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MODELING APPROACH FOR ASSESSING THE IMPACT OF PHYSICOCHEMICAL PROPERTIES ON BIOEQUIVALENCE OF CYCLOSPORINE OPHTHALMIC EMULSION

Ross Walenga, Andrew Babiskin, Mohammad Absar, Xinyuan Zhang, Liang Zhao, Robert Lionberger

Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration

CONTACT INFORMATION: Ross Walenga, Ross.Walenga@fda.hhs.gov.

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PURPOSE

According to the draft product-specific guidance for cyclosporine ophthalmic emulsion from the U.S. Food and Drug Administration,[1] generic drug applicants are provided either an in vivo or in vitro option for establishing bioequivalence (BE) to the reference-listed product (RESTASIS). For the in vitro option, a test product should be qualitatively (Q1) and quantitatively (Q2) the same as the reference product, show acceptable comparative drug release rates, include information on drug distribution within the different phases of the formulation, and have comparable physicochemical properties to that of the reference product with regard to globule size distribution, viscosity profile as a function of applied shear, pH, zeta potential, osmolality, and surface tension. This study seeks to predict drug bioavailability and tear film breakup time (TBUT) based on the viscosity profile, surface tension, and osmolality using a modeling approach, with the aim of assessing the relative influence of these parameters on BE determination.

METHODS

- Physics-based model of TBUT based on Braun[2] solves for change in one-dimensional transient human tear film profile, where breakup occurs at upper limit of the glycocalyx.
- Five compartment model of tear film based on Cerretani and Radke[3] (as shown in Figure 1) is used to predict corneal and conjunctival bioavailability in humans. The five compartments include the tear film, the upper and lower menisci, and the upper and lower conjunctival sacs.
- Model parameters include viscosity, surface tension, and osmolality.
- Viscosity is modeled via a power law relationship as $\mu = \kappa\left(\frac{\partial u}{\partial y}\right)^{n-1}$, where μ is the viscosity, $\frac{\partial u}{\partial y}$ is the shear rate, while κ and n are parameters.
- Model includes effects of drainage, evaporation, lacrimation, and osmotic absorption.
- Five Q1/Q2 test formulations are considered in addition to the reference product (three samples from each).
- Corneal and conjunctival permeability are varied to assess impact of these parameters (Table 1).
- Percentage of mixing between menisci and conjunctival sacs (ε) was varied from minimum possible amount (ε = 0.66) to complete mixing (ε = 1).
- Geometric mean ratio of test to reference for conjunctival bioavailability (T/R) was calculated using modeled results from three samples from each formulation and assuming a parallel study design.
- Sensitivity analyses of conjunctival bioavailability and ΔTBUT were done, where bioavailability represented the fractional amount of drug absorbed predicted by the model, and ΔTBUT was the change in TBUT from the dry eye baseline of 2.3 s (measured by Tung et al.[4]) predicted 20 minutes after drug instillation.
- Both models were written and solved using MATLAB 2016.

Case	Permeability (m/s)	
	Cornea	Conjunctiva
1	5.5×10^{-9}	1.8×10^{-9}
2	1.1×10^{-8}	3.7×10^{-9}
3	1.1×10^{-8}	1.1×10^{-8}
4	1.1×10^{-7}	3.7×10^{-8}

Table 1. Bioavailability prediction cases with corresponding values of corneal and conjunctival permeability.

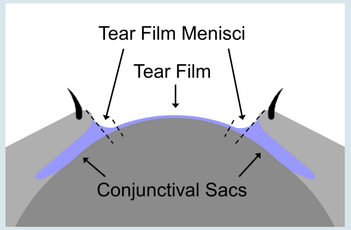

Figure 1. Locations of the five compartments used for bioavailability calculations, illustrated in the sagittal plane of a subject in the supine position.

RESULTS

- TBUT model prediction for dry eye case matches measured value of 2.3 s from Tung et al.[4] with assumed glycocalyx height of 133 nm (Figure 2).
- TBUT model prediction for Refresh Liquigel with glycocalyx height of 400 nm is 43.4 s (Figure 2), compared to fluorescein tear film breakup time (FTBUT) measurement of 17 s.[5]
- However, literature suggests that FTBUT measurements may under-predict TBUT by a factor of as high as 2.5.[6]
- The maximum possible tissue concentration predictions of Restasis for permeability Case 2 were 877.2 ± 26.7 ng/g in the cornea and 1041.1 ± 32.0 ng/g in the conjunctiva, which would occur if no clearance were present (which the model does not include).
- For comparison, maximum measured tissue concentration values in single-dose study of 50 µL of Restasis instilled into rabbits were 747.7 ng/g in the cornea and 848.8 ng/g in the conjunctiva.[7]
- T/R predictions for four permeability cases and five test formulations are shown in Table 2.
- Sensitivity analyses of bioavailability and ΔTBUT of viscosity profile, surface tension, and osmolality are given in Figure 3 and Figure 4.
- ΔTBUT predictions were made for each test formulation and the reference product (data not shown). In all cases the mean values of ΔTBUT for the test products were higher than the reference product.

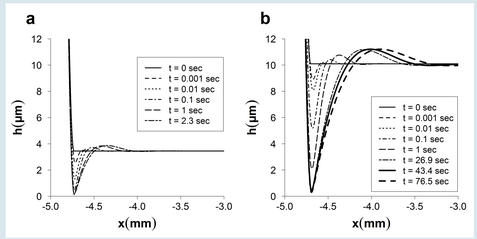

Figure 2. Tear film height (h) as a function of distance from the cornea center (x) as predicted by tear film breakup time (TBUT) model at different times, where t = 0 corresponds to the beginning of the interblink cycle, for the a) dry eye condition and b) after instillation of Refresh Liquigel onto the eye of a dry eye patient. The value of x = -5.0 mm corresponds with the location of the upper eye lid.

Table 2. Geometric mean ratio of test to reference comparison (T/R) of conjunctival bioavailability using a parallel study design with the 90% confidence intervals (CIs) for the four permeability cases listed in the Methods, where ε = 1.

		Test 1	Test 2	Test 3	Test 4	Test 5
Case 1	T/R	1.08	1.04	1.21	1.02	1.12
	Lower 90% CI	102.50%	99.41%	112.19%	99.21%	103.98%
	Upper 90% CI	114.08%	108.69%	130.41%	104.46%	121.44%
Case 2	T/R	1.08	1.04	1.21	1.02	1.12
	Lower 90% CI	102.61%	99.35%	112.25%	99.20%	103.95%
	Upper 90% CI	113.85%	108.72%	130.22%	104.51%	121.33%
Case 3	T/R	1.08	1.04	1.21	1.02	1.12
	Lower 90% CI	102.86%	99.45%	112.13%	99.28%	103.99%
	Upper 90% CI	113.22%	108.58%	129.81%	104.58%	120.99%
Case 4	T/R	1.07	1.04	1.19	1.02	1.11
	Lower 90% CI	102.93%	99.43%	111.14%	99.49%	103.72%
	Upper 90% CI	111.44%	107.89%	126.57%	104.49%	118.82%

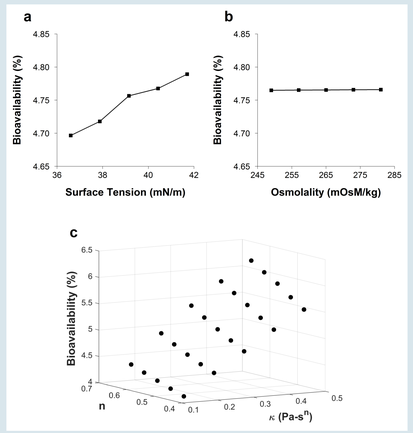

Figure 3. Predictions of total bioavailability (including the cornea and conjunctiva), where ε = 1, as a function of a) surface tension, b) osmolality, and c) viscosity in terms of non-Newtonian power law parameters n and κ.

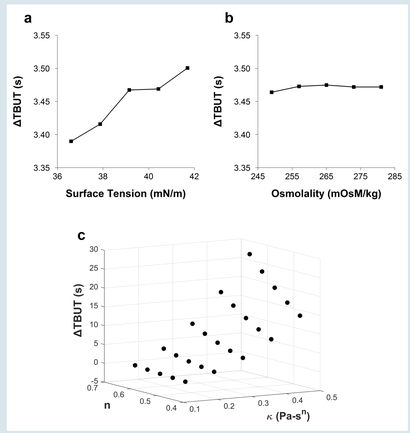

Figure 4. Predictions of change in tear film breakup time from the dry eye baseline of 2.3 sec (ΔTBUT) as a function of a) surface tension, b) osmolality, and c) viscosity in terms of non-Newtonian power law parameters n and κ.

CONCLUSIONS

- Case study predictions of test and reference formulations indicated that test to reference geometric mean ratios (T/R) of conjunctival bioavailability and corresponding 90% confidence intervals were relatively insensitive to permeability.
- Complete mixing of tear film fluid with conjunctival sac fluid in each blink cycle represented the slightly more stringent condition for T/R comparisons of conjunctival bioavailability, based on results for ε = 0.66 (not shown) and ε = 1 (Table 2).
- Parameter sensitivity analysis of ΔTBUT, corneal bioavailability, and conjunctival bioavailability predictions demonstrated a significant sensitivity to viscosity, little sensitivity to surface tension, and practically no sensitivity to osmolality.

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