toxicity (Thorsteinsson et al., 2003; Nagamune et al., 2000).

For these reasons, cationic amphiphiles derived from amino acids may represent an alternative to traditional synthetic cationic surfactants. Compared to most cationic surfactants, their advantages lie in the use of raw materials derived from renewable sources in the synthetic process, in their biodegradability, and low cytotoxic potential (Morán et al., 2004). Among the several papers which have appeared over the last decades on the synthesis and properties of biocompatible cationic amino acid-based surfactants, the most promising results have been achieved when lysine and arginine were employed as starting amino acids (Pinazo et al., 2011; Singare and Mhatre, 2012). These derivatives were prepared using renewable raw materials, whereby they can be considered ready biodegradable surfactants. Moreover, they exhibited good antimicrobial activity against Gram-positive and Gram-negative microorganisms, while showing low citotoxicity compared to TCS (Pinazo et al., 2011). Furthermore, gemini surfactants from lysine and arginine have been reported to possess better physical-chemical properties, such as lower critical micelle concentration and efficiency in reducing the surface tension of water, than the corresponding single-chain surfactants (Colomer et al., 2011). Taking these properties into account, cationic gemini surfactants based on amino acids can be considered suitable candidates for special biomedical applications.

In this study, we have focussed on the potential employment of $C_6(LL)_2$, a cationic gemini lysine-based surfactant in drug delivery systems, designing the usability of cationic niosomes in the topical administration of antibiotics,such as tetracycline, and also their use as pharmaceutical tools of chemotherapeutics,such as methotrexate, via parenteral route. Biodegradation, toxicity, hemolytic and antimicrobial activities of $C_6(LL)_2$ demonstrated the advantages which this surfactant has over traditional synthetic cationic surfactants. In this study, we investigated the influence of formulation factors on the physical-chemical properties of the vesicles (i.e., particle size, size distribution, vesicles surface charge and morphology), drug entrapment efficiency, *in vitro* release in fluids simulating parenteral administration and *ex-vivo* skin permeation. Given the general aim of conducting a more comprehensive study, we incorporated niosomes into a gel dosage form, and therefore obtained niosomal gel as a viable multi-component topical formulation. Its performance in terms of permeation enhancement was then tested.

2. Materials and methods

2.1. Chemicals

The lysine-based gemini surfactants (N^{α}-N^{ω}-bis(N^{α}-lauroyl-lysine) α,ω-hexylendiamine $C_6(LL_2,)$ are made up of two symmetrical long-chain N^{α}-lauroyl-lysine residues of 12 carbon atoms linked by amide bonds to a diaminohexane spacer chain (Fig. 1) (Colomer et al., 2011). This was obtained using renewable raw materials according to the previously described method. Briefly, the protected N^{α}-lauroyl-N^{ε}-Cbz-lysine was condensed to the 1,6-diaminohexane in the presence of an activating agent. A final deprotection reaction was carried out in order to obtain the target compound. Details about the purification and spectral characterization (HPLC, NMR and EA) of this surfactant are provided elsewhere (Colomer et al., 2011).

Cholesterol (Ch), tetracycline (Te), methotrexate (Me) and carboxymethyl cellulose were purchased from Sigma (Sigma-Aldrich, Milan, Italy, 98% purity). All organic solvents were supplied from Sigma-Aldrich (Milan, Italy) and are of high-performance liquid chromatography grade.

2.2. Preparation of colloidal formulations

Multilamellar niosomal vesicles (MLVs) were prepared byapplying the hydration of lipidic film method (Tavano et al., 2014). Accurately weighed amounts of $C_6(LL)_2$ (2.40×10^{-5} moles, corresponding to 0.017 g) and Ch (2.40×10^{-5} moles, corresponding to 0.009 g) were dissolved in ethanol in a round-bottom flask. After mixing, the solvent was evaporated under reduced pressure and constant rotation to form a thin lipid film. This was subsequently hydrated with 10 mL of distilled water or 10 mL of methotrexate aqueous solution (3.15×10^{-4} M) at 60 °C for 30 min, to respectively obtain empty and Me-loaded large MLV.

Tetracycline-loaded niosomes were obtained by dissolving 2.4×10^{-6} moles of Te in the initial surfactant solution, evaporating it to form a thin lipid film and then hydrating it with 10 mL of distilled water. After preparation, the dispersions were left to equilibrate at 25 °C overnight to allow complete annealing and partitioning of the drug between the lipid bilayer and the aqueous phase. Small unilamellar vesicles were obtained from MLV by sonication in an ultrasonic bath for 30 min at 60 °C. Purification of niosomes from entrapped materials was carried out by exhaustive dialysis for 4 h (details are reported in Section 2.3.3), using Visking

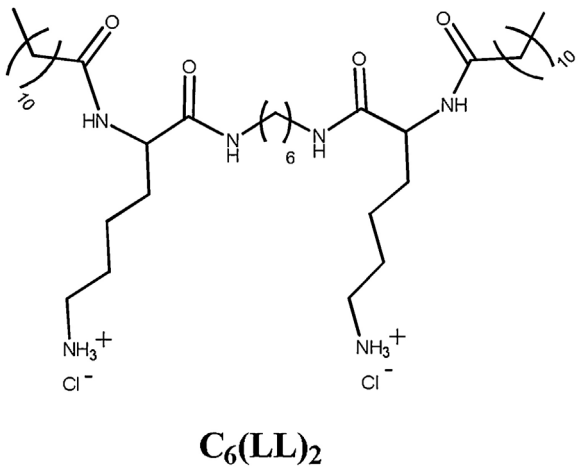

Fig. 1. Molecular structure of the $C_6(LL)_2$ surfactant.

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