Development of Sustained Release Lipid-Based Matrix Microparticles for Vaginal Delivery using Twin-Screw Hot Melt Extrusion

V. Mohylyuk[1,2], T. Hutton[1], S. Dadou[1,2], S. Li[1,2], D.S. Jones[1], G.P. Andrews[1,2]

[1] Pharmaceutical Engineering Group, School of Pharmacy, Queen's University Belfast, BT9 7BL, Northern Ireland

[2] China Medical University - Queen's University Belfast joint College (CQC), Queen's University Belfast.

aaps PharmSci 360

ADVANCING PHARMACEUTICAL SCIENCES, CAREERS, AND COMMUNITY

PURPOSE

- The development of sustained-release formulations for drugs administered via the vaginal route has the potential to increase treatment efficiency and patient compliance.
- One promising strategy to formulate such dosage forms is the incorporation of microparticles into a bio-adhesive gel.

OBJECTIVE

- **To assess feasibility of formulating matrix microparticles using lipid-based carrier systems**,
  - namely, Syncrowax™ **HGLC** (hydrophobic insoluble lipid) or Gelucire® 50/13 (**G-50/13**; hydrophilic lipid),
  - with Avicel® PH-101 (**MCC**) or hypromellose **K100M** used as diluents.

METHODS

- Model drugs chosen for the study included azidothymidine (AZT) and metronidazole (MTZ).
- **Placebo formulations** prepared by molten-liquid filling of hard gelatine capsules (#3 0.27 ml, Coni-Snap®; Capsugel, Belgium).
- **The drug-loaded microparticles** prepared by twin-screw hot melt extrusion (TS-HME; Microlab L/D 20:1; Rondol Ind. SAS, France) and cutting extrudates with a scalpel.
- Placebo formulations were **screened** for tensile strength, water uptake/ weight loss (**WU/WL**) and, surface morphology.
- TGA, DSC, polarized-light hot-stage microscopy were used for **characterisation**.
- The **solubility** of each model drug at pH 4.5 was investigated using the shake-flask method.
- The in-vitro **drug release** properties of the formulated microparticles were assessed using USP-II (paddle) in sodium acetate buffer adjusted to pH 4.5 (to simulate vaginal fluid).

RESULTS

- WU/WL testing of placebo formulations allowed to narrow down the experimental plan (***Fig.1***)
- HGLC (T_m 48 ℃) based particles were prepared with TS-HME at conditions intended to minimize the effect on drug particle size reduction (conveying elements only; 20 rpm) and to maintain full crystallinity of the drug (not more than 62 ℃).
- model drugs AZT (T_m 110 ℃) and MTZ (T_m 152 ℃)
  - up to 90℃: did not dissolve in excipients (DSC),
  - between 90 and 190 ℃: observed dissolution of AZT in G-50/13 (Tm 33℃) as well as MTZ and AZT in HPMC (T_g 57 ℃).
- Microscopy observation revealed the development of the cracks during the cooling down of lipid-based formulations (***Fig. 2***).
- Drug release from particles (approx. 2.2x3 mm) without diluent at 10 and 20% w/w drug load demonstrated slow and incomplete release (***Fig. 3 left***), that can be explained with percolation threshold.
- Introduction of hydrophilic diluents (10% w/w) allowed to significantly increase drug release rate (***Fig. 3 right***).
- In accordance with Lapidus-Lordi equation [1], the increase surface area to volume ratio is increasing drug release rate, so preparing sustained release microparticles with additional particle size reduction can be considered.

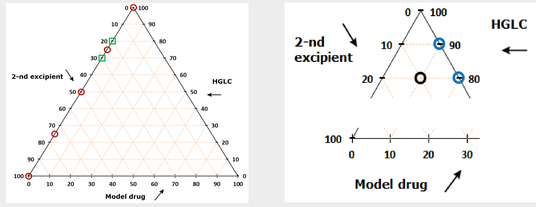

Fig. 1. *Ternary diagram for investigated* ***placebo*** *(left) and* ***drug-loaded formulations*** *(right).*

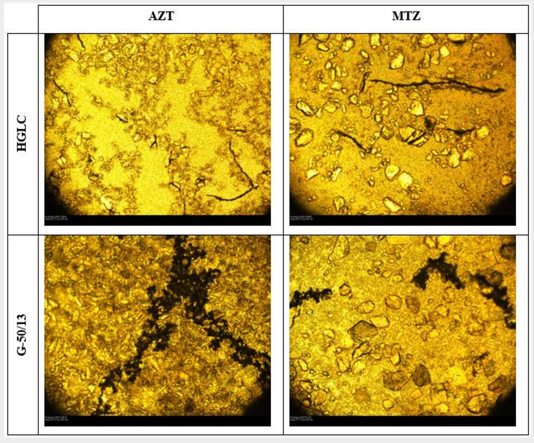

Fig. 2. *Illustration of* ***cracks appeared*** *after heating up and cooling down until room temperature.*

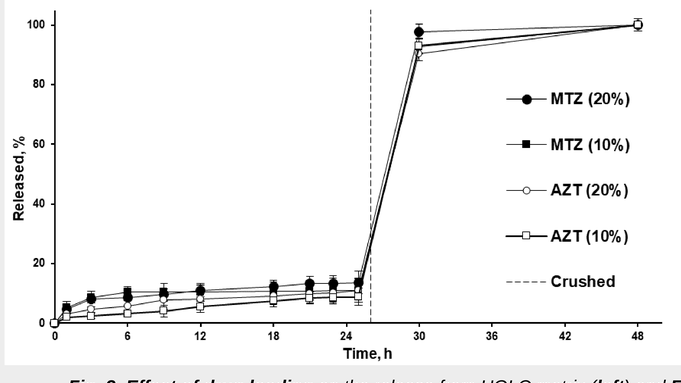

Fig. 3. Effect of drug loading *on the release from HGLC matrix (****left****) and* ***Effect of diluents*** *on the drug release from HGLC matrix (****right****).*

CONCLUSIONS

- The number of drug-loaded formulations was successfully reduced due to the screening of placebo formulations with WU/WL test.
- Insoluble matrix system based on the insoluble lipid Syncrowax™ HGLC (≥80 % w/w) and loaded with model drugs AZT or MTZ was successfully prepared using the twin-screw hot melt extrusion method and provided as sustained release.
- The addition of diluents as Avicel® PH-101 or hypromellose type K100M (at the 10% w/w level) can be used for the adjustment of drug release profile.
- The development of cracks in the Syncrowax™ HGLC lipid matrix during the cooling down stage could be accounted as an additional aspect of drug release facilitation.

REFERENCE

1. Lapidus, H. and N.G. Lordi, Drug release from compressed hydrophilic matrices. J Pharm Sci, 1968. 57(8): p. 1292-301.

QUEEN'S UNIVERSITY BELFAST

SCHOOL OF PHARMACY