Understanding Drug Distribution and Release in Ophthalmic Emulsions

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PURPOSE

Establishing bioequivalence (BE) of ophthalmic emulsions in the absence of in vivo data can be challenging. The objective of this study is to understand the underlying mechanism and process of drug distribution and release (Figure 1A) in the context of formulation and (release) environment-associated variables that are important for BE assessment.

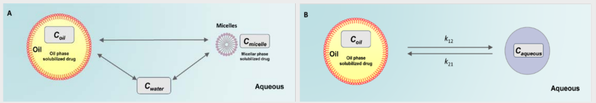

Figure 1. A) The phase composition and complex drug diffusion in the microenvironment of an emulsion formulation; B) The simplified scenario of phase composition and drug diffusion in an emulsion formulation.

METHODS

A novel kinetic method for determining drug partitioning (Figure 2) was used to quantitatively evaluate the rate and extent of drug distribution within a simplified biphasic emulsion system (Figure 1B).

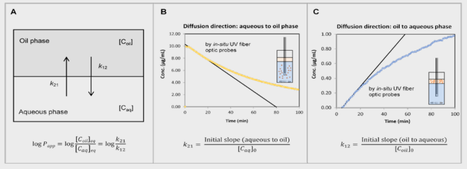

Figure 2. Theoretical basis of the kinetic method to determining partition coefficient.

The experimental setup consisted of a dissolution work station providing agitation control, in-situ UV fiber optics for real time concentration analysis and a circulating water bath for temperature control (Figure 3). Cyclosporine (CyA) and diflupredate (DFP) were used as the model drugs. The formulation-variables included the amount of polysorbate 80, glycerin, and carbomer copolymer as well as the oil-aqueous interfacial area. The investigated (release) environment-associated variables were concentrations of sodium dodecyl sulfate (SDS) and ethanol, ionic strength, temperature, and agitation rate.

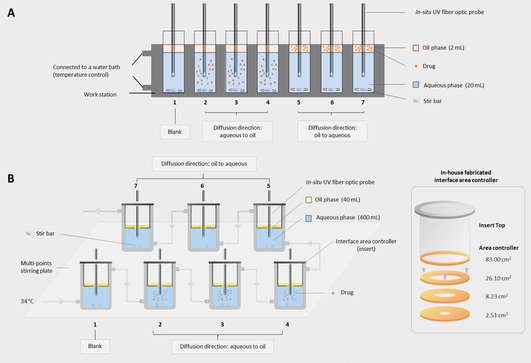

Figure 3. A) The experimental setup for evaluating the effects of formulation- and environment-associated variables, including the fiber optic dissolution work station and 25 mL mini vessels. B) The experimental setup for evaluating the effect of interfacial area, consisting of 1000 mL jacketed beakers and in-house fabricated interfacial area controller with switchable bottom inserts.

RESULTS

Table 1. Apparent partition coefficient values of CyA and DFP with respect to polysorbate 80 concentration determined by kinetic method and equilibrium concentration method (mean ± sd, n=3).

Drug	Concentration of Polysorbate 80 (%, w/w)	Log P_{app} = log (k_{21}/k_{12}) Kinetic method	Log P_{app} = log ($[C_{oil}]_{eq}$/$[C_{aq}]_{eq}$) Equilibrium concentration method
CyA	0	4.764 ± 0.109	4.533 ± 0.367
	0.005	4.723 ± 0.083	4.607 ± 0.108
	0.01	4.669 ± 0.043	4.551 ± 0.194
	0.1	4.047 ± 0.231#	4.115 ± 0.120
	1.0	3.299 ± 0.078#	3.204 ± 0.042
DFP	0	3.542 ± 0.084	3.504 ± 0.066
	0.004	3.471 ± 0.028	3.425 ± 0.008
	0.01	3.405 ± 0.052	3.350 ± 0.070
	0.025	3.304 ± 0.050	n/d
	0.04	3.098 ± 0.071	3.174 ± 0.009
	0.1	2.957 ± 0.096	2.893 ± 0.020
	0.25	2.662 ± 0.030	n/d
	0.4	2.413 ± 0.062	2.476 ± 0.097
	4.0	n/d	1.885 ± 0.076

n/d: Not determined.
#: Aqueous concentrations were analyzed by HPLC or UPLC after sampling.

Table 2. Apparent partition coefficient values of CyA and DFP with respect to changes in several formulation variables as determined by the kinetic method (mean ± sd, n=3).

Drug	Formulation variable	Tested condition	Log P_{app}
CyA	Glycerin (w/w)	0%	4.669 ± 0.043
		0.2%	4.691 ± 0.133
		1.0%	4.881 ± 0.269
		2.0%	5.006 ± 0.164
	Carbomer (w/w)	0%	4.764 ± 0.109
		0.005%	4.354 ± 0.111
		0.05%	3.898 ± 0.258
		0.005% in 0.1% polysorbate 80	4.287 ± 0.170
	Interfacial area to aqueous volume ratio (cm^2/mL)	0.006	4.414 ± 0.265
		0.020	4.774 ± 0.330
		0.065	4.658 ± 0.207
		0.207	4.764 ± 0.180
DFP	Glycerin (w/w)	0%	3.205 ± 0.042
		0.2%	3.137 ± 0.072
		1.0%	3.145 ± 0.076
		2.0%	3.236 ± 0.057
	Interfacial area to aqueous volume ratio (cm^2/mL)	0.006	2.904 ± 0.392
		0.020	3.246 ± 0.310
		0.065	3.137 ± 0.212
		0.207	3.216 ± 0.131

Figure 4. Biphasic diffusion rate constants determined by the kinetic method with respect to the concentrations of polysorbate 80. A) CyA; B) DFP. (mean ± sd, n=3).

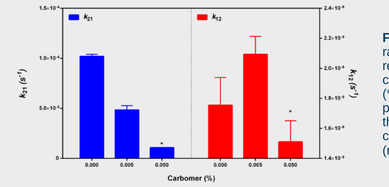

Figure 5. Biphasic diffusion rate constants of CyA with respect to the concentrations of carbomer (* The experiment was performed at 400 rpm due to the high viscosity of carbomer solution). (mean ± sd, n=3).

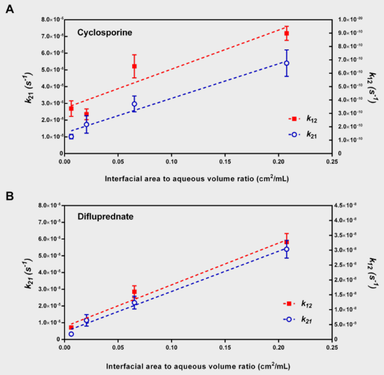

Figure 6. Biphasic diffusion rate constants with respect to the interfacial area. A) CyA; B) DFP. (mean ± sd, n=3).

Table 3. Apparent partition coefficient values of CyA and DFP with respect to changes in several environment variables as determined by the kinetic method (mean ± sd, n=3).

Drug	Environment variable	Tested condition	Log P_{app}
CyA	SDS (w/w)	0%	4.764 ± 0.109
		0.25%	1.704 ± 0.188
		0.50%	0.417 ± 0.315
		1.00%	0.476 ± 0.309
		0.50% in 0.01% polysorbate 80	0.943 ± 0.268
	Ethanol in polysorbate 80 (0.01%, w/w)	0%	4.669 ± 0.043
		10%	4.488
		20%	3.913 ± 0.128
		25%	3.268 ± 0.262
	Ionic strength in polysorbate 80 (0.01%, w/w)	0	4.669 ± 0.043
		0.141	4.801 ± 0.111
		0.3	4.923 ± 0.151
	Temperature in polysorbate 80 (0.01%, w/w)	25°C	4.498 ± 0.088
		34°C	4.669 ± 0.043
		43°C	N/A
DFP	SDS (w/w)	0%	3.542 ± 0.084
		0.25%	2.385± 0.097
		0.50%	1.389 ± 0.152
		1.00%	0.936 ± 0.160
		0.50% in 0.04%vpolysorbate 80	1.442 ± 0.198
	Ethanol in polysorbate 80 (0.04%, w/w)	0%	3.098± 0.071
		10%	2.854 ± 0.049
		20%	2.490 ± 0.131
		30%	1.904 ± 0.314
	Ionic strength in polysorbate 80 (0.01%, w/w)	0	3.210 ± 0.286
		0.141	3.317 ± 0.097
		0.3	3.215 ± 0.171
	Temperature in polysorbate 80 (0.04%, w/w)	25°C	3.204 ± 0.108
		34°C	3.205 ± 0.042
		43°C	3.160 ± 0.046
	Agitation in polysorbate 80 (0.04%, w/w)	0	2.844 ± 0.668
		50	3.300 ± 0.188
		125	3.196 ± 0.083
		200	3.186 ± 0.065

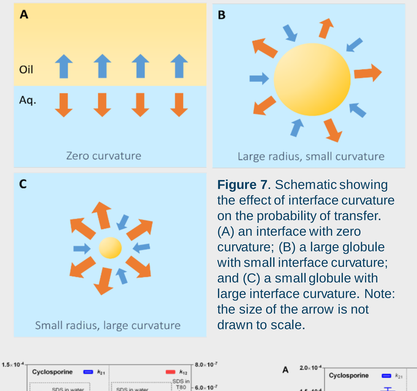

Figure 7. Schematic showing the effect of interface curvature on the probability of transfer. (A) an interface with zero curvature; (B) a large globule with small interface curvature; and (C) a small globule with large interface curvature. Note: the size of the arrow is not drawn to scale.

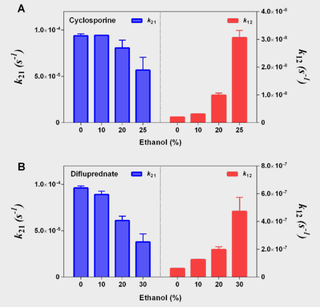

Figure 8. Biphasic diffusion rate constants with respect to the concentrations of ethanol. A) CyA; B) DFP. (mean ± sd, n=3).

Figure 9. Biphasic diffusion rate constants with respect to the concentrations of SDS. A) CyA; B) DFP. (mean ± sd, n=3).

Figure 10. Biphasic diffusion rate constants as a function of temperature. A) CyA; B) DFP. (mean ± sd, n=3).

Figure 11. Biphasic diffusion rate constants of DFP with respect to the stirring rate. (mean ± sd, n=3).

CONCLUSIONS

The formulation- and environment-associated variables impacted the drug distribution and release in biphasic emulsion systems.

This study provided insight into the drug distribution and diffusion in complex ophthalmic emulsions. It could serve as a tool to assist with formulation design as well as development of in vitro methods to determine the product sameness to support BE assessment of ophthalmic emulsions.

Factor change		Rate (to aq.)	Extent (to aq.)
Formulation-associated variables	Surfactant (e.g., Polysorbate 80) conc. ↑	↑↑↑	↑↑↑
	Carbomer conc. ↑	CyA ↑	CyA ↑
	Glycerin conc. (viscosity) ↑	CyA ↓ DFP —	CyA ↓ DFP —
	Total surface area (i.e., globule size) ↑	↑↑	— (Underestimating due to curvature effect)
Environment-associated variables	SDS conc. ↑	↑↑↑	↑↑↑
	Ethanol conc. ↑	↑↑	↑↑
	Ionic strength ↑	CyA ↓ DFP —	CyA ↓ DFP —
	Temperature ↑	CyA ↓ DFP ↑	CyA ↓ DFP —
	Stirring rate ↑	DFP ↑	DFP —

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DISCLAIMER

This poster reflects the views of the authors and should not be construed to represent FDA's views or policies.

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