Add your Assigned Poster Number by replacing this text

Impact of Changes in Ophthalmic Emulsion Globule Size Distribution and Viscosity on Tear Film Thickness and Menisci Characteristics

Sandeep Kumar[1], Nicholas Cook[1], Glenwood Gum[1], Linda Manza[1], Vatsala Naageshwaran[1], Mathew Lyulkin[1], Xiaoming Xu[2], Deval Patel[2], Haiou Qu[2], Ross Walenga[3], Ming-Liang Tan[3], Andrew Babiskin[3], Mohammad Abul Kaisar[3]

[1] Absorption Systems, a Pharmaron company, San Diego, CA
[2] Office of Testing and Research, Office of Pharmaceutical Quality, Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA), Silver Spring, MD
[3] Office of Research and Standards, Office of Generic Drugs, CDER, FDA, Silver Spring, MD

PURPOSE

The purpose of this study was to obtain tear film thickness and menisci measurements on rabbit ocular surface after instillation of cyclosporine ophthalmic emulsion formulations with differences in viscosity and globule size distribution (GSD). This information will support the development of a mechanistic absorption model to better understand and predict formulation effects on the bioavailability of cyclosporine to the cornea and the conjunctiva in humans [1-5].

OBJECTIVE

To develop an in vivo rabbit model that can be used to examine the influence of certain physicochemical properties on the predicted local bioavailability of ophthalmic emulsion products, using cyclosporine ophthalmic emulsion as a model system, and thereby help inform critical quality attribute (CQA) limits that are expected to be more clinically relevant.

METHODS

Sixteen female Dutch Belted (DB) rabbits were enrolled in the study and a total of 13 formulations were instilled at a volume of 35 µL onto the right eye (OD) on two separate occasions for each formulation and for each animal. Formulations tested included, five cyclosporine emulsion formulations (EMULCYA-F1 to F5), three placebos (P1, P2 and P3) which were compositionally identical to Restasis® but had different physicochemical characteristics, along with three lots of the reference listed drug (RLD) Restasis, the artificial tear product Refresh Liquigel®, and sterile water. Each formulation was tested for tear variables like central tear film thickness (TFT), upper tear film meniscus cross-sectional area (UMA) and lower tear film meniscus cross-sectional area (LMA) [6]. All measurements were conducted using the Heidelberg Spectralis® Eye Explorer (HEYEX) software with anterior segment optical coherence tomography (AS-OCT) scans following procedures that had been validated in a previous study. A total of 416 experiments were done.

Table 1: Globule Size Distribution (GSD) (intensity weighted; 10x diluted with DI water) of various cyclosporine emulsions (Mean ± SD, n=3).

FDA Test Formulation	Sample	Z-Average (d.nm)	PdI	Di(10) (nm)	Di(50) (nm)	Di(90) (nm)
FDA Formulation 1	EMUL-CYA-F1	112.3 ± 1.2	0.298 ± 0.007	57.4 ± 5.3	143.4 ± 5.5	299.6 ± 18.6
FDA Formulation 2	EMUL-CYA-F3	92.2 ± 1.4	0.290 ± 0.007	49.0 ± 4.2	115.7 ± 4.7	243.7 ± 12.6
FDA Formulation 3	EMUL-CYA-F4A	117.3 ± 2.3	0.306 ± 0.020	64.3 ± 8.5	148.0 ± 6.5	315.1 ± 22.6
FDA Formulation 4	EMUL-CYA-F4B	120.1 ± 1.4	0.317 ± 0.015	59.5 ± 8.0	158.5 ± 3.2	329.8 ± 21.1
FDA Formulation 5	EMUL-CYA-F5	204.4 ± 6.1	0.323 ± 0.036	110.0 ± 10.9	257.7 ± 16.2	562.7 ± 84.3
Restasis[ǂ]	Restasis	117.9 ± 2.0	0.35 ± 0.04			

*GSD encompasses size and size distribution.
ǂ DLS values reported in *International Journal of Pharmaceutics* 550.1-2 (2018): 229-239 for 10x dilution[3]

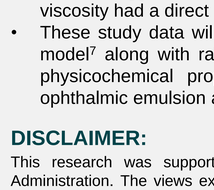
Table 2: Viscosity of various cyclosporine emulsions (Mean ± SD, n=3).

FDA Test Formulation	Sample	Apparent Viscosity (mPa.s)	Rate index
FDA Formulation 1	EMUL-CYA-F1	643.8 ± 20.0	0.460 ± 0.004
FDA Formulation 2	EMUL-CYA-F3	238.6 ± 3.7	0.572 ± 0.000
FDA Formulation 3	EMUL-CYA-F4A	246.6 ± 2.0	0.572 ± 0.004
FDA Formulation 4	EMUL-CYA-F4B	140.6 ± 7.5	0.635 ± 0.005
FDA Formulation 5	EMUL-CYA-F5	249.6 ± 3.5	0.566 ± 0.009
Placebo P1	EMUL-CYA-P1	667 ± 24	0.457 ± 0.000
Placebo P2	EMUL-CYA-P2	508 ± 70	0.493 ± 0.027
Placebo P3	EMUL-CYA-P3	1548 ± 29	0.442 ± 0.002
Restasis[ǂ]	Restasis	170.94 ± 13.61	0.52 ± 0.01

ǂ DLS values reported in *International Journal of Pharmaceutics* 550.1-2 (2018): 229-239 for 10x dilution[3]

RESULTS

Figure 1. Schematic Representation of AS-OCT Scan Types



A- Center of cornea
B- Upper Meniscus
C- Lower Meniscus

Figure 2. Representative AS-OCT images of TFT, UMA and LMA before and after instillation of Refresh Liquigel.

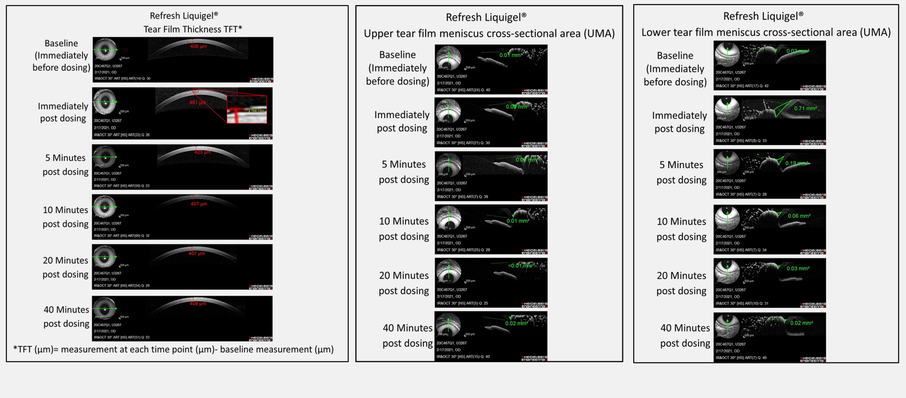
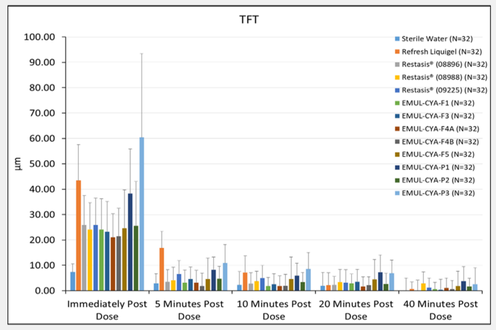
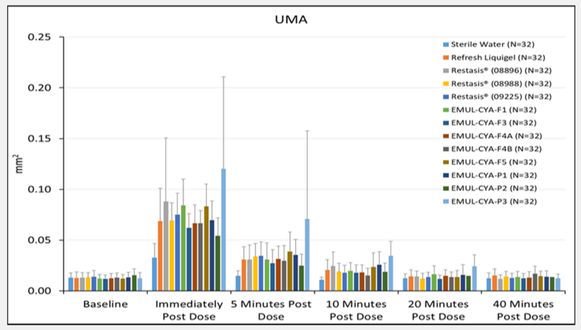


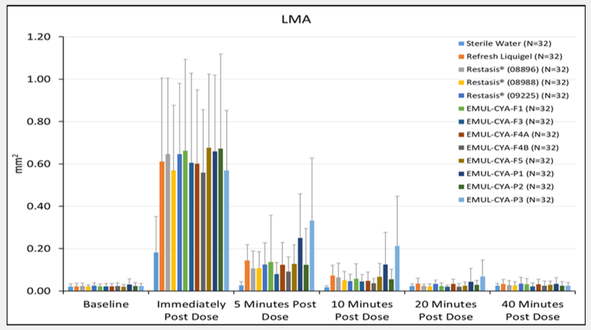
Figure 3. Tear variable measurements were taken at baseline (just before test article instillation), immediately after instillation, and at 5, 10, 20, and 40 minutes post instillation for each formulation. Data expressed as Mean ± SD.



Tear Film Thickness (TFT)



Upper Tear Film Meniscus Cross-Sectional Area (UMA)



Lower Tear Film Meniscus Cross-Sectional Area (LMA)

- Overall, instillation of all 13 formulations resulted in immediate increase in the levels of tear variables like TFT, UMA and LMA. TFT and LMA levels were followed by a sharp decrease by 10 minutes and then a more gradual decrease. UMA levels were followed by a sharp decrease by 5 minutes post instillation.
- The study showed that physicochemical characteristics such as viscosity and GSD are CQAs, which impacted the tear variables, albeit in different ways.
- Among all tear variables, change in TFT appears to be the most sensitive measure to capture differences in GSD and viscosity as compared to UMA and LMA.
- In addition, TFT data revealed that earlier time points within 10 minutes post instillation should enable a sensitive comparison among formulations that vary in GSD and viscosity.
- Different lots of Restasis showed similar tear variables. This further supports the idea that observed differences in tear variables can be attributed to changes in the critical quality attributes (e.g., GSD, viscosity) of the formulations.

CONCLUSIONS

- Results suggest that for cyclosporine ophthalmic emulsions, CQAs such as GSD and viscosity had a direct impact on TFT.
- These study data will be utilized for the validation of a previously developed in silico model[7] along with rabbit pharmacokinetics data, to examine the influence of certain physicochemical properties on the predicted local bioavailability of cyclosporine ophthalmic emulsion and thereby help inform CQA-specific bioequivalence (BE) limits.

DISCLAIMER:

This research was supported by a contract (75F40119F19001) from the U.S. Food and Drug Administration. The views expressed in this poster do not necessarily reflect the official policies of the Department of Health and Human Services; nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.

REFERENCES

1. Rahman et al., *Molecular Pharmaceutics* (2014); 11.3: 787-99.
2. Petrochenko et al., *International Journal of Pharmaceutics* (2018); Vol: 550, Issue:1: 229-39.
3. Dong et al., *Journal of Controlled Release* (2019); 313: 96-105.
4. Dong et al., *Journal of Controlled Release* (2020); 327: 360-70.
5. Hu et al., *The AAPS Journal* (2018); 20.3: 62.
6. *Wang et al., Arch Ophthalmol. (2008);126.5: 619-25.*
7. Walenga et al., *Journal of Pharmaceutical Sciences* (2019);108.1: 620-9.

Contact information:
sandeep.kumar@pharmaron.com