What Is the True Driving Force for Drug Absorption in the Presence of Solubilizing Excipients?

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Purpose

The use of enabling formulations to increase the apparent solubility of poorly soluble compounds and their oral bioavailability has increased tremendously. However, many studies show that even when enabling formulations are employed, the drug oral bioavailability is difficult to predict and not necessarily improved. In this research, the influence of solubilizing excipient (i.e. surfactant) on the supersaturation and absorption of a poorly soluble model compound across a membrane was investigated.

Methods

Absorption study was performed using PermeGear© diffusion cells with a volume of 30 mL and surface area of 7.07 cm2. Regenerated cellulose dialysis membrane 6-8 kDa was employed in the absorption study. Aliquot of solution was taken and drug concentration was measured as a function of time using HPLC with a Symmetry C18 column (4.6 mmX150 mm,5 μm) and 70:30 methanol/water isocratically at 1 mL/min and λ=280 nm. Polysorbate 80 (PS80), and estradiol (E2) were used as model surfactant and drug, respectively.

Results

In the absence of surfactant, there is a linear relationship between E2 degree of supersaturation (DOS) and flux across the membrane up to a concentration of 10 μg/mL, at which E2 experiences amorphous phase separation (APS), where flux plateaus. The effective permeability of E2, which is assumed to be constant at various DOS, was calculated to be 3.8x10-5 cm/s via Fick's first law equation. In the presence of surfactant, a similar linear trend between DOS and flux was observed, which then plateaus, except that this linear relationship occurs at a lower slope. However, the E2 concentrations at which this linear trend is observed in the presence of surfactant is much higher than those in the absence of surfactant. Interestingly, when dosed at higher DOS, surfactant micelles can sequester as high as 4 times higher than that at E2 equilibrium solubility. In addition, at the same dose, the presence of surfactant diminishes E2 flux across the membrane. Further investigations are currently undertaken to evaluate flux at higher DOS, the E2 concentration at which APS occurs in the presence of surfactant, and the micellar structures at equilibrium and supersaturated state.

Conclusion

Flux study was able to distinguish the true driving force for drug absorption across the membrane in the absence and presence of surfactant. The fact that at the same dose surfactant actually diminishes drug flux indicates that flux study can be useful in the in vitro in vivo correlation evaluation.