(Poster Number)
W5057

Influence of Excipients on Physicochemical Characteristics of Ocular Semisolid Formulations and Their *In Vitro* Drug Release

[1]Shilpa Patere, [2]Khaetthareeya Sutthanut, [3]Bryan Newman, [3]Stephanie Choi, [4]Michael Jay and [1]Xiuling Lu

[1]Department of Pharmaceutical Sciences, University of Connecticut, Storrs, CT, USA

[2] Faculty of Pharmaceutical Sciences, Khon Kaen University, Thailand

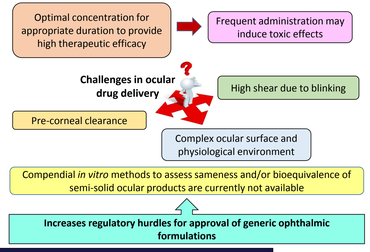
[3] Division of Therapeutic Performance, Office of Research and Standards, Office of Generic Drugs, U.S. Food and Drug Administration, Washington DC, USA

[4] Division of Molecular Pharmaceutics, University of North Carolina at Chapel Hill, Chapel Hill, NC, US

UCONN UNIVERSITY OF CONNECTICUT

INTRODUCTION

- Formulation design and performance evaluation of ophthalmic semisolid products presents a major challenge for formulation scientists
- Tobramycin, a widely used aminoglycoside antibiotic for the treatment of bacterial infections, exhibits polymorphism and high water solubility and was selected as the model drug
- Tobramycin ophthalmic ointment (0.3%) was used for this study



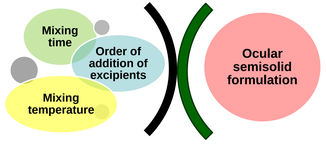
PURPOSE

- ✓ To develop methodologies to evaluate the effect of excipients on physicochemical characteristcics of semi-solid ocular formulations
- ✓ To study the feasibility of *in vitro* methods to predict *in vivo* performance of generic products compared to innovator's ocular semisolid product encompassing release studies in simulated tear solutions

METHODS

- Formulations were prepared using two different methods with three different forms of API and three different sources of petrolatum (Source A, B and C) and compared with reference tobramycin ointment 0.3% (Reference)

Optimization



Physicochemical characterization

- Particle size of API using microscopy
- Solubility and membrane binding studies of API
- Content uniformity of formulations
- Differential scanning colorimetry (Modulated temperature)
- Rheological evaluation of formulations
- Release studies using different dissolution techniques

Formulations	Petrolatum source	API	Method
I	A	Micronized mixture of amorphous and crystalline	Levigation
II	B		
III	A	Micronized pure crystalline form I	
IV	B		
V	B		High speed mixing
VI	B	Non-micronized	Levigation
Reference Tobramycin Ointment (0.3%) (Reference)			

Solubility and membrane binding studies

- Tobramycin was added to artificial tear solution 1 or 2 (TS1 and TS2), incubated at 37° C for 2h centrifuged and analyzed
- Standard tobramycin solutions prepared in TS1 were incubated with artificial membranes (cellulose acetate and polyether sulphone) at R.T. for 1h, analyzed for assay and were compared with negative control (no membrane)

Artificial tear solutions	Composition
Tear solution 1	Sodium bicarbonate, Calcium chloride, Sodium chloride
Tear solution 2	Lysozyme, D-glucose, gamma globulin, Sodium chloride, Bovine serum albumin, Calcium chloride dihydrate

Composition of tear solutions

Content uniformity

Dissolve 30 mg of ointment (Reference/Generic) in 5ml of ether → Extract using three 5 ml portions of water (1h each) in a rotating shaker → Collect aqueous fraction. Remove traces of ether

HPLC analysis by pre-column derivatization	
Column	Zorbax Bonus RP at R.T.
Mobile phase	Methanol and water
Wavelength	λ_{ex} 390nm and λ_{em} 480nm
Flow rate	0.2 ml/min

Modulated temperature differential scanning colorimetry (MTDSC) : Performed by heating sample from 50° C to 300° C at a rate of 2° C/min with modulation period of 60s and modulation amplitude of ±1° C

Rheology was studied using AR-G2 rheometer

a) Strain sweep tests (0.05-20%) at constant frequency (1 Hz) to determine relaxation time and yield stress
b) Steady state flow tests to study the viscosity behavior using flat plate geometry
c) Temperature sweep tests to determine viscosity at various temperature using cone plate geometry

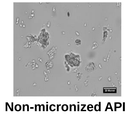
In vitro release studies

USP apparatus IV	Temperature: 34° C, 37° C Flow rate: 18 and 30ml/min
	Release medium: TS1 (50 ml) pH 7.4
Immersion cell With paddle apparatus	Temperature: 34° C RPM: 50 and 200 rpm

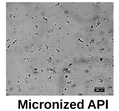
Statistics: ANOVA analysis was performed to determine significant differences in the rheological parameters between the formulations

RESULTS

Particle size analysis



Non-micronized API Mean particle size (>10μ)



Micronized API Mean particle size (< 10μ)

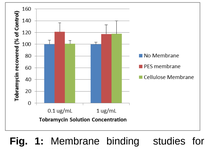


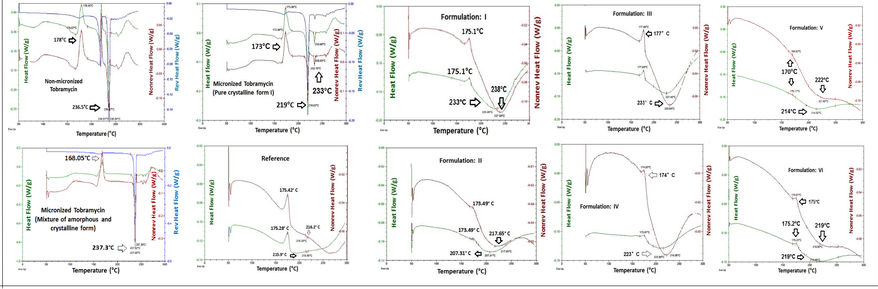
Fig. 1: Membrane binding studies for tobramycin (25°C) (n=3)

Solubility and membrane binding studies

- ✓ Solubility of tobramycin in TS1 and TS2 was found to be > 700mg/ml
- ✓ No binding of tobramycin to either of the membranes was observed at the concentrations studied (Fig. 1)

✓ Content uniformity of all the formulations was found to be between 90-120% (acceptable range specified in USP)

MTDSC



Rheology

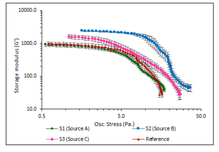


Fig. 2: Storage modulus (G') of formulations prepared using three different sources of petrolatum and the Reference (34°C, n=3)

- ✓ Petrolatum source significantly influenced the rheology of the manufactured ointment formulations (Fig. 2)
- ✓ Formulations I and III prepared using source A petrolatum showed comparable rheological behavior to the Reference (Fig. 3)
- ✓ Yield stress of formulation V prepared using high speed mixing was significantly different ($p<0.05$) from all other formulations (Fig. 4)
- ✓ A significant difference ($p<0.05$) was observed in the yield stress of formulations I, III and the Reference compared to formulations II, IV, V and VI
- ✓ Differences were observed in the viscosity of the formulations at different shear rates and temperatures (Fig. 5 and 6)

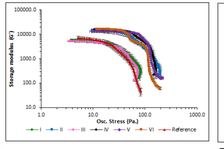


Fig. 3: Storage modulus (G') of various formulations (25°C, n=3)

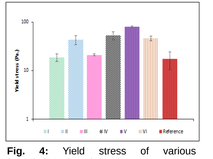


Fig. 4: Yield stress of various formulations (25°C) (n=3)

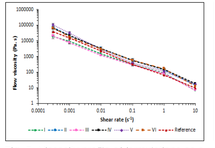


Fig. 5: Viscosity profile of formulations as a function of shear rate (25°C) (n=3)

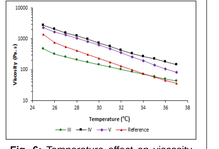


Fig. 6: Temperature effect on viscosity profile of formulations using cone fixture (n=3)

In vitro release studies

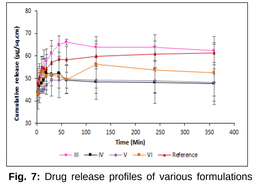


Fig. 7: Drug release profiles of various formulations using USP apparatus IV at 37°C (n=3)

- ✓ Concentration of drug released was found to be below the linear detection sensitivity of the analytical method at 34° C
- ✓ Burst release was observed from all the formulations at 37° C with a flow rate of 30 ml/min in USP apparatus IV. Release profiles of formulation III and the Reference were found to be similar especially at later time points, while formulations IV and V exhibited much lower drug release. The large variation in formulation VI might be due to the non-micronized API used in this formulation (Fig. 7).

CONCLUSIONS

- ➢ Different sources of petrolatum, forms of API and method of preparation influence the rheological parameters and MTDSC behavior of formulations
- ➢ Dissolution temperature, exposed surface area and speed were found to play a critical role in the release of the drug from semi-solid formulations
- ➢ Formulation with physicochemical properties and rheological behavior similar to Reference may show comparable *in vitro* release behavior

FUNDING

Funding for this project was made possible, in part, by the Food and Drug Administration through grant 1U01FD005174-01. The views expressed in this poster do not reflect the official policies of the U.S. Food and Drug Administration or the U.S. Department of Health and Human Services; nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.