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 can provide valuable information on the performance of the 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 is important 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. The in vitro drug release testing of the four ointment formulations were performed with pH 7.4 artificial tear fluid with 0.5% 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% HP-beta-CD at 34°C using spherical joint Franz diffusion cells (area: 0.64 cm²). Fresh rabbit corneas were used and the experimental duration was 4 hours (n=6).

Results
The in vitro release profiles of four Q1/Q2 equivalent ointments with manufacturing differences showed better fit using the Higuchi model (R² > 0.98) for all three release testing methods, compared to the other two models. The compendial release methods (USP apparatus 2 and USP apparatus 4) demonstrated better discriminatory ability than the Franz diffusion cell method. Ex vivo drug release through the rabbit corneas displayed zero order release kinetics. The in vitro release rate of the four formulations possessed the same rank order as the ex vivo release flux. A plot of the in vitro release rate against the ex vivo release flux of the four ointment formulations, yielded to a straight line (R² > 0.98) for all three release methods.

Conclusion
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 non-compendial method. Strong correlation was established between the in vitro release rate and ex vivo release flux of the Q1/Q2 equivalent ointments.

![Graph showing in vitro release rate against ex vivo transcorneal permeation flux for four ointment formulations.](image)

**Figure 1.** 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.