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Positively charged microemulsions for topical application

Elena Peira, M. Eugenia Carlotti, Chiara Trotta, Roberta Cavalli, Michele Trotta*

Dipartimento di Scienza e Tecnologia del Farmaco, Università degli Studi di Torino, Via P. Giuria 9, 10125 Turin, Italy

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Abstract

The study reports pig-skin permeation and skin accumulation of miconazole nitrate (MCZ) from positively charged microemulsions containing water, 1-decanol/1-dodecanol (2:1, w/w), lecithin and/or decyl polyglucoside at different weight ratios, propylene glycol, 1,2 hexanediol and a cationic charge-inducing agent (stearylamine (ST), L-alanine benzyl ester (ALAB) or cetyltrimethylammonium bromide (CTAB)). Zeta-potential values of the positively charged microemulsions ranged from 14.2 to 37.5 mV and mean droplet size from 6.0 to 16.8 nm.

In vitro pig-skin permeation of MCZ after a single 24 h application was negligible for all microemulsions; accumulation from positively charged microemulsions was nearly twice that from their negatively charged counterparts.

The increased accumulation might be ascribed to the interaction between positive microemulsive systems and negatively charged skin sites; no significant difference was observed among the various cationic charge-inducing agents.

Skin accumulation from the microemulsion containing most lecithin was lower than those of other microemulsions; this was ascribed to the phase transformation from microemulsion to a liquid crystal system after skin contact.

These results suggest that positively charged microemulsions could be used to optimize drug targeting without a concomitant increase in systemic absorption; ALAB, an ester of a natural aminoacid, is an appropriate cationic charge-inducing agent.

Keywords: Positively charged microemulsion; Miconazole; Topical application; Skin accumulation

1. Introduction

Epithelial cells carry a negative charge upon their surface, due to the presence of negatively charged protein residues on the outer side of their membranes, and to selective active ion pumps (Rojanasakul et al., 1992). All epithelia should thus be selective to positively charged delivery systems that interact with cells, leading to increased drug permeability and prolonging the pharmacological effect.

In recent years, positively charged liposomes and emulsions have been used as drug carriers. Positively charged liposomes prepared with stearylamine (ST), a cationic lipid, have been used for ocular delivery of Acyclovir (ACV) (Law et al., 2000). Since the cornea provides a negatively charged surface it allows positively charged liposomes to permeate it. Positively charged liposomes increased absorption of ACV, because of a stronger binding effect to the cornea surface than occurs with negatively charged liposomes.

It has also been shown (Nagarsenker et al., 1999) that incorporation of ST into liposomes results in more consistent and higher AUC values for tropicamide; this formulation was found to be more effective in dilating the pupil than drug-loaded neutral liposomes.

Elbaz et al. (1993) prepared the first positively charged submicron emulsion using stearylamine. It was later demonstrated that a positively charged submicron emulsion formulation of piroxicam used in the management of corneal alkali-burning had a pronounced effect on both ulceration rate and epithelial defects compared to all the other test treatments, such as piroxicam solution or blank emulsion (Klang et al., 1999).

Drug-loaded positively charged submicron emulsions might also bind to negatively charged sites present on the skin, making the development of topically applied positively charged submicron emulsion promising. This hypothesis is supported by the results of Conrads and Zahn (1987) who showed maximum binding of anionic surfactants with the stratum corneum at pH

* Corresponding author. Tel.: +39 011 6707667; fax: +39 011 6707687.
E-mail address: michele.trotta@unito.it (M. Trotta).

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2, and decreased binding with increased pH. It can therefore be deduced that the stratum corneum is a positively charged membrane at low pH, and becomes negatively charged at high pH, above the isoelectric point of keratin.

Recently, positively charged submicron emulsions of about 130 nm, incorporating econazole and miconazole nitrate, have been proposed as a new type of colloidal drug carrier (Youenang Piemi et al., 1999).

During the last decade, numerous studies have suggested that a novel type of vehicle, i.e. the microemulsion, has the potential to increase cutaneous drug delivery of both hydrophilic and lipophilic drugs compared to conventional vehicles, and thereby fulfil the many promises of the cutaneous drug-delivery route (Kreilgaard, 2002).

Microemulsions are a special class of transparent dispersions, which actually have little in common with emulsions (Tadros et al., 2004). Unlike submicron emulsions, which are only kinetically stable, microemulsions are thermodynamically stable systems and are characterized by a highly-dispersed internal phase with droplet size ranging from 5 to 50 nm. As a consequence of their thermodynamic stability, microemulsions can be prepared by an inexpensive process through autoemulsification. These dispersed systems are isotropic, as opposed to liquid crystals which are anisotropic (Langevin et al., 1985). Moreover, investigations have shown that the unique structural organization of the phases in microemulsions may contribute to additional solubility regions, increasing their loading capacity versus non-structured solutions containing the same fractions of the constituents (Kreilgaard, 2002). As far as the authors have been able to determine, no reports have described positively charged microemulsions for pharmaceutical applications, so it is of interest to verify the potential of such systems.

MCZ, one of the broad-spectrum antifungal agents, is a weak base ($pK_a = 6.7$) characterized by relatively high molecular weight and melting point. This drug is poorly soluble in water (1.03 μg/ml) (Pedersen et al., 1993) and in mineral oil (10 μg/ml) (Fujii et al., 2002), which reduces its efficacy for many therapeutic applications. MCZ is usually employed at 2% (w/w) in topical suspensions for the treatment of dermatophytoses, superficial mycoses and mixed infections, or as an oral gel in treating Candidal infections; two to daily applications are required.

The aim of the present research was to develop and characterize positively charged microemulsions containing MCZ and to investigate the in vitro behavior of the formulations, using pig-skin.

2. Materials and methods

2.1. Materials

Soybean lecithin (Epikuron® 200, phosphatidylcholine content above 95%) was from Lucas Meyer (Hamburg, G) and was used without further purification. 1-Decanol, 1-dodecanol, and 1,2-hexanediol were from Fluka (Buchs, CH); decyl polyglucoside (Oramix® NS 10) was from Seppic (Milan, I). Cetyltrimethylammonium bromide (CTAB) was from Merck (Darmstadt, D). Propylene glycol (PG) was from Carlo Erba (Rodano, Milan, I), miconazole nitrate (MCZ), stearylamine (ST), and L-alanine benzyl ester (ALAB) were from Sigma (St. Louis, MO, USA). Distilled water was purified using a Milli-Q system (Millipore®, Bedford, MO). All chemicals were of analytical grade.

Table 1
Microemulsion compositions

Components	M1 (%, w/w)	M2 (%, w/w)	M3 (%, w/w)
1-Decanol/1-dodecanol (2:1)	1.61	1.59	1.53
Epikuron 200	6.22	1.90	–
Oramix NS 10	4.35	12.00	13.04
1,2-Hexanediol	6.80	4.20	3.38
Propylene glycol	11.60	9.80	15.95
Phosphate buffer pH 5.8	68.42	69.51	65.10
Miconazole nitrate	1.00	1.00	1.00

2.2. Microemulsion formulations

Microemulsions were prepared by weight using appropriate amounts of oil phase (1-decanol:1-dodecanol 2:1, w/w), surfactant (Oramix® NS 10 or a mixture of lecithin and Oramix® NS 10), aqueous phase (phosphate buffer 0.01 M at pH 5.8) and co-surfactant (PG and 1,2-hexanediol). The microemulsion compositions (w/w) are given in Table 1. Drug-loaded microemulsions were obtained by dissolving MCZ (1.0%, w/w) in the previously prepared microemulsion.

One of three different charge-inducing agents was added to the various batches of drug-loaded microemulsions: ST (1%, w/w), ALAB (2%, w/w) or CTAB (1.2%, w/w).

2.3. Physical characterization

Microemulsion droplet size was determined at 25 °C by photon correlation spectroscopy (PCS) using light-scattering equipment (90 Plus, Brookhaven Instruments Corporation, New York, USA). Measurements were obtained at an angle of 90° on microemulsions after filtration through a microporous filter with 0.45 μm pore diameter (Millipore®). Scattering intensity data were analyzed with a digital correlator and fitted by the inverse Laplace transformation method. Each system was analyzed twice, and ten size determinations were made for each sample. Viscosity values were determined in triplicate using an Ubbelohde micro-viscometer (Schott-Geräte, Hofheim, D).

Zeta potential of the microemulsions was measured using the ZetaPlus-Zeta Potential Analyzer (Brookhaven Instruments Corporation, New York, USA). Measurements were obtained on microemulsions after filtration through a microporous filter with 0.45 μm pore diameter. Each system was analyzed twice, and ten size determinations were made for each sample.

After 6 h application onto the skin the microemulsions were recovered and observed under polarized light to distinguish between microemulsion systems (isotropic) and liquid crystals (anisotropic).