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How does the emulsifier concentration affect API stability in emulsion gels and skin penetration?

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Introduction: The partitioning of APIs and functional excipients (e.g. the preservative phenoxyethanol) in emulsion systems is affected by various factors such as emulsifier type and concentration. As polysorbate 80 is an often-used emulsifier and good solubilizer, this emulsifier was chosen in varying concentrations (0.15%, 1.5% and 5.0%) to determine the influence on chemical stability and skin penetration in correlation to the micellar solubilization of betamethasone dipropionate (BDP) in emulsion gels. In addition, polyethylene glycol 400 (PEG 400) was added to increase BDP partitioning into the aqueous phase.

Methods: In order to determine solubility, BDP was added to various solutions (0.15%, 1.5%, 3.0% and 5.0% polysorbate 80 or 20%, 40%, 60% PEG 400 in citric buffer, w/w) to form suspensions. After 24 h, the clear filtrates were analyzed.

Emulsion gels were prepared with 30% medium chain triglycerides, 0.5% xanthan gum, polysorbate 80 (0.15%, 1.5%, 5.0%), 0.5% phenoxyethanol and 0.064% BDP. Either citric buffer pH 5 or phosphate buffer pH 8 were used as aqueous phase. Another emulsion gel with 1.5% emulsifier and 13.5% PEG 400 was prepared (all w/w).

For API stability measurements, 0.5 g of every emulsion gel was mixed with 10 mL of an aqueous 10% calcium chloride solution. BDP and degradation products were extracted with methanol acidified with 0.1% trifluoric acid. The formulations were tested at the start and after 3, 6, 9 and 12 weeks of storage at 25 °C or 40 °C.

Emulsion gel and acceptor medium (citric buffer) were filled into separate dialysis chambers (membrane cut-off of 5 or 300 kDa) and equilibrated at 25 °C for 24 h (n=5). The concentrations of BDP, phenoxyethanol and polysorbate 80 were recalculated assuming a dilution of the aqueous phase of the emulsion gel with the acceptor.

BDP penetration into the epidermis was determined using viable pig ear skin as described by Herbig et al. [1]. All samples were analyzed by a UHPLC coupled to a photodiode array detector or

a mass detector (polysorbate 80, skin samples).

Results: A good correlation between the solubility of BDP and the polysorbate 80 concentration was seen (R^2>0.999). Upon addition of PEG 400, significantly more BDP was dissolved in citric buffer.

With increasing emulsifier concentration in the emulsion gels, significantly higher BDP degradation was seen at 40 °C and pH 8 ($p<0.05$). Upon addition of the cosolvent PEG 400, the stability of BDP decreased regardless of the buffer system used compared to the cosolvent-free formulation.

Varying emulsifier concentrations showed no impact on the free BDP and phenoxyethanol concentration in the emulsion gels. Upon addition of PEG 400 more BDP was distributed into the aqueous phase due to increased solubility. BDP solubilization was demonstrated with increasing emulsifier concentrations (micellar molecular weight 127 kDa [2]), when using a membrane allowing micellar transport.

The emulsifier concentration had no significant impact on the ex vivo skin penetration. The formulation with PEG 400 showed significantly lower values due to decreased thermodynamic activity.

Conclusion: Due to an increased solubilization of BDP in the aqueous phase with increasing emulsifier concentration, more BDP was degraded at accelerated conditions. Rational formulation design is necessary for ensuring the ideal emulsifier concentration for minimized degradation and sufficient formulation stabilization.

[1] M.E. Herbig et al. A custom-tailored model to investigate skin penetration in porcine skin and its comparison with human skin, Eur. J. Pharm. Biopharm., 95, 99-109 (2015).
[2] A.C. Braun et al. Predicting critical micelle concentration and micelle molecular weight of polysorbate 80 using compendial methods, Eur. J. Pharm. Biopharm., 94 (2015) 559–568.