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Manufacturing Differences on Physicochemical and *In Vitro* Release Characteristics of Semisolid Ophthalmic Ointments

Quanying Bao[1], Jie Shen[1], Bryan Newman[2], Yan Wang[2], Stephanie Choi[2], Diane J. Burgess[1]

1-University of Connecticut, School of Pharmacy, Storrs, CT 06269

2- FDA/CDER, OGD/ORS, Division of Therapeutic Performance, MD 20993

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PURPOSE

- The *in vitro* evaluation of semisolid ophthalmic ointment products is very challenging due to their complex properties.
- Even for ointments that are qualitatively (Q1) and quantitatively (Q2) equivalent, their physicochemical properties may be remarkably different depending on the manufacturing process.
- In addition, such formulations with different physicochemical properties may demonstrate significantly different *in vitro* and *in vivo* performance.
- Therefore, it is imperative to investigate and understand the influence of the manufacturing process on the physicochemical properties of semisolid ointment products.

MATERIALS & METHOD

Materials

Loteprednol etabonate (LE) was purchased from Pure Chemistry Scientific Inc. White petrolatum was purchased from Fisher ®. Mineral oil USP was purchased from Sigma-Aldrich. Unless otherwise specified, all materials were of analytical grade.

Method

Three different manufacturing processes were used to prepare LE ophthalmic ointments (Q1/Q2 equivalent):

i. **SRT -** simple mixing at room temperature
ii. **HMIC -** hot melting at 65°C and mixing with immediate cooling in a -20°C
iii. **HMRT -** hot melting at 65°C and mixing with cooling at room temperature

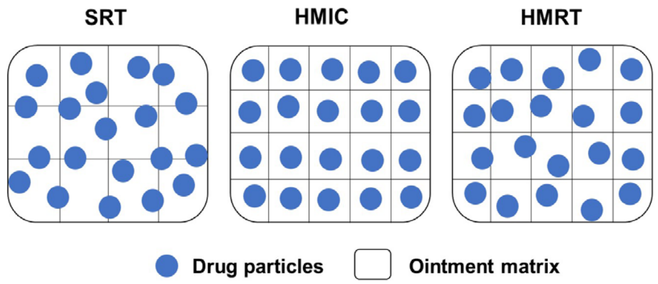

Figure 1. Manufacturing processes of ophthalmic ointments

- All formulations were prepared with a loteprednol etabonate mean particle size of 19 µm.
- The following physicochemical properties were characterized: drug content and uniformity, drug crystal morphology 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 carried out using USP apparatus 4 with semisolid adapters (Sotax) in pH7.4 artificial tear fluid with 0.5% SDS at 37°C.

RESULTS

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

Ointments	Average Drug Loading ± SD (%, w/w)	RSD (%)
SRT	0.476 ± 0.014	2.94
HMIC	0.486 ± 0.006	1.23
HMRT	0.506 ± 0.017	3.36

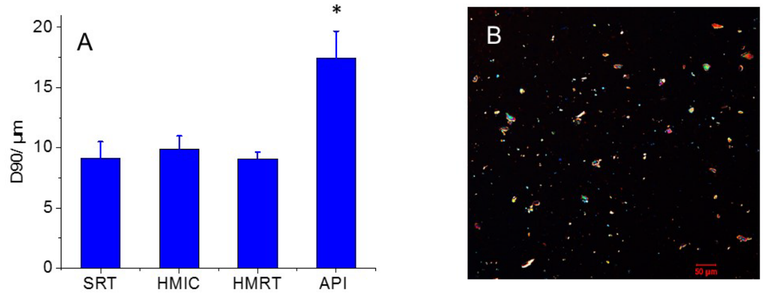

Figure 2. **A**) Particle sizes and **B**) representative image of the LE ointment *via* PLM (*n*=3)

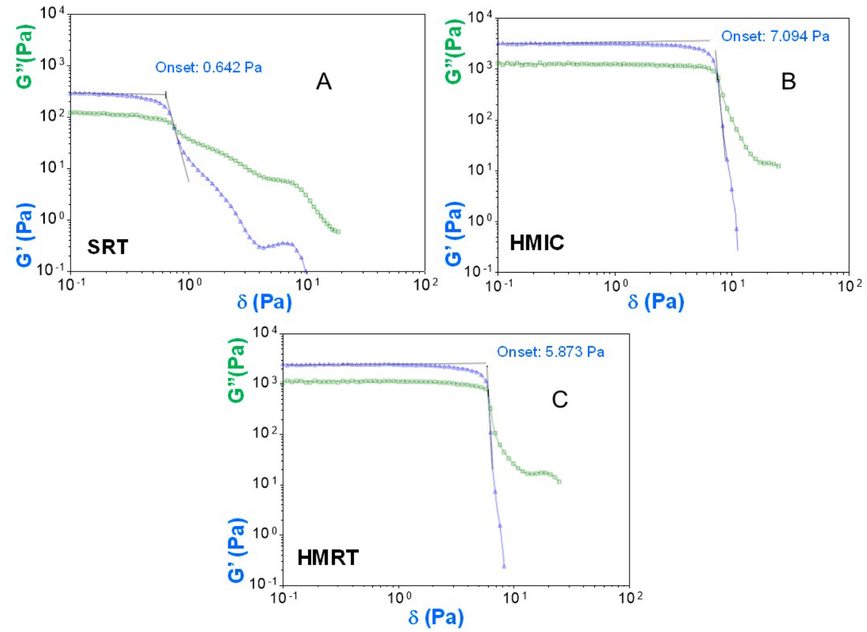

Figure 3. Rheological profiles of LE ointments prepared using **A**) SRT; **B**) HMIC and **C**) HMRT *via* plotting the log moduli (storage modulus G' and loss modulus G'') *vs.* log (oscillatory stress δ)

Table 2. Rheological parameters of LE ointments prepared with different manufacturing processes (*n*=3)

Ointments	Onset Point (Pa)	Crossover Modulus (Pa)	Storage Modulus (Pa)	Viscosity (Pa·s)
SRT	0.522 ± 0.089 **	72.88 ± 15.61**	290.73 ± 25.78 **	41.88 ± 24.99 **
HMIC	6.348 ± 1.220	682.94 ± 55.01	2864.3 ± 272.1	295.10 ± 51.19
HMRT	5.397 ± 0.803	607.21 ± 74.54	2200.3 ± 269.9	227.50 ± 12.18

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 HMIC

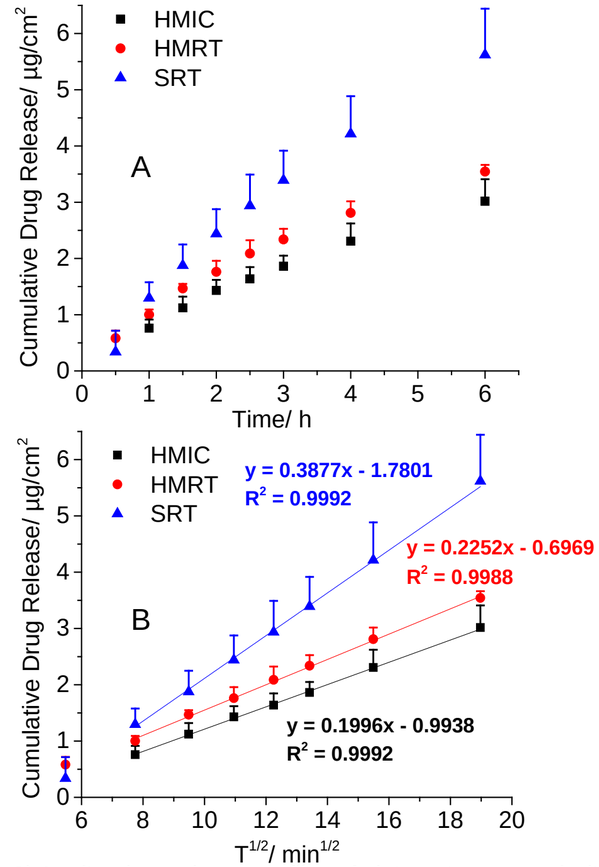

Figure 4. **A**) *In vitro* drug release profiles of ointments prepared with different manufacturing processes and **B**) regression profiles of the three formulations using the Higuchi model (*n*=3)

CONCLUSION

- Manufacturing process differences were shown to greatly impact the physicochemical properties and *in vitro* drug release rate of Q1/Q2 equivalent semisolid ointments.
- Compared with simple mixing, the ointments prepared *via* the hot melting process displayed higher rheological properties (OP, CM, SM, and viscosity) and slower drug release rates. This suggests that the hot melt process may facilitate stronger interactions between drug particles and the ointment matrix, resulting in a microstructure that is more compact and thus resistant to drug release.

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