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Impact of Excipient Sources on *In Vitro* Drug Release Characteristics of Semisolid Ophthalmic Ointments

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PURPOSE

- Investigation of the effect of excipient sources on the physicochemical properties of and in vitro release from qualitative (Q1) and quantitative (Q2) equivalent semisolid ophthalmic ointment products.
- Although the excipients are manufactured according to the same USP standards, there may be differences (for example, different types or amounts of impurities). In addition, for semisolid excipients such as white petrolatum, there may be differences in molecular weight (MW) range and microstructure.
- Such differences may result in different physicochemical properties and *in vitro* drug release rates. Therefore, it is essential to understand the influence of the source of excipients on the performance of semisolid ophthalmic ointment products.

MATERIALS & METHOD

Materials

Loteprednol etabonate (LE) was purchased from Pure Chemistry Scientific Inc. White petrolatum was purchased from there different sources: Vaseline® (VWP), Fisher® (OWP) and Fougera Pharmaceutical Inc.(NWP). Mineral oil USP was purchased from Sigma-Aldrich. Unless otherwise specified, all materials were of analytical grade.

Method

- Three formulations of loteprednol etabonate that are Q1/Q2 equivalent were prepared using different sources of white petrolatum (VWP, OWP and NWP) *via* hot melting at 65°C and mixing with cooling at -20°C (HMIC).
- The three formulations were prepared with a loteprednol etabonate mean particle size of 19 µm.
- The ointments were characterized as follows: drug content and uniformity; drug crystal and size distribution; and rheology (onset point (OP), crossover modulus (CM), storage modulus (SM), and viscosity properties). *In vitro* dissolution testing of the three formulations was performed using USP apparatus 4 with semisolid adapters (Sotax) in pH 7.4 artificial tear fluid with 0.5% SDS at 37°C.

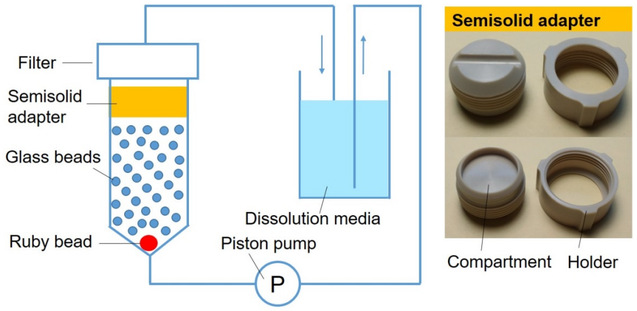

Figure 1. USP apparatus 4 with semisolid adapters (Sotax)

RESULTS

Table 1. The drug loading and uniformity of LE ointment formulations (*n*=3)

Ointments	Average Drug Loading ± SD (%, w/w)	RSD (%)
HMICVWP	0.518 ± 0.010	1.93
HMICOWP	0.486 ± 0.006	1.23
HMICNWP	0.473 ± 0.004	0.85

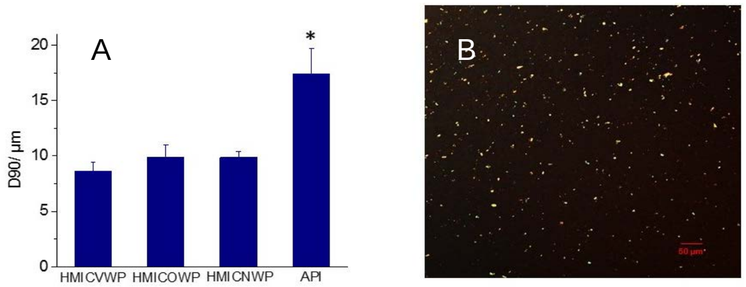

Figure 2. **A**) Particle sizes and **B**) representative image of the LE ointment *via* PLM (*n*=3)

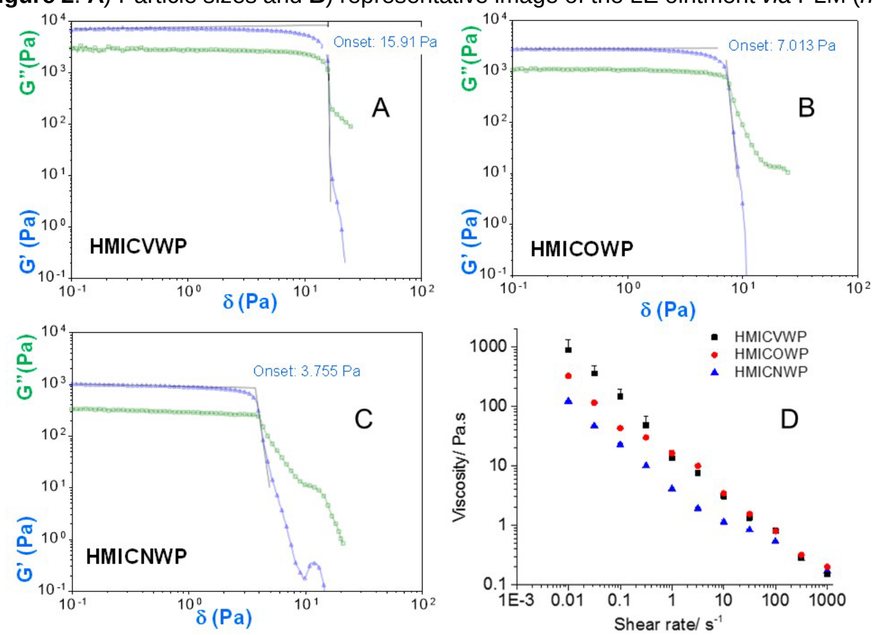

Figure 3. Rheological profiles of LE ointments **A**) HMICVWP; **B**) HMICOWP and **C**) HMICNWP via plotting the log moduli (storage modulus G' and loss modulus G'') *vs.* log (oscillatory stress δ) and **D**) rheograms of the three ointments (*n*=3)

Table 2. Rheological parameters of LE ointments prepared with different sources of white petrolatum (*n*=3)

Ointments	Onset Point (Pa)	Crossover Modulus (Pa)	Storage Modulus (Pa)	Viscosity (Pa·s)
HMICVWP	15.517 ± 0.089	896.47 ± 138.2	8008.3 ± 1143	878.33 ± 438.8
HMICOWP	6.348 ± 1.220 **	682.94 ± 55.01	2864.3 ± 272.1 **	295.10 ± 51.19
HMICNWP	3.912 ± 0.690 **	193.33 ± 49.11 **	859.4 ± 201.5 **	121.27 ± 1.67 *

The viscosity were obtained by applying a shear rate of 0.01 1/s on the ointments at 37°C
* p<0.05; ** p<0.01 compared with HMICVWP

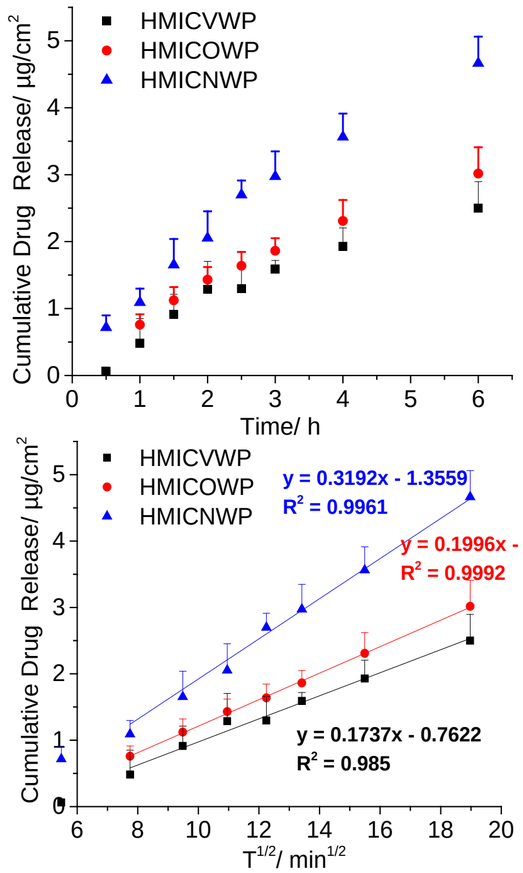

Figure 4. **A**) *In vitro* drug release profiles of ointments prepared with different white petrolatum sources and **B**) regression profiles of the three formulations using the Higuchi model (*n*=3)

CONCLUSION

- The current USP monograph of white petrolatum does not consider the rheological properties, which may be important for the performance of ophthalmic ointments.
- Different sources of white petrolatum were shown to significantly impact the physicochemical properties and *in vitro* drug release rate of Q1/Q2 equivalent semisolid ointments. Compared with NWP, the ointments prepared with VWP as well as OWP displayed higher rheological properties (OP, CM, SM and viscosity), and therefore demonstrated slower drug release rates.

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