The Influence of Aqueous Ethylcellulose Coating on the Performance of Hydrophilic Polyethylene Oxide Mini-Matrices Containing a Freely Water Soluble Drug

Hue Vuong, Marina Levina, Thomas P. Farrell and Ali R. Rajabi-Siahboomi

Poster Reprint
CRS 2011

Abstract Summary

This study investigated the influence of an aqueous ethylcellulose film coating on in vitro release of a freely water-soluble model drug, metoprolol succinate, from polyethylene oxide (PEO) mini-matrices.

Introduction

There is a growing interest in multi-particulate (MP) modified release (MR) drug delivery systems. Multiparticulates can provide more reliable in vivo dissolution performance when compared to a single unit dosage form, resulting in consistent dose-to-dose bioavailability and clinical effect.[1]

Mini-tabs combine the advantages of MP dosage forms with the established manufacturing techniques of tableting and have fewer constraints compared to extrusion-spheronization process.[2] Mini-tabs produced via direct compression are an attractive alternative to pellets, since the use of liquids is avoided. Like other MP technologies, mini-tabs can be filled into hard capsules, which may be consumed as is, or opened and the contents mixed with food for easy administration to elderly, children and those who may have difficulty to swallow.[3] Additional benefits include excellent size uniformity, regular shape and a smooth surface, offering an ideal substrate for MR coatings.

A majority of oral extended release (ER) drug delivery dosage forms are matrix based systems that rely on fast formation of a hydrated gel layer around a tablet in the presence of water or biological fluids. To enable that, different swellable hydrophilic polymers are commercially available, notably high viscosity grades of hydroxypropyl methylcellulose (HPMC) being the most commonly used. More recently, polyethylene oxide, PEO (POLYOX™ WSR) has been explored as an alternative carrier for hydrophilic ER matrices.[4]

Ethylcellulose (EC) is a water-insoluble polymer with good ability to form films and an excellent safety profile. It is widely used in organic and aqueous film coating applications to achieve extended drug release.[5]

The aims of this study were to investigate the effect of coating using Surelease® aqueous ethylcellulose system on the performance of PEO ER mini-matrices, containing a freely water-soluble drug, metoprolol succinate (157 mg/mL)[6].

Experimental Methods

Mini-tabs used in this study contained 10% w/w metoprolol succinate (S & D Chemicals Ltd), 86.5% w/w PEO (POLYOX™ WSR Coagulant, Dow Chemical Co.), 0.5% w/w fumed silica (Aerosil® 200, Evonik), 2% w/w stearic acid (Meade King Robinson) and 1% w/w magnesium stearate (Peter Greven). The mini-tabs were manufactured by direct compression on a modified, instrumented, 10-station rotary press (Piccola, Riva) fitted with 2 mm round standard concave tooling (Notter GmbH); at 0.6 kN compression force and 35 rpm to a target weight of 6.0 mg.

The mini-tabs were seal-coated with a 20% w/w aqueous solution of PVA-based Opadry® II Clear (Colorcon) to a 5% weight gain (WG); followed by a 15% w/w aqueous EC dispersion (Surelease®, Colorcon) up to 20% WG. The trials were conducted in a GPCG 1.1 fluid-bed coater (Glatt) using a bottom spray (Würster column) set up. Coating process parameters are listed in **Table 1**.

Table 1. Coating Process Parameters

Process parameters	Seal-coat	ER coat
Air volume (m^3/h)	105	110
Inlet air temperature (°C)	57 - 60	55 - 58
Exhaust air temperature (°C)	48 - 49	44 - 46
Product temperature (°C)	46 - 48	42 - 45
Atomizing air pressure (bar)	1.5	1.5
Spray rate (g/min)	4 - 5	6 - 8
Process time (min)	33	110

The mechanical strength of uncoated and seal-coated mini-tabs was determined using hardness (4M, Schleuniger) and friability (Copley TA, Erweka GmbH) testers. The mini-tab thickness was measured using a micrometer (Mitutoyo, Japan).

Drug release from uncoated and coated mini-tabs was determined by dissolution testing conducted in a Sotax bath according to the USP monograph for "Metoprolol Succinate Extended-Release Tablets"[7] using Apparatus 2 (paddles) at 50 rpm in 500 mL of pH 6.8 phosphate buffer at 37 ± 0.5ºC. A dual beam UV/VIS spectrophotometer (Lambda 25, Perkin Elmer) was used for the detection of the API at a wavelength of 274 nm. Measurements were performed in triplicate, and mean and standard deviation values were calculated.

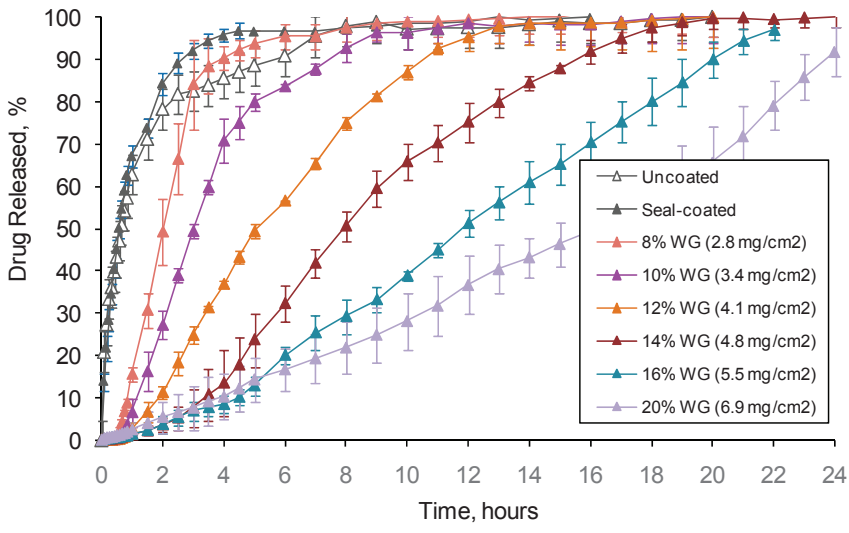
The release was measured for a 25 mg drug dose, i.e. 42 mini-tabs per sample, this number of mini-tabs can fit into size 0 capsule. However, in this study dissolution was conducted for non-capsulated samples.

Results and Discussion

Low ejection force values (17.36 ± 1.94 N) were recorded during tableting. Mini-tabs with 6.0 ± 0.2 mg weight and 1.922 ± 0.040 mm thickness were produced. The uncoated and coated mini-tabs exhibited good appearance, showing no visual defects. Breaking force measurement of the mini-matrices was not possible due to plastic deformation of POLYOX™. However, friability was found to be very low (less than 0.01%).

Figure 1 shows that uncoated and seal-coated PEO mini-matrices released drug within 3 hours. Application of Surelease® film resulted in slower drug dissolution with the lower release rates obtained for higher coating weight gains. For 12 hour and longer release of freely water-soluble metoprolol succinate, at least 12% WG of barrier membrane coating was required. Application of 16-20% WG Surelease® resulted in nearly zero order drug release profiles from the mini-tabs over 23 hours.

Figure 1. Metoprolol Succinate Release from Mini-tabs Coated with Surelease® (n = 3)

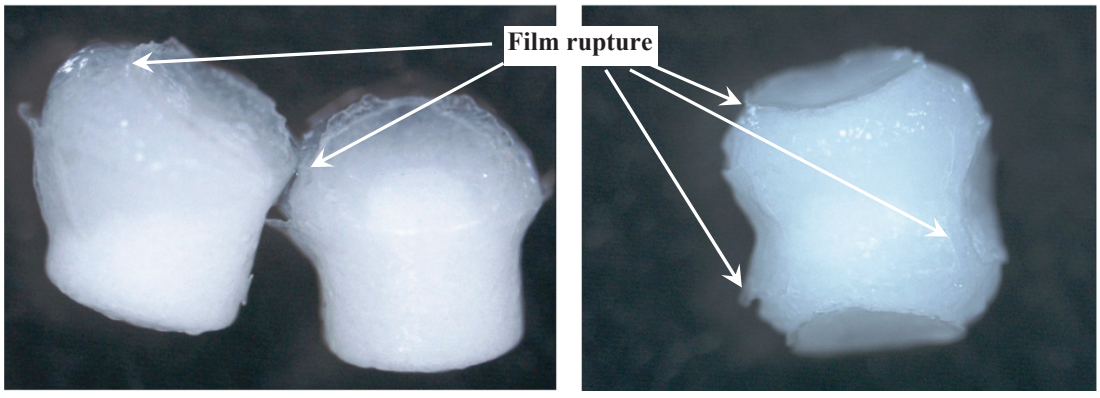


For all tested mini-matrices coated with Surelease®, the internal pressure as a result of swelling and relaxation of the PEO matrix caused rupture of the ethylcellulose film during dissolution testing[8]. The barrier membrane broke at the mini-tab edge (which is the weakest point of the coating) and the fracture propagated around the circular base of the core, thus allowing the developed pressure to squeeze out the swelling core.

Axial relaxation of the mini-matrices caused the insoluble, but permeable, ethylcellulose membrane to consistently open along the circumference of one of the mini-tab faces initially (**Figure 2a**), and subsequently on the opposite face, in addition to the side of the mini-tab (**Figure 2b**). A possible explanation for the coating rupture to occur just on one face of the mini-tab initially can be the fact that during tableting, powder particles in the die located near the top are compressed to a greater extent compared to those at the bottom. During dissolution testing, the particles that were subjected to a higher level of deformation showed greater axial relaxation, leading to the subsequent barrier membrane rupture initially on one face of the tested mini-tabs.

For mini-matrices with higher Surelease® coating weight gains, the film remained intact for longer periods of time as a higher swelling force of the mini-matrix was required to overcome the mechanical resistance of the barrier membrane.

Figure 2. Swelling of PEO Mini-Matrices and Rupture of Surelease® Coating during Dissolution Testing



Conclusions

Robust metoprolol succinate POLYOX™ mini-tabs were manufactured, with good weight uniformity and mechanical properties. Release of freely water soluble metoprolol succinate from uncoated and seal-coated mini-matrices occurred within 3 hours. An application of Surelease® barrier membrane to mini-tabs resulted in extending drug dissolution up to 24 hours. As the weight gain of ethylcellulose coating increased, the release profile shifted towards zero order.

For all mini-matrices with Surelease® barrier membrane, film rupture around tablet edges was consistently observed during dissolution testing. For lower coating weight gains, this occurred much earlier as compared to 12-20% WG of Surelease®.

References

1. Riis T., Bauer-Brandl A., Wagner T., Kranz H. pH-independent drug release of an extremely poorly soluble weakly acidic drug from multiparticulate extended release formulations. *Eur. J. Pharm. Biopharm*. 2007:65(1):78-84.
2. Alderborn G. Tablets and compaction. in: Pharmaceutics; The Science of Dosage Form Design. M.E. Aulton (Ed.); Churchill, Livingstone, UK: Churchill; 2002, 404-410.
3. Lopes C.M., Souso Lobo J M, Pinto J F, Costa P. Compressed mini-tablets as a biphasic delivery system. *Int. J. Pharm.*, 2006:323(1-2):93-100.
4. Colombo P, Bettini R, Santi P, Peppa N A. Swellable matrices for controlled drug delivery: gel-layer behavior, mechanisms and optimal performance. *Pharm. Sci. Tech. Today*. 2000:3(6): 198-204.
5. Frohoff-Hülsmann M A, Schmitz A, Lippold B C. Aqueous ethyl cellulose dispersions containing plasticizers of different water solubility and hydroxypropyl methylcellulose as coating material for diffusion pellets I. Drug release rates from coated pellets. *Int. J. Pharm*. 1999:177(1):69–82.
6. Ravishankar H, Patil P, Samel A, Petereit H, Lizio R, Jayanthi I. Modulated release metoprolol succinate formulation based on ionic interactions: in vivo proof of concept. *J. Contr. Rel*. 2006:111(1-2): 65-72.
7. Metoprolol succinate extended-release tablets. United States: USP 28-NF23; 2005.
8. McGinity J.W. (Ed.). Aqueous polymeric coatings for pharmaceutical dosage forms, 2nd edition. New York, NY: Marcel Dekker, Inc.; 1997, pp 78-79.