Poster Number 05T0430

Physical Formulation Features and Ocular Absorption from Topical Suspensions: Toward Mechanistic Understanding

Elisa Toropainen[1], Dunja Novakovic[2], Sara Fraser[2], Marjo Tuomainen[1], Marja Hagström[2], Eva del Amo[1], Kati-Sisko Vellonen[1], Jonne Peltoniemi[2], Unni Tengvall[1], Laura Pelkonen[1], Mika Reinisalo[1], Marika Ruponen[1], Seppo Auriola[1], Tapani Viitala[2], Mohammad Absar[3], Stephanie Choi[3], Clare Strachan[2], Arto Urtti[1,2]

[1]School of Pharmacy, University of Eastern Finland, Kuopio, Finland; [2]Faculty of Pharmacy, University of Helsinki, Helsinki, Finland; [3] Office of Research and Standards, Office of Generic Drugs, CDER, US FDA, Maryland, USA

2016 AAPS ANNUAL MEETING AND EXPOSITION
NOVEMBER 13–17, 2016
COLORADO CONVENTION CENTER, DENVER
aaps®

PURPOSE

The purpose was to study the effects of particle size and viscosity of ophthalmic suspensions on ocular drug absorption. Furthermore, we aimed to develop methods for *in vitro in vivo* extrapolation of ophthalmic suspension performance that would help mechanistic understanding and evaluation of formulation bioequivalence.

METHOD

Indomethacin suspensions (5 mg/ml) were prepared using milling method. Indomethacin suspensions with different particle sizes and viscosity were prepared. The suspensions had pH of about 5.9 and osmotic pressure about 240 mOsm/mg. The particle size was determined using laser diffraction.

Ocular indomethacin absorption was determined in New Zealand albino rabbits. Ophthalmic suspension (25 µl, 5 mg/ml) was instilled on the upper corneo-scleral limbus of the rabbit eyes. The rabbits were sacrificed at different time points and indomethacin was quantified in the cornea and aqueous humor with triple quadruple LC/MS.

Dissolution rate of indomethacin from suspension particles was determined in flow through device (Fig. 1). Suspension samples were placed in the upper compartment and indomethacin concentrations were determined from the lower compartment using UPLC. Simulation model for the dissolution system was built using STELLA software (High Performance Systems).

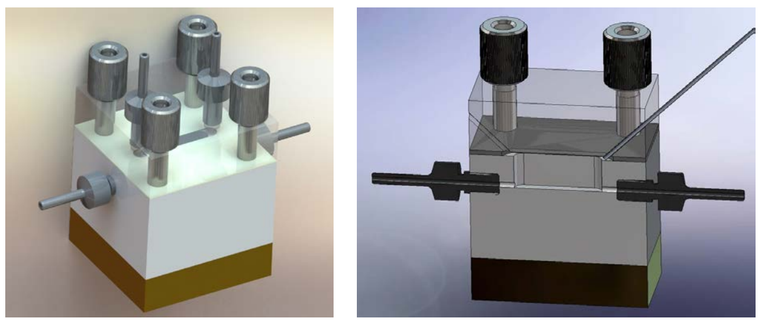


Figure 1. Dissolution device. Suspension is injected through port to the upper compartment. Flow of suspension in the lower compartment provides sink conditions. Polycarbonate filter was placed between the compartments.

RESULTS

Physical characteristics of the commercial indomethacin suspensions and test suspensions are presented in Table. The suspensions can be classified to three viscosity classes (low, medium, high) and two disctinct particles sizes (low, high). Osmotic pressure and pH are similar among the formulations.

Table. Physical characteristics of the indomethacin suspensions.

Sample	Particle size d(0.5) µm	Calculated viscosity (mPa s)	Osmolality (mOsm/kg)	pH
INDO1	0.43	≈ 1.3 (HPMC ES)	241	5.80
INDO2	1.33	≈ 7.0 (HPMC4000)	239	5.90
INDO3	0.37	≈ 15 (HPMC K35M)	239	5.84
INDO4	3.24	≈ 1.3 (HPMC ES)	241	5.82
INDO5	3.49	≈ 7.0 (HPMC4000)	242	5.89
INDO6	3.12	≈ 15 (HPMC K35M)	236	5.91
Commercial	5.58	≈ 7 (measured)	232	5.90

Figure 2 shows the $AUC_{0\text{-}240min}$ and C_{max} values of indomethacin formulations in the aqueous humor after topical instillation of the suspensions. Mean AUC values were affected by the particle size and viscosity of the suspensions 2-fold and 4-fold, respectively. The particle size had very small effect on C_{max} values, while viscosity was having 2-3 fold influence on the peak indomethacin concentrations in the aqueous humor. Note that statistical significance of the differences has not been tested.

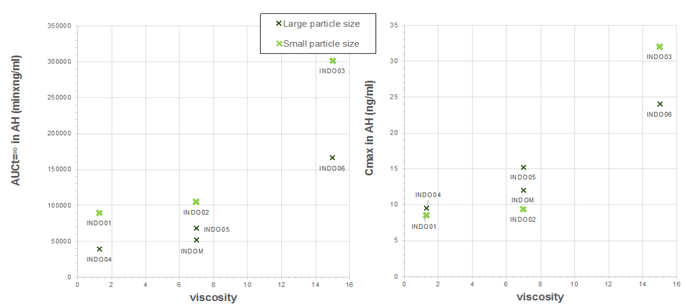
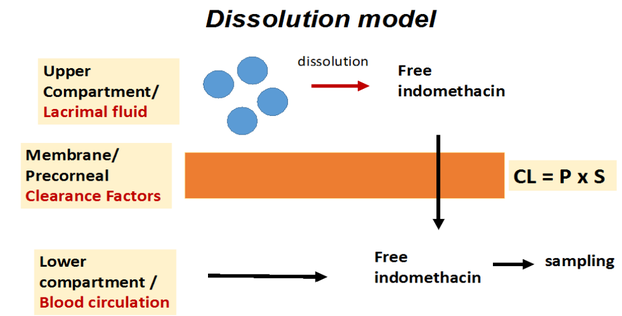


Figure 2. $AUC_{0\text{-}240min}$ and C_{max} values of indomethacin in rabbit aqueous humor after topical instillation of 5 mg/ml suspension.

Dissolution rates in the flow device were within 1.3 fold range for the formulations with 7-fold range of AUC in the aqueous humor. Dissolution rate did not predict the AUC. Clearance from the medium in the upper compartment should mimic *in vivo* situation in the lacrimal fluid. Clearance is defined as CL = P x S, where P is the permeability and S is the surface area of the membrane. Clearance in the device was 7 µl/min resulting in 1.3 fold range of dissolution rates, while the the dissolution rates at sink conditions are expected to show range of several folds.

The kinetic simulations suggest that at higher membrane permeability (CL = 20-40 µl/min), dissolution differences of the formulations should reach 2-3 fold range that is close to the range of AUC values *in vivo*. Precorneal clearance is sum of normal tear turnover (0.7 µl/min), conjunctival clearance (mainly to systemic circulation; 5-10 µl/min) and induced lacrimation. It has been estimated (Ocular Surface 3: 81, 2005) that human lacrimal system can adapt flow rates up to 50 µl/min without overflow indicating that clearance values of 20-40 µl/min are realistic goals for *in vitro* dissolution methods for ophthalmic suspensions. Overall design logic of the dissolution methodology is illustrated below.



CONCLUSION

Viscosity and particle size affect ocular absorption of indomethacin from topical suspensions. *In vitro* dissolution method in combination with kinetic simulations may become predictive tool in ophthalmic suspension development.

Acknowledgements

The work supported by FDA Grant 1U01FD005180-01.

.