Mathematical Modelling of Receiver-Mediated Flux Enhancement in Hollow Fibre Membrane Drug Permeability Studies

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Background: Hollow fibre membranes (HFMs) offer a continuous flow-through setup and a large surface area-to-volume ratio, making them an attractive choice for *in vitro* drug permeability studies. Solubilising agents may be added to receiver media to prevent loss of transmembrane sink conditions and reduce nonspecific binding. Recently published research indicates that flux is enhanced in HFM when surfactant is added to the receiver medium. This study further interrogates this observation to develop a mathematical model which links receiver media composition to mass transfer.

Methods: Permeability studies using the model drug griseofulvin (GRS) were performed in a HFM consisting of 36 modified poly(ether sulphone) hollow fibres (10 KDa cutoff, 115 cm^2 surface area). GRS solutions were pumped through the lumen of the hollow fibres and recycled, while receiver media were pumped co-currently outside the fibres in a single pass. Flow rate experiments were performed to quantify boundary layer and membrane resistances. The effect of nine solubilising additives, including six surfactants, two cyclodextrins, and bovine serum albumin, at various concentrations on flux was investigated. Experiments were conducted over two hours at a fixed flow rate with negligible advection. GRS solubility in each receiver medium was determined, and back-diffusion of solubilising additives was evaluated. A mathematical model was developed which links solubility-enhanced reductions in membrane and receiver-side boundary layer resistances to flux. To assess the broader applicability of the model, a series of drug cocktail permeability studies with antipyrine, phenytoin, and meloxicam were conducted.

Results: Flow rate experiments confirmed that the mass transfer coefficient scales with the cubed root of the donor fluid velocity, consistent with laminar flow and convection-enhanced diffusion. At low flow rates with a negligible transmural pressure gradient, no single resistance was rate limiting. Flux enhancement varied across solubilising additives, with the ratio of flux enhancement following the rank order but not the magnitude of the solubility ratio (Spearman's $\rho = 0.93$, $p < 0.001$, $n = 18$). Cetrimonium bromide 2% w/v, the most effective solubiliser, was associated with a ~96-fold GRS solubility enhancement but only a ~5-fold increase in flux. Cyclodextrins exhibited notable back-diffusion of up to ~12%, whereas other additives showed minimal or no detectable reverse permeation. At low solubility ratios, increases in observed flux are likely attributed to improved recovery of drug from the apparatus. At high solubility ratios, modelling suggests that donor-side boundary layer resistance becomes rate limiting and flux therefore plateaus. This hypothesis was consistent with the flux data observed for antipyrine and phenytoin in the drug cocktail study. Meloxicam, however, showed deviation which was likely due to back-diffusion of cyclodextrins.

Conclusions: This study demonstrates that solubilising components in receiver media can significantly increase drug flux in HFM, with models identifying reductions in membrane and receiver-side boundary layer resistance as the primary mechanism of flux enhancement. These findings provide a mechanistic framework for the informed selection of receiver media additives in permeability assays and formulation screening. The development of physiologically relevant receiver media merits further investigation.