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# Correlation between free aqueous preservative concentration in emulsion gels measured by equilibrium dialysis and antimicrobial efficacy

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**Introduction:** Antimicrobial testing is a time consuming and cost-intensive but essential method for evaluation of newly developed pharmaceutical formulations for topical use. Partition between oil and aqueous phase of semisolid formulations and the lipophilicity of the preservative are key factors for effective antimicrobial efficacy [1,2]. In this study the correlation between free preservative concentration measured by equilibrium dialysis and the successful preservative effectiveness testing (PET) for Pseudomonas aeruginosa, Staphylococcus aureus, Candida albicans and Aspergillus brasiliensis (analysed according to Ph. Eur. and USP [3,4]) was investigated.

**Methods:** Equilibrium dialysis was performed to calculate the free preservative concentration in the aqueous phase. Emulsion gels with varying oil phases (liquid paraffin/ medium chain triglycerides) and emulsifier types (PEG-21-stearylether, polysorbate 80) were prepared. PEG 400 was added to further formulations. Donor media contained 0.5% phenoxyethanol in the emulsion gels. Donor and acceptor medium (citric buffer) were filled in PTFE-cells (n=5) separated by a 5 kDa hydrophilic cellulose ester membrane and equilibrated at 25 °C for 24 h. The membranes were extracted in methanol. Additionally, partition coefficients between the oil phases and citric buffer were measured. Samples were analysed via UPLC with PDA detector. The phenoxyethanol concentration in the aqueous phase of the donor was calculated according to [1]. A two-sided t-test was used for statistical analysis ($\alpha$=0.05). PET-test was performed according to Ph. Eur. 5.1.3.

**Results:** Medium chain triglycerides showed a significantly ($p<0.010$) higher partition coefficient for phenoxyethanol (log P 0.709 ± 0.070) than liquid paraffin (log P -0.746 ± 0.052) as it was a H-bond acceptor and therefore, increased the solubility in the oil phase.

The 5 kDa membrane allowed the transport of un-bound phenoxyethanol. Increased emulsifier concentrations reduced the free amount of the preservative due to micellar interactions. The addition of PEG 400 led to significantly increased preservative concentrations in the aqueous phase ($p<0.02$). The higher the lipophilicity of the oil phase and the lower the content of the aqueous phase with regard to dissolved ingredients, the more preferably phenoxyethanol is distributed to the water phase and, consequently, the higher was the efficacy against the microbes. Required phenoxyethanol concentrations in the aqueous phase for a successful PET-test

were: Ph. Eur.: 1.085±0.315%; USP: 0.640±0.407%. High standard deviations underlined the variability in the response of microorganisms. Aspergillus brasiliensis was the most resistant and Staphylococcus aureus the most sensitive microorganism for emulsion gels preserved with phenoxyethanol. The criteria of the pharmacopeias showed significant differences in the PET-test acceptance of the emulsion gels for the fungi as the USP had less stricter requirements.

**Conclusion:** Free preservative concentration can be measured with equilibrium dialysis. This method might be used as a predictive tool for estimation of the required preservative concentration for antimicrobial stability. Emulsifier concentrations and oil phase composition influenced the partition of preservative into the aqueous phase. For successful PET-testing Aspergillus brasiliensis should be used as the key factor as it is the most resistant microorganism for topical formulations.

**References**

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