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Equilibrium Dialysis with various membranes for API transport studies

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Introduction:
The distribution of the active pharmaceutical ingredient (API) within multiphase dermal formulations with regard to its impact on API-degradation and skin penetration is little understood. This contribution determines the betamethasone dipropionate (BDP) distribution behaviour with the Dianorm® Equilibrium Dialyser initially produced for analysis of protein receptor bindings [1]. BDP shows UV-detectable degradation products, has low water solubility and has been used in approved formulations [2]. For a robust method development buffer-methanol mixtures were used as one-phase systems to examine the impact of various membranes on the diffusion of BDP. In a second step the micellar solubilisation of BDP in aqueous polysorbate 80 (PS) mixtures was studied (which might affect its degradation) [3].

Methods:
Solvent 1 contained citric buffer pH 5 and methanol (70/30 v/v) while solvent 2 was an aqueous 5% PS (w/w) mixture. Donor medium (dispersion of BDP in solvent) and acceptor medium were filled in PTFE-cells (n=5) separated by membranes and equilibrated at 25 °C for 6 h and 24 h, respectively. The process was performed under sink conditions. Membranes made of polycarbonate (0.1 µm, 0.45 µm), PTFE (0.1 µm, 0.45 µm), cellulose (5 kDa), regenerated cellulose (8 kDa, 25 kDa, 50 kDa) and hydrophilic cellulose ester (HCE, 0.5 kDa, 5 kDa, 20 kDa, 100 kDa) with various molecular weight cut offs (MWCO) were used. Membranes were extracted in methanol. Samples were analysed via UPLC with PDA detector. Statistical analysis was performed with one-way ANOVA and an equivalence test to control the equilibrium of the donor and acceptor medium (α=0.05).

Results:
The solubility of BDP varied between the solvents: 0.456±0.010 µg/ml in citric buffer, >37 mg/ml in methanol, 0.023±0.002 mg/ml in solvent 1 and 0.278±0.000 mg/ml in solvent 2 (5% PS).

As 6 h of running time of the dialysis experiment with solvent 1 were too short for equilibration, 24 h were selected. All membranes except those made of regenerated cellulose (8 kDa: p=0.206, 25 kDa: p=0.321, 50 kDa: p=0.268) reached an equilibrium between donor and acceptor media after 24 h ($p<0.05$). The BDP recovery rate was highest for polycarbonate, PTFE and cellulose membranes (111.8±6.9%). Less than half of the initial BDP concentration (49.7±5.6%) was recovered using the HCE membranes. No significant differences were found within the varying MWCOs of the HCE membranes (p=0.057). The recovery decreased with increasing thickness of the membranes.

5% PS aqueous solutions loaded with 22 µg/ml BDP were dialyzed through HCE membranes with MWCOs of 5 kDa and 100 kDa over 24 h. MWCO of 5 kDa is too low for unhindered diffusion of micellar-bound BDP (molecular weight of PS micelles is around 112-127 kDa depending on quality/distributor) [4]. Thus, only low BDP concentration was found in the acceptor medium (1.2±1.1%, p=1.000). With the 100 kDa membrane micellar BDP transport was determined 45.2±1.3% (p=0.012).

Conclusion:
Membranes showed varying recovery rates depending on their thickness. Micellar solubilisation of BDP as well as its (micellar) transport through membranes with suitable MWCO is possible. A robust method for determination of API transport with the Dianorm® Equilibrium Dialyser was established. Further research is needed to identify the reasons for the low recovery rate. The behaviour of semisolid formulations has to be investigated in the future.

Literature:
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