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Micellar and non-micellar transport with various membranes

Julia Puschmann (1, 2), Michael Herbig (2), Christel C. Müller-Goymann (1)

(1) Institut für Pharmazeutische Technologie, TU Braunschweig
(2) Almirall Hermal GmbH

Introduction:
The partition behaviour of various components of topical formulations within the different phases (oil, micelles, aqueous) is an important aspect. Distribution of API might have high impact on the stability regarding possible degradation mechanism in the aqueous phase. The Dianorm® Equilibrium Dialyser with its two-chamber-system shall be used for the determination of the micellar and free transport through membranes with various molecular weight cut offs (MWCO) to measure the amount of API in the aqueous phase. Whether micellar solubilisation in water prevents or supports API degradation has to be investigated [1,2]. Furthermore a non-micellar solubilised substance is used as a control substance to guarantee the permeability of the membranes. Polysorbate 80 (PS) in different concentrations was chosen as a surfactant with known CMC and micellar molecular weight to differentiate between micellar and free transport [3].

Methods:
Various PS mixtures (0.15%, 1.5%, 5.0% (w/w)) in citric buffer pH 5 were prepared. Donor media contained betamethasone dipropionate (BDP) and phenoxyethanol in the PS mixtures. Additionally, emulsion gels containing 0.5% phenoxyethanol with varying PS-concentrations were tested. Donor and acceptor medium (citric buffer) were filled in PTFE-cells (n=5) separated by membranes and equilibrated at 25 °C for 24 h. Membranes made of hydrophilic cellulose ester (HCE) with various MWCO (0.5 - 100 kDa) were used and extracted in methanol. Samples were analysed via UPLC with PDA detector. Effective permeability coefficient (Peff) was calculated for BDP and phenoxyethanol [4]. An equivalence test was performed to control the equilibrium of donor and acceptor media (α=0.05).

Results:
BDP-solubility increased linearly with increasing PS-concentration due to micellar solubilisation. The impact of the MWCO on the substance transport was measured with the 1.5% PS mixture. 0.5 kDa HCE membrane inhibited BDP transport as the molecular weight of BDP is 505 Da [5]. With increasing MWCO more BDP diffused into the acceptor phase. Only the 100 kDa membrane allowed equilibrium due to the enabled micellar transport. However, the recovery rate decreased (0.5 kDa: 89.5%, 100 kDa: 53.9%). It is assumed that BDP undergoes binding reactions with the membrane.

Three different PS mixtures comparing the 5 kDa and 100 kDa membranes were dialysed. Equilibrium for phenoxyethanol was reached within 0.15% and 1.5% PS mixtures ($p<0.05$).

The PS-concentration and the varying MWCO of the membranes had no effect on the Peff of phenoxyethanol (Peff=0.6±0.07x102 cm/h). The Peff of phenoxyethanol of dialysed emulsion gels was 0.3±0.02x102 cm/h (n=44). The reduction of Peff between PS mixtures and emulsion gels is caused by the additional partition of phenoxyethanol in the oil phase of the emulsion. Around 4.3 times lower Peff-values of BDP were detected with increased PS-concentration. Reason for this is the enhanced micellar solubilisation of BDP. Due to enabled transport of micelles Peff increased with higher MWCO (5 kDa: Peff=1.9±0.17x102 cm/h; 100 kDa: Peff=2.6±0.09x102 cm/h).

Conclusion:
Phenoxyethanol was detected as an indicator for the effective membrane permeability. As a non-micellar solubilised substance it supports the differentiation between free and micellar drug transport. The effect of varying oil and emulsifier systems on the partition behaviour regarding the degradation of BDP and the antimicrobial effect of phenoxyethanol has to be determined.

References:
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