Bi-phasic Mass Transfer and Trans-membrane Diffusion in Emulsions

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1. FDA/CDER/OPQ/OTR/DRPQ, Silver Spring, MD 20993; 2. FDA/CDER/OGD/ORS, Silver Spring, MD 20993; 3. FDA/CDER/OTS/OCP, Silver Spring, MD 20993; 4. FDA/CDER/OPQ/OLDP, Silver Spring, MD 20993; 5. FDA/CDRH/OSEL/DBCMS, Silver Spring, MD 20993.

Purpose

Dialysis membranes, in either dialysis or reverse dialysis setup, are commonly used in drug release studies of complex dosage forms such as emulsions, liposomes, suspensions etc. In particular, the overall drug release from oil-in-water emulsions through the dialysis membrane is considered to be a result of two sequential steps: (1) drug partitioning from emulsion oil globules into the aqueous medium, and (2) drug diffusion across the dialysis membrane. As the emulsions undergo dilution with aqueous media in either dialysis or reverse dialysis configuration, a new equilibrium of drug partitioning between oil and aqueous phase is re-established, followed by trans-membrane diffusion. The current study was carried out using emulsion as a model system to investigate the kinetics of both steps and to provide a theoretical basis on the feasibility and limitation of using dialysis methods in a drug release study.

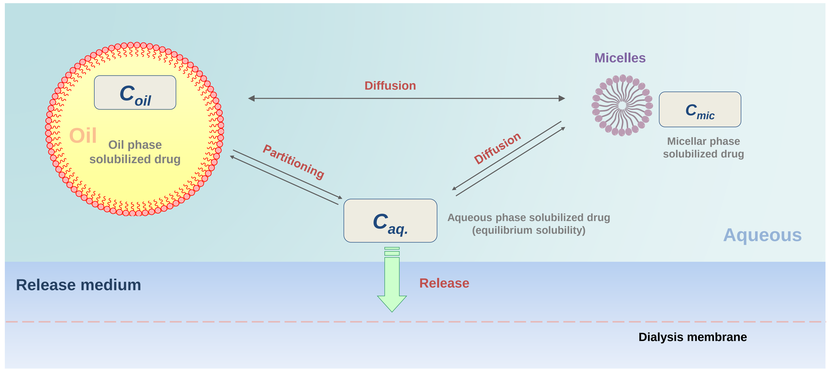

Figure 1. Role of drug partitioning/diffusion on drug distribution and release of emulsions.

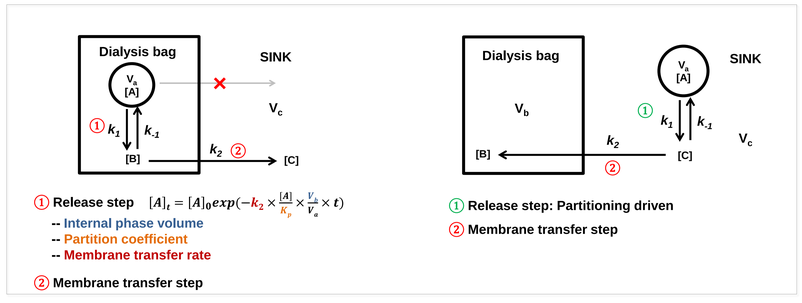

Figure 2. Kinetics of transfer involving dialysis or reverse dialysis membranes.

Method

A bi-phasic mass transfer study of difluprednate (DFP) between castor oil and aqueous phases was performed using PION µDISS Profiler™. The real-time change of drug concentration in aqueous phase over time was monitored through an *in-situ* fiber optic UV probe. To investigate the trans-membrane diffusion kinetics of emulsions, several cyclosporine emulsions were prepared using castor oil and aqueous phase containing Tween 80. The drug diffusion across dialysis membrane from emulsions and pure drug solution were evaluated.

Results

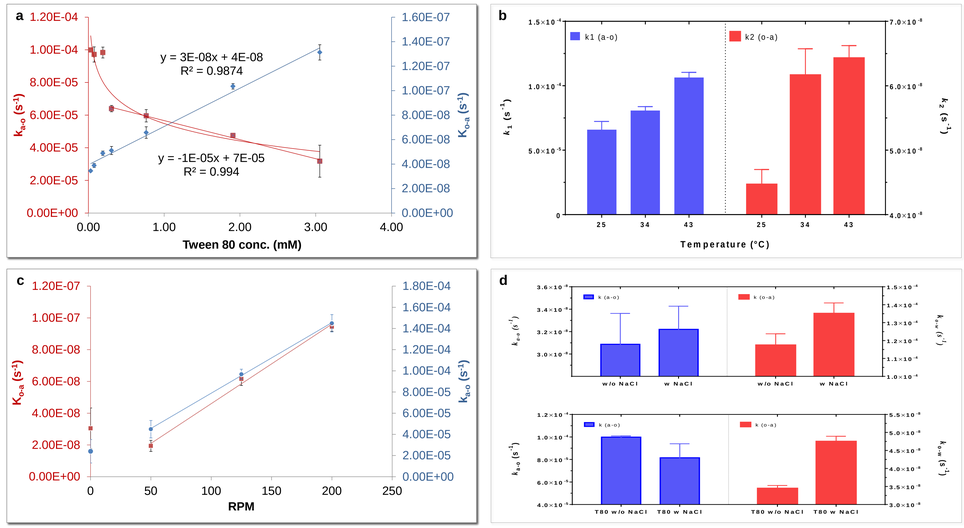

Figure 3. The effects of various experimental conditions on the bi-phasic transfer rate constants of DFP (a: Tween concentration; b: temperature; c: stirring rate; d: ionic strength).

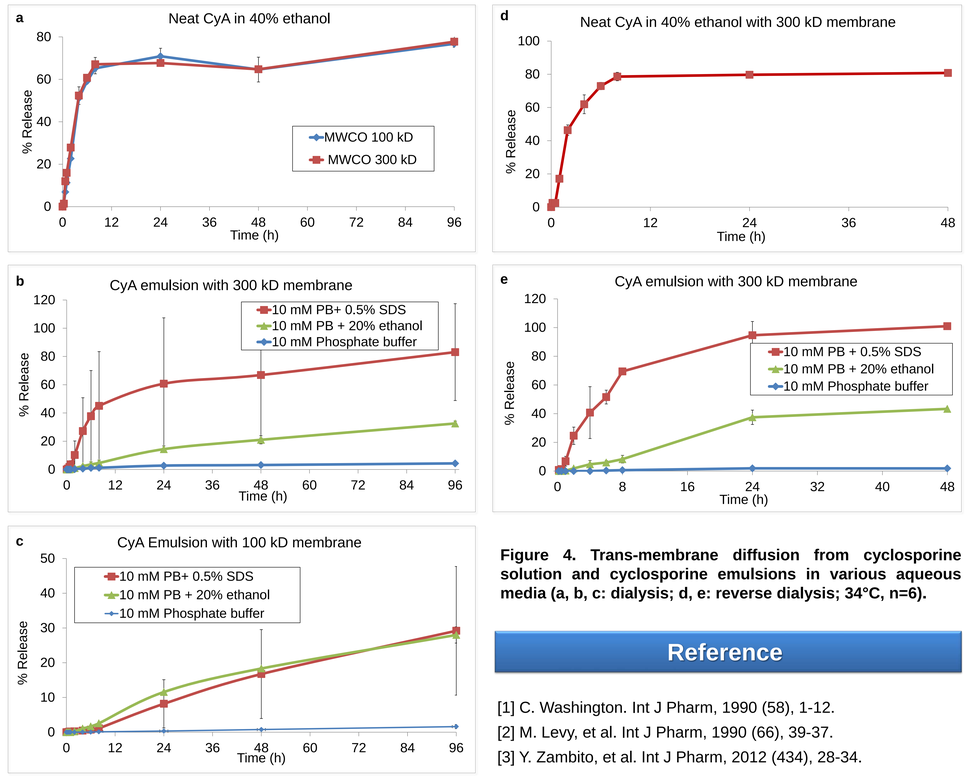

Figure 4. Trans-membrane diffusion from cyclosporine solution and cyclosporine emulsions in various aqueous media (a, b, c: dialysis; d, e: reverse dialysis; 34°C, n=6).

Table 1. Effect of Tween concentration on apparent LogP of DFP.

Conc. of Tween 80 (mM/L)	Log P_{app}
0.00	3.504 ± 0.066
0.03	3.425 ± 0.008
0.08	3.350 ± 0.070
0.31	3.174 ± 0.009
0.76	2.893 ± 0.020
3.05	2.476 ± 0.097
30.53	1.884 ± 0.015

Table 2. Effect of stirring rate on apparent LogP of DFP.

Stirring rate (rpm)	Log P_{app}
0	2.897 ± 0.623
50	3.364 ± 0.258
125	3.196 ± 0.083
200	3.186 ± 0.065

Table 3. Effect of temperature on apparent LogP of DFP.

Temperature (°C)	Log P_{app}
25	3.169 ± 0.112
34	3.117 ± 0.078
43	3.220 ± 0.047

Table 4. Effect of ionic strength on apparent LogP of DFP.

Media	Log P_{app}
Water w/o NaCl	3.608 ± 0.165
Water w/ NaCl	3.602 ± 0.085
0.004% T80 w/o NaCl	3.462 ± 0.028
0.004% T80 w/ NaCl	3.235 ± 0.156

Table 5. The drug diffusion kinetics across dialysis membrane from cyclosporine emulsions and pure drug solution.

Membrane MWCO	Release media	Rate constant (s^{-1})	
		Dialysis	Reverse dialysis
300 kD	10 mM PB (pH 7.4)	5.01E-07	2.21E-07
	10 mM PB + 0.5% SDS	1.72E-05	2.46E-05
	10 mM PB + 20% ethanol	1.75E-06	3.05E-06
	40% ethanol	2.36E-05	2.83E-05
100 kD	10 mM PB (pH 7.4)	3.40E-08	N/A
	10 mM PB + 0.5% SDS	3.64E-07	N/A
	10 mM PB + 20% ethanol	9.27E-07	N/A
	40% ethanol	2.42E-05	N/A

Conclusions

Mass transfer kinetics of drug between oil and aqueous phase as well as into release media were successfully determined. Based on obtained rate constants and LogP_{app}, it is possible to determine drug concentration in various components of an emulsion after a change in equilibrium (e.g. dilution, salt addition, etc.) as well as time to reach the new equilibrium (e.g. time to complete drug release). The current setup allows for evaluation of the impact of surfactant, temperature, stirring rate, ionic strength etc. on both rate and extend of drug availability.

Acknowledgements

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Disclaimer

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Reference

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