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Novel gel-niosomes formulations as multicomponent systems for transdermal drug delivery

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ABSTRACT

The percutaneous permeation profiles of sulfadiazine sodium salt, propranolol hydrochloride and tyrosol from novel liquid crystal-niosomes formulations as multicomponent systems, were investigated. The new carriers were prepared from mixture of water/surfactant, AOT or Pluronic L64 as anionic and nonionic surfactants, respectively, in order to obtain lamellar LLC phases. The same surfactants were used to prepare also the vesicular systems (niosomes) that were added to the corresponding gel. The obtained multicomponent drug carrier was characterized by deuterium nuclear magnetic resonance spectroscopy, in order to understand if the introduction of the drug or drug-loaded niosomal suspension, as third component in the formulations, could influence the microstructure of the system and then the drug delivery across the skin. Simple AOT and L64-based niosomal formulations and LLCs phases were then prepared and used as control. Different drugs percutaneous availability was achieved, and the results revealed that the obtained gel-niosomes carriers were affected by the chemical structure of the drugs and by their affinity for the components. As a consequence these systems could be proposed as novel transdermal drug delivery systems, since they were found able to control the percutaneous permeation of small drugs across the skin.

1. Introduction

In recent years, the transdermal route of administration has found wide applications and gained considerable commercial success, winning the competition with oral, intravenous or intramuscular routes [1]. A problem that has been faced is the low penetration of most compounds through the outermost layer of the skin, the stratum corneum (SC). The SC consists of terminally differentiated keratinocytes, referred to as corneocytes, embedded in a lipid-rich intercellular matrix. The main constituents of this matrix are ceramides (CER), cholesterol (CHOL) and long-chain free fatty acids. These lipids are organized in crystalline lamellae at room temperature and play a key role in the barrier function of human skin. Absorption of substances into and across skin takes place by passive diffusion through the lipid domains of SC, since the driving force is the difference in the drug concentration between drug carriers and blood. In order to reduce temporary the SC barrier and improve drug vehiculation, penetration enhancers are developed to alter the SC lipid structural organization, avoiding side effects and allowing a better control than other conventional delivery methods [2].

Among the several approaches, one possibility to increase the amount of drug vehiculated across the SC, is the use of lyotropic liquid crystals (LLCs), due to their stability, low interfacial tension arising at the oil/water interface and capability to increase the solubility of drugs, which are either insoluble or slightly soluble in water [3].

The LLC are excellent examples of self-assembling nanomaterials. They are usually formed from water and one or more surfactants at very definite proportions. Their phase sequence (cubic, hexagonal, lamellar) depends on both the different components concentration and temperature. Among the different mesophases, the lamellar ones represent the best approaches to be used as transdermal drug delivery systems, due to their special skin similarly structure.

In fact, the structural units for the lamellar phase are double layers formed by surfactant molecules disposed in a bidimensional stacking of infinite layers, delimited by water. The polar heads of the molecules are in contact with the aqueous medium, while the hydrocarbon chains are interdigitating in order to avoid water. This phase is rather fluid and the bilayers can slip easily one on the other. This structure is very similar to that occurring in living organisms

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and for this reason lamellar LLC represents optimal candidate for the transdermal vehiculation of drugs [4]. An improvement of the pharmaceutical properties of these drug delivery systems can be obtained by the addition of vesicular systems in the LLCs lamellae. Several works, in fact, reported that the LLC networks can serve as an encapsulating matrix, escorting and protecting the embedded vesicles entrapping active entities and can enhance their stability prolonging the circulation time without losing drug [5]. In addition these multicomponent systems have attracted particular interest in the design of dermal and transdermal delivery systems due to the possibility to achieve prolonged and programmed drug percutaneous permeation through the skin [6]. In a previous work, our research group has carried out investigation on the complex systems based on Pluronic F127 and Tween 60 vesicles, to study the rheological interaction between polymer and vesicles and to evaluate the potential use of the systems as efficient drug delivery formulation [7]. Results demonstrated that the binary systems can act as transdermal controlled and prolonged delivery systems of diclofenac sodium salt.

In this light, we decide to evaluate the effect of the chemical structure of different surfactants and vehiculated drug on the physico-chemical properties and drug percutaneous permeation profiles of novel multicomponent formulations. For these reasons we used Pluronic L64 or Aerosol OT (AOT) as surfactants and sulfadiazine sodium salt (Sul), propranolol hydrochloride (Pro) and tyrosol (Tyr) as model drugs. LLCs samples were prepared at fixed ratio between Pluronic L64 or AOT and water, in order to obtain lamellar LLC phases and the corresponding surfactant was used to prepare also the vesicular systems (niosomes) that were added to the gel. Pluronic L64 is a non-ionic copolymer of ethylene oxide (EO) and propylene oxide (PO) blocks arranged in a triblock structure, in which the hydrophobic polypropylene oxide (PPO) group links two hydrophilic polyethylene oxide (PEO). The amphiphilic nature of Pluronic makes it extremely useful in various fields as emulsifier, stabilizer and pharmaceutical additive. The presence of ethylene oxide moieties may reduce opsonisation and clearance by the reticuloendothelial system, leading to improved pharmacokinetic properties of the carriers. Several works reported the use of L64 as surfactant to obtain niosomes useful as parenteral and transdermal delivery systems vehiculation of different drugs [8]. AOT is a versatile double-tailed anionic surfactant whose phase equilibria with water and organic solvent has been extensively investigated, because its non toxicity, spontaneously formed and thermodynamically stable long lived micellar forms and it is known as a transdermal drug delivery vehicle [9]. Drugs with anionic, cationic and nonionic chemical structures and different properties such as Sul, Pro and Tyr, respectively, were incorporated into L64 and AOT lamellar LLC phases as free drug solutions or as drug-loaded niosomal suspension. Deuterium resonance spectroscopy (^{2}H NMR) were used to evaluate the occurred structural modifications caused by the incorporation of drugs as a third component in the surfactant–water systems. Finally the percutaneous permeation profile of all the drugs from the lamellar LLC phases obtained from L64 and AOT were performed, in order to understand how the different formulations could give rise to a different transdermal delivery of drugs.

2. Materials and methods

2.1. Materials

Pluronic L64, poly(ethylene oxide)-block-poly(propylene oxide)-block-poly(ethylene oxide) copolymer, was provided from BASF (Mount Olive, NJ, USA). AOT (sodium bis(2-ethylhexyl) sulfosuccinate), sulfadiazine sodium salt, propranolol hydrochloride and tyrosol were supplied by Sigma–Aldrich, Milan, Italy. The drug content in the permeation studies was analyzed by UV-VIS JASCO V-530 spectrometer using 1 cm quartz cells at the pertinent wavelengths. Ultrapure water from a Millipore Synergy® purification unit was used. Deuterium oxide (Sigma–Aldrich, Milan, Italy) was used in order to perform ^{2}H NMR measurements.

Table 1
Details on the preparation of drug-loaded gels.

Samples	Surfactant name	Surfactant (g)	D_2O (g)	Drug	Drug (g)
G-AOT-Sul	AOT	0.90	2.07	Sulfadiazine sodium salt	0.03
G-AOT-Pro	AOT	0.90	2.07	Propranolol hydrochloride	0.03
G-AOT-Tyr	AOT	0.90	2.07	Tyrosol	0.03
G-L64-Sul	L64	2.25	0.72	Sulfadiazine sodium salt	0.03
G-L64-Pro	L64	2.25	0.72	Propranolol hydrochloride	0.03
G-L64-Tyr	L64	2.25	0.72	Tyrosol	0.03

2.2. Preparation of drug-loaded LLC gels

LLC gel samples were prepared using a fixed ratio between surfactants and water, in order to obtain lamellar LLC phases. The percentage of drug added to each formulation was 1% in weight. Details on the preparation were reported in Table 1. Briefly, the preparation is as follows: 0.03 g of hydrophilic drug was dissolved in the appropriate amount of water and mixed with each surfactant. Samples were mixed several times and heated at 40 °C, until a homogeneous mixture was obtained and stored at room temperature. The samples were analyzed only after one week. Details on the samples preparation are reported in Table 1.

2.3. Preparation of niosomes

Multilamellar niosomal vesicles (MLVs) were prepared vortexing and subsequent sonication. Accurately weighed amounts of L64 or AOT were putted in a round-bottom flask in the presence of 10 mL of mixture of distilled and deuterated water (empty niosomes) or 10 mL of mixture of distilled and deuterated water containing 0.03 g of drug (drug-loaded niosomes) at 25 and 60 °C for AOT and L64, respectively, for 30 min, to form large multilamellar vesicles. After preparation, the dispersion was 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 (SUV) were prepared starting from MLV by sonication in an ultrasonic bath for 30 min at 25 and 60 °C for AOT and L64, respectively. The niosomes purification was also carried out by exhaustive dialysis for 6 h, using Visking tubing (20/30), manipulated before use in according to Fenton's method [10]. Final formulations were stored at 4 °C until used in subsequent experiments (Table 2).

2.3.1. Characterization of niosomes

2.3.1.1. Morphology. The morphology of hydrated niosome dispersions was examined by transmission electron microscopy (TEM). A drop of dispersion was stratified onto a carbon-coated copper grid and left to adhere on the carbon substrate for about 1 min. The dispersion in excess was removed by a piece of filter paper. A drop of 2% phosphotungstic acid solution was stratified and, again, the solution in excess was removed by a tip of filter paper. The sample was air-dried and observed under a ZEISS EM 10 electron microscope at an accelerating voltage of 80 kV.

2.3.1.2. Size and distribution. The niosomes size and standard deviation were determined by dynamic light scattering (DLS) analysis using 90 Plus Particle Size Analyzer (Brookhaven Instruments