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Investigation of the penetration of vehicle components and active drug from fluorosurfactant-based microemulsions

D. Mahrhauser (a), J. Schöll (a), M. Hoppel (b), H. Kählig (b,c) and C. Valenta (a,b)

(a) University of Vienna, Department of Pharmaceutical Technology and Biopharmaceutics
(b) University of Vienna, Research Platform "Characterisation of Drug Delivery Systems on Skin and Investigations of Involved Mechanisms"
(c) Institute of Organic Chemistry, University of Vienna

Introduction

Microemulsions are established formulations for transdermal drug delivery, but the mechanisms and factors controlling their transdermal drug penetration enhancement are still not clear. Since the components of a microemulsion are known to facilitate drug transport across the barrier it was the objective of the present study to monitor the penetration route of the incorporated drug and the fluorosurfactant as specific vehicle component and to examine whether synergies arise regarding their stratum corneum uptake. To this end, the penetration depth of each compound was elucidated through tape stripping studies via simultaneous quantification of diclofenac-sodium (DS) and the fluorosurfactant. The active component (DS) as well as the fluorosurfactants were directly quantified from the same strip by HPLC and 19F NMR, respectively. Moreover, ATR-FTIR experiments with the formulations and pure fluorosurfactants were performed to elucidate their effects on skin integrity.

Experimental methods

Skin penetration experiments

Tape stripping studies were carried out on porcine ear skin with an oleic acid solution incorporated with 0.7% (w/w) diclofenac-sodium as control and with two selected microemulsions containing the fluorosurfactants Hexafor 670 (Hex) or Chemguard S-550-100 (Sin), isopropyl alcohol as co-surfactant in the relation 1:1 (w/w), oleic acid as oily component, distilled water and 0.7% (w/w) diclofenac-sodium. 5 mg/cm^2 of formulation were applied and after 1 h exposure the stratum corneum layers of the porcine ear skin were removed by Corneofix® tapes. This procedure was repeated for each individual tape stripping experiment until the entire stratum corneum was stripped off. The tape strips were then immersed in 2 mL CH3OD. Each tape strip was quantified by HPLC and 19F NMR. The quantified cumulative amounts of both components were further used for calculation of their relative slopes in order to examine whether any relation exists between their penetration behaviours.

19F NMR

NMR spectra were recorded on a Bruker Avance III 600 NMR spectrometer (Bruker BioSpin GmbH, Germany) operating at 564.69 MHz for 19F. A 5-mm quadruple observe probe

equipped with z-axis gradient coil was used. All measurements were performed in deuterated methanol at a temperature of 298 K. Other typical acquisition parameters chosen were: 15 ppm spectral with, 32 000 data points, 90° excitation pulse, 2 s acquisition time and 1000 scans. As an external reference to calibrate the 19F, the chemical shift scale CCl3F was used. The processing and the analysis of the NMR spectra were performed within the Topspin Software (version 3.0; Bruker BioSpin GmbH).

ATR-FTIR studies

Infrared spectra of porcine ear skin samples were obtained using a Tensor 27 FTIR instrument (Bruker Optics, Germany) equipped with a Bio-ATR I tool at the skin surface temperature of 32°C. The skin samples were placed surface down on the ZnSe ATR crystal. ATR-FTIR spectra were recorded before and after impregnation with a formulation.

Results

The curve shapes of the calculated relative slopes of diclofenac-sodium and fluorosurfactants from the microemulsions proceeded almost equal, but completely different to the DS-curve from the oleic acid solution.

Both microemulsions as well as the oleic acid solution provoked significant changes in the absorbance spectra of the SC ($P < 0.05$). Interestingly, after the application of pure fluorosurfactants no shifts of the CH2 stretching bands could be detected.
On the one hand the FTIR-results indicated a penetration enhancement of diclofenac-sodium due to a conformational disorder of the SC lipids induced by oleic acid, but on the other hand the nearly identical slope curves of diclofenac-sodium and fluorosurfactant from the microemulsions also suggested an influence of the employed fluorosurfactants. However, the shift of the CH2 stretching absorbances only occurred when the fluorosurfactants were part of the microemulsion systems. Apparently, their combination and the arising microstructure of the prepared microemulsions exerted specific effects on skin integrity resulting in an enhanced diclofenac-sodium penetration.

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