The Influence of Hydrophilic Pore-Formers on Metoprolol Succinate Release from Mini-Tabs Coated with Aqueous Ethylcellulose Dispersion

ABSTRACT SUMMARY

This study investigated the influence of incorporating a water-soluble pore-former based on polyvinyl alcohol (PVA) into aqueous ethylcellulose dispersion (Surelease®) film coating on invitro release of a model drug metoprolol succinate, from mini-tabs.

INTRODUCTION

There is a growing interest in multiparticulate (MP) modified release (MR) drug delivery systems. After ingestion the MP units are released from the capsule in the stomach and predictably transit to the small intestine[1], dispersing along the gastrointestinal tract, leading to consistent drug release with reduced risk of local irritation. MPs generally provide a more reliable in vivo dissolution performance when compared to a single unit dosage form, resulting in consistent dose-to-dose bioavailability and clinical effect.[2] Mini-tabs combine the advantages of MP dosage forms with the established manufacturing techniques of tableting and have fewer constraints compared to extrusion-spheronization.[3] Additionally, 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 are filled into hard capsules, which may be used as whole or opened and mixed with food for easy administration to elderly and children.[4] Additional benefits of mini-tabs include excellent size uniformity, regular shape and a smooth surface, offering an ideal substrate to coat with polymeric membranes for MR purposes. Ethylcellulose (EC) is a water-insoluble polymer with good ability to form films and excellent safety profile. It is widely used in organic and aqueous film coating applications to achieve extended release (ER) of drugs.[5] The aims of this study were to investigate the influence of incorporating different levels of pore-former into aqueous EC system (Surelease) on the release of a freely water-soluble (157 mg/mL[6]) drug metoprolol succinate, from coated mini-tabs.

EXPERIMENTAL METHODS

Mini-tabs used in this study contained 10% w/w metoprolol succinate (S & D Chemicals Ltd), 85.5% w/w lactose (FastFlo, Kerry Bio-Science), 0.5% w/w fumed silica (Aerosil 200, Evonik),2% w/w stearic acid (Meade King Robinson) and 2% 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 double radius 16-tip tooling (B & D Italia); at 12 kN compression force and 30 rpm to a target weight of 8.0 mg. Mini-tabs (0.6 kg batch size) were seal-coated with a 20% w/w aqueous solution of a PVA-based

Opadry® II Clear, high performance film coating (Colorcon) to 5% weight gain (WG), followed by a 15% w/w aqueous EC dispersion (Surelease, Colorcon) with pore-former (the same Opadry II Clear) at two different ratios (85:15 and 80:20, Table 1) up to 16% WG. The trials were conducted in a GPCG 1.1 fluid bed coater (Glatt) using bottom spray (Würster column) set up. Process parameters are listed in Table 2.

Table 1. Surelease/pore-former dispersion preparation

Surelease: Pore Former Ratio	Amount (g)		
	Surelease dispersion*	Pore former solution**	Water
85:15	357	105	238
80:20	336	140	224

**** Surelease dispersion at 25% solids***

***** Pore-former solution at 15% solids***

Table 2. Coating process parameters

Process parameters	Seal-coat	ER coat
Air volume (m^3/h)	105	110
Inlet air temperature (°C)	56 - 60	54 - 60
Exhaust air temperature (°C)	46 - 48	43 - 46
Product temperature (°C)	45 - 47	42 - 43
Atomizing air pressure (bar)	1.5	1.5
Spray rate (g/min)	3 - 4	5 - 7
Process time (min)	40	100

The mechanical strength of uncoated and seal-coated mini-tabs was determined using hardness (4M, Schleuniger) and friability (Copley TA, Erweka GmbH) testers. Drug release from coated mini-tabs was evaluated 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 Instruments) was used for the detection of metoprolol succinate at a wavelength of 274 nm. Three samples of mini-tabs were tested (n = 3);mean and standard deviation (SD) values were calculated. Drug release was measured for a 25 mg drug dose, i.e., 32 mini-tabs per sample.

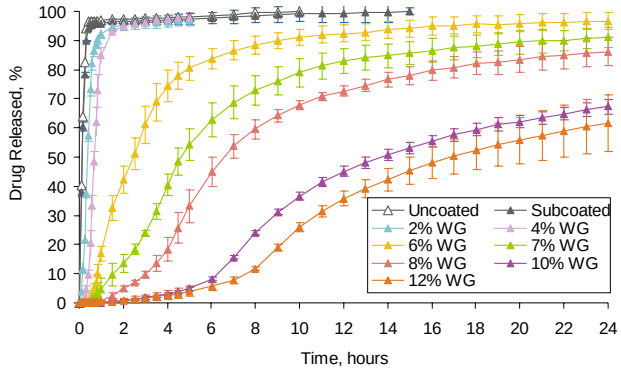
RESULTS AND DISCUSSION

The coated mini-tabs exhibited good appearance, showing no visual defects. The mechanical strength of the mini-tabs improved significantly after the application of a seal-coat. Breaking force increased from 2.1 kp (uncoated) to 3.0 kp (seal-coated) and friability was reduced from 0.46% to less than 0.01% respectively. Disintegration time of seal-coated tablets was less than 10 minutes. Figure 1 shows that swelling of the coated mini-tabs occurred after exposure to the dissolution medium caused by the ingress of the buffer and, hence, the development of hydrostatic pressure contributing osmotically to the diffusion driven drug release.[8]

Figure 1. Appearance of the ER coated mini-tabs (10% WG) after 24-hour dissolution time

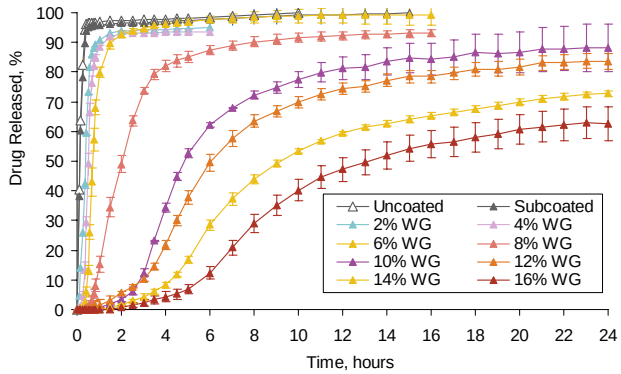
Figures 2 and 3 show that for both pore-former concentrations, immediate release of drug was produced for low coating WG,2%-4% and 2%-6% respectively. With an increase in coating levels up to 16%, metoprolol succinate release rate decreased significantly. All profiles demonstrated consistent release with low variability as indicated by standard deviation values.

Figure 2. Metoprolol succinate release from mini-tabs coated with Surelease/pore-former (85:15)



Slower release rates were produced for mini-tabs containing lower pore-former concentration. For example, at 10% WG only 62% of the drug was released from 85:15 coating compared to 86% metoprolol succinate dissolved from 80:20 system, after 24-hour dissolution testing. This significant difference in the amount of drug release can be explained by the increased permeability of the film when more pore-former was used.

Figure 3. Metoprolol succinate release from mini-tabs coated with Surelease/pore-former (80:20).



Additionally, a lag time developed that increased with increasing coating weight gain. A similar finding was reported previously when coating drug layered sugar spheres with Surelease dispersion containing HPMC or PVA/PEG as the pore-former.[9, 10]

CONCLUSIONS

Robust metoprolol succinate mini-tabs were manufactured using multi-tip tooling and their mechanical strength was significantly improved by the application of 5% WG of an Opadry II seal-coat. Drug release rate from mini-tabs coated with ethylcellulose coating was modulated by varying the amount of hydrophilic pore-former and/or the level of film coating applied. Mini-tabs offer a reliable alternative to conventional multiparticulate systems with consistent substrate from which drug release is effectively modulated.

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