Impact of Process and Quality Control on the Physicochemical Properties of Tobramycin Ophthalmic Ointments

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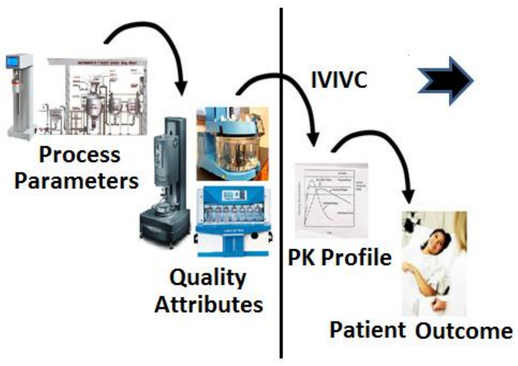
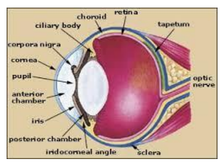
INTRODUCTION





- Complex ocular surface and physiological environment
- High shear due to blinking
- Pre-corneal clearance

Ophthalmic ointments were developed to withstand the high shear of blinking to improve the ocular bioavailability and provide sustained drug release

- Tobramycin (TOB), a water soluble aminoglycoside antibiotic, was selected as the model drug and Tobrex® (0.3% w/w) ophthalmic ointment, manufactured by Alcon as the reference product
- In house prepared qualitative (Q1) and quantitative (Q2) equivalent ointments (with low percent of API, 0.3% w/w) manufactured using different processes can have different physicochemical properties that may lead to variation in performance
- Understanding the impact of process and quality control parameters on product performance is critical for developing generic ophthalmic semisolids

OBJECTIVE

- To prepare Q1/Q2 oleaginous ointments using different preparation methods, sources of excipients and TOB API
- To investigate the feasibility of *in vitro* techniques in identifying critical process and quality attributes to discriminate Q1/Q2 ointments

METHODS

Sources of PET USP (A, B and C) — 3
Sources of TOB API (X, Y and Z) — 3
Preparation method (L, U1 and U2) — 3

Q1/Q2 ointments with differences in their physicochemical properties

D-optimal screening design of experiments (DoE) to evaluate impact of two variables [method of preparation (X1) and source of petrolatum (PET) (X2)] on rheological properties

Sample ID	Method of preparation	PET USP source
DoE-1	U2	C
DoE-2	U1	B
DoE-3	L	B
DoE-4	U1	A
DoE-5	U2	B
DoE-6	L	A
DoE-7	U2	A
DoE-8	L	A
DoE-9	U1	C
DoE-10	L	C
DoE-11	U1	B
DoE-12	U2	C

Twelve DoE ointments (Q1/Q2) were prepared using TOB Z, three different sources of PET USP (A, B and C) and preparation methods (L, U1 and U2)

Method	Level	Speed (rpm)	Mixing time (Min.)	Resting time (Min.)
U1	3	1130	9	5
	2	970	1	5
	1	810	1	
U2	9	2100	9	5
	2	970	1	5
	1	810	1	

L: Levigation, U1 and U2: Unguator high speed mixing method 1 and 2

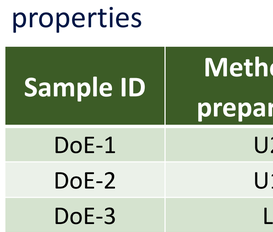
Statistical analysis: Analysis of variance (ANOVA) with Tukey's was used for comparing all the parameters. P<0.05 was considered statistically significant.

Physicochemical characterization (Q3)

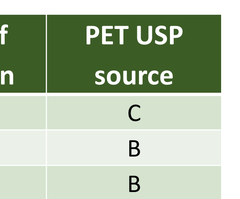
- Microscopy to evaluate particle size distribution
- Content uniformity
- Modulated temperature differential scanning colorimetry (MTDSC)
- Gas chromatography – Mass spectroscopy (GC-MS)
- Thermogravimetric analysis (TGA)
- Rheological studies using three different techniques 1) Steady state flow 2) Temperature sweep and 3) Strain sweep

RESULTS

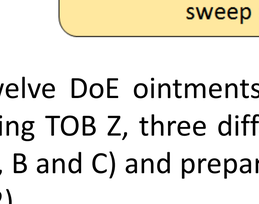
Representative microscopic images (Scale bar: 40µm, 50x magnification)



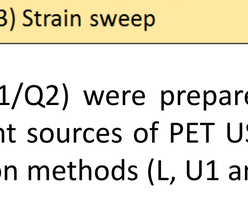
Blank PET



Ointment with TOB X



Ointment with TOB Y



Ointment with TOB Z

Table 1: Particle size analysis of three TOB API (n=3)

Source of TOB	D_{10} (µm)	D_{50} (µm)	D_{90} (µm)	D_{99} (µm)
X	2.23±0.2	5.80±0.5	24.6±2.3	53.67± 1.7
Y	1.46±0.18	4.6±0.5	9.33±0.6	13.6±0.9
Z	1.26±0.17	3.94±0.2	7.53±0.6	11±0.3

- ✓ Particle size of TOB X was significantly higher ($p<0.05$) than TOB Y and TOB Z (Table 1), with no significant reduction after incorporation in the formulations
- ✓ Particle size of TOB Y and TOB Z was comparable before and after incorporation in the formulations
- ✓ Results suggested no significant influence of preparation technique on particle size reduction of TOB API

Content Uniformity

- ✓ Content uniformity of ointments with TOB Y and TOB Z were in the acceptable range of 90-110% with deviation from mean within ±10%
- ✓ Larger TOB particles from source X reduced the homogeneity of ointments with high SD due to low percent content of TOB (0.3% w/w)

MTDSC

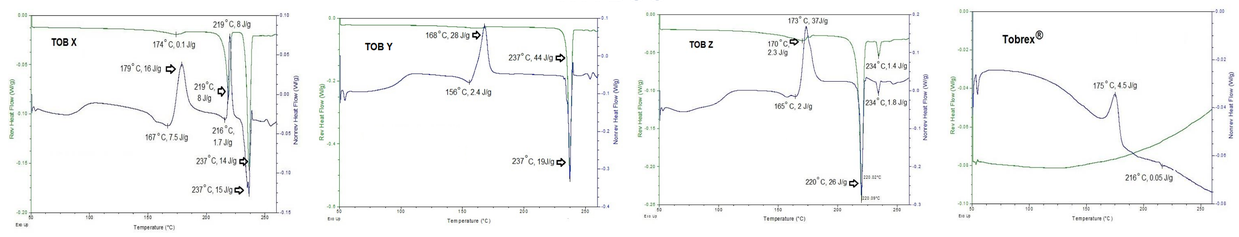


Fig. 1: MTDSC of TOB X, Y, Z and Tobrex®

- ✓ MTDSC of TOB Z demonstrated major endothermic peak at 220°C corresponding to the monohydrate form of TOB and comparable to the endothermic peak of Tobrex® (Fig. 1)

GC-MS

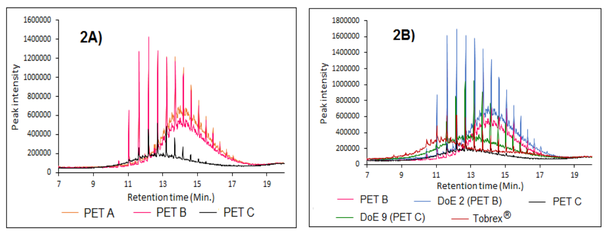


Fig. 2: GC-MS chromatograms A) PET B) Ointments with their PET and Tobrex®

- ✓ All three PET produced individual chromatographic fingerprints depicting differences in their composition (Fig. 2A)
- ✓ Chromatograms of ointments were comparable to their PET but with a shift in the hump intensity on higher side
- ✓ Ointments with PET A, B and Tobrex® showed broad range of linear alkanes (C21-C33) with high peak intensities (Fig. 2B)
- ✓ PET C and ointments with PET C showed narrow distribution of linear alkanes (C22-C27) with low peak intensities suggesting presence of large amounts of highly branched and ring paraffin's (Fig. 2B)

TGA

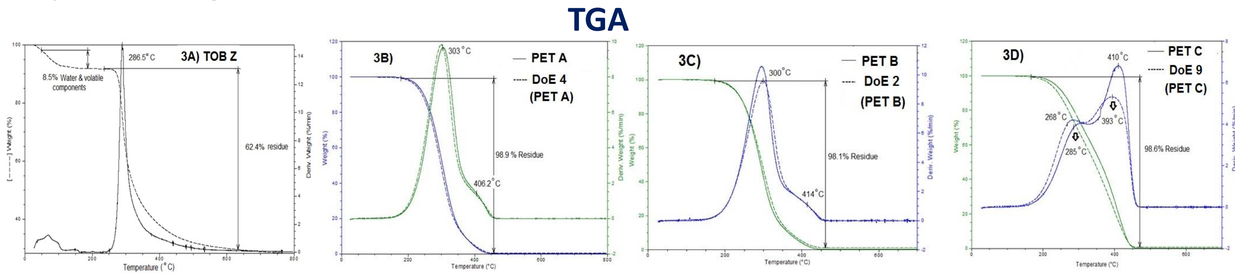
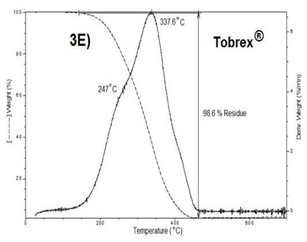


Fig. 3: TGA analysis A) TOB Z B-D) Ointments with their pure PET base E) Tobrex®



- ✓ Different derivative loss peaks in TGA signify presence of components with different degradation profiles
- ✓ TOB from all three sources showed comparable derivative weight loss peaks (Fig. 3A)
- ✓ DoE 4 (PET A) and DoE 2 (PET B) demonstrated minor and major loss peaks comparable to the pure PET base used in their preparation (Fig. 3B and C)
- ✓ Loss peak intensity of DoE 9 (PET C) was shifted on lower side compared to pure PET C which could be due to the breaking of highly branched chains and/or some change in the microstructure of PET C during high speed mixing process (Fig. 3D). Derivative loss peaks of Tobrex® showed a major peak at 337°C and a minor peak at 247°C (Fig. 3E).

Rheological studies

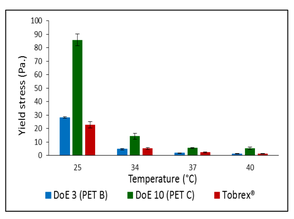


Fig. 4: Yield stress by strain sweep (n=3)

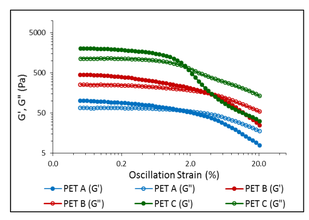


Fig. 5: Representative G' and G" by strain sweep (40°C)

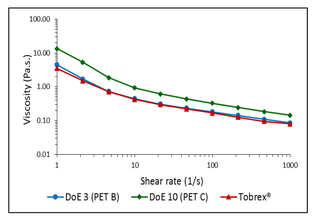


Fig. 6: Viscosity by steady state flow (n=3)

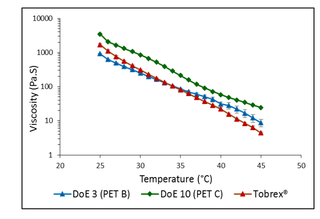


Fig. 7: Viscosity by temperature sweep at 0.1% strain (n=3)

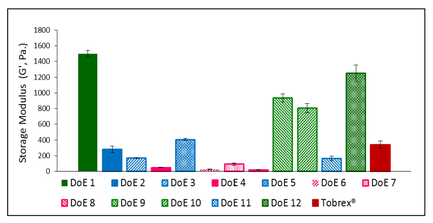


Fig. 8: G' of 12 DoE ointments by strain sweep method (40°C, n=3)

- ✓ Statistical difference between the yield stress by strain sweep method was comparable at all the studied temperatures (Fig. 4)
- ✓ Rheological parameters [storage modulus (G') and loss modulus (G")] were found to be different for the three PET sources at 40°C (Fig. 5)
- ✓ Ointments demonstrated shear thinning behavior in the steady state flow method using cone geometry (Fig. 6)

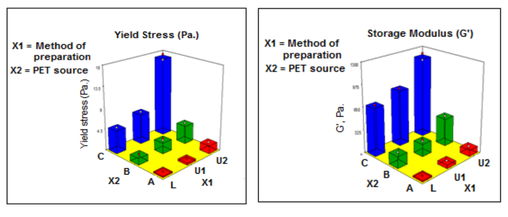


Fig. 9: Impact of method of preparation and source of PET on yield stress and G' (40°C)

- ✓ Statistical difference between viscosity by temperature sweep method was comparable from 35°C to 40°C (Fig. 7)
- ✓ Variations were observed in the rheological parameters of all the DoE ointments (Fig. 8)
- ✓ PET source showed more significant influence on rheological parameters compared to the method of preparation (Fig. 9)

CONCLUSION

- Particle size distribution of API is crucial to obtain good content uniformity in ophthalmic ointments with low percent of API
- Differences in the hydrocarbon composition and rheological parameters of the PET source influence the properties and quality attributes of oleaginous ophthalmic ointments
- Source of PET plays a more critical role in determining the rheological properties of ointments compared to the method of preparation

FUNDING

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