M8019

In Vitro-Ex Vivo Correlation of Drug Release from Semisolid Ophthalmic Ointments

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PURPOSE

- A comprehensive evaluation of qualitatively and quantitatively (Q1/Q2) equivalent ophthalmic ointments with manufacturing differences is challenging due to the complexity of these formulations.
- *In vitro* drug release testing and *ex vivo* transcorneal drug permeation may provide valuable information on the performance of Q1/Q2 equivalent ointments prior to any animal studies.
- Good correlation between *in vitro* and *ex vivo* drug release may be indicative of good *in vitro* and *in vivo* correlation. Accordingly, it may be useful to investigate *in vitro* as well as *ex vivo* drug release from Q1/Q2 equivalent ophthalmic ointments and evaluate any correlation between these release profiles.

METHODS

- Four Q1/Q2 equivalent loteprednol etabonate ointments were prepared using different processing methods and excipient sources (OWP from Fisher® and NWP from Fougera®).
- The *in vitro* drug release testing of the four ointment formulations were performed with pH 7.4 artificial tear fluid with 0.5% (w/v) SDS at 37°C using three different apparati (Franz diffusion cells, USP apparatus 2 with enhancer cells and USP apparatus 4 with semisolid adapters). Three models (zero order, logarithmic and the Higuchi model) were used to study the release kinetics of the ointment formulations.
- The transcorneal permeation studies were performed with pH 7.4 artificial tear fluid with 9% (w/v) HP-beta-CD at 34°C using spherical joint Franz diffusion cells (area: 0.64 cm^2). Fresh rabbit corneas were used and the experimental duration was 4 hours (*n*=6).

Table 1. Manufacturing methods for the Q1/Q2 equivalent loteprednol etabonate ophthalmic ointments.

Formulations	Manufacturing process	Petrolatum
F1	Hot melting with immediate cooling at -20°C	OWP
F2	Hot melting with cooling at room temperature	NWP
F3	Simple mixing at room temperature	OWP
F4	Simple mixing at room temperature	NWP

RESULTS

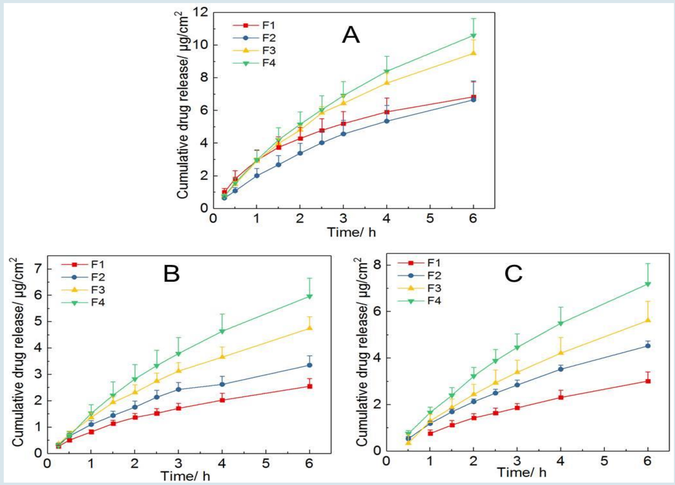

Figure 1. Release profiles of the loteprednol etabonate ointments obtained using: **A**) Franz diffusion cell method; **B**) USP apparatus 2 with enhancer cells; and **C**) USP apparatus 4 with semisolid adapters method (*n* = 6).

Table 2. Model fitting of release profiles of loteprednol etabonate ointments using USP app 4 with semisolid adapters (representative data, other methods had similar trends).

	Zero order model		Logarithmic model		Higuchi model	
Formulation	$k_0 \times 10^2$	R^2	k_{log}	R^2	k_H	R^2
F1	0.73 ± 0.08	0.983 ± 0.009	2.86 ± 0.28	0.978 ± 0.011	0.20 ± 0.02	0.985 ± 0.002
F2	1.10 ± 0.05	0.981 ± 0.006	4.28 ± 0.20	0.977 ± 0.008	0.30 ± 0.01	0.997 ± 0.008
F3	1.43 ± 0.18	0.987 ± 0.004	5.53 ± 0.37	0.978 ± 0.010	0.39 ± 0.05	0.983 ± 0.002
F4	1.83 ± 0.23	0.980 ± 0.004	7.14 ± 0.91	0.979 ± 0.008	0.50 ± 0.06	0.988 ± 0.002

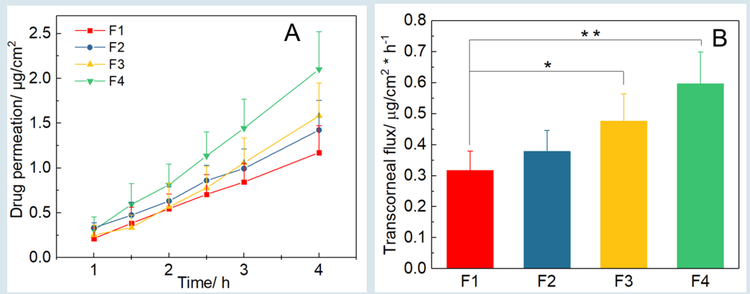

Figure 2. A) Transcorneal permeation profiles; and **B**) Transcorneal flux of loteprednol etabonate ointments obtained using spherical joint Franz diffusion cells (*n* = 6).

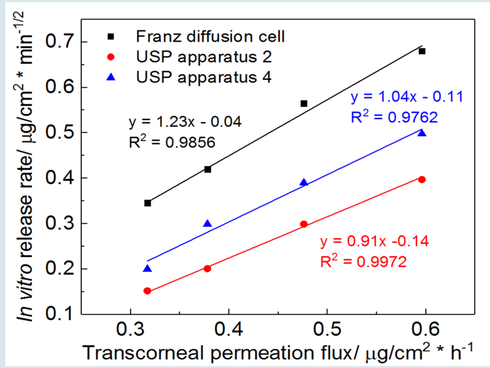

Figure 3. Plot of *in vitro* release rate against *ex vivo* transcorneal permeation flux (n=6) for the four ointment formulations. Straight lines (R2 > 0.98) were obtained for all three release methods.

CONCLUSIONS

- The *in vitro* drug release profiles of Q1/Q2 equivalent ophthalmic ointments obtained using the three different release methods followed the Higuchi release kinetics.
- The compendial methods possessed better discriminatory capability compared to the non-compendial method.
- Strong correlation was established between the *in vitro* release rate and *ex vivo* release flux of the Q1/Q2 equivalent ointments with different manufacturing processes.

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