Barrier Membrane Coating of Hydrophilic Matrices of a Very Soluble Drug, Metoprolol Tartrate at High Dose: A Strategy to Eliminate the Initial Burst Release

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Abstract Summary

Extended release hydrophilic matrix tablets of metoprolol tartrate were formulated using high viscosity hypromellose (METHOCEL™ premium cellulose ethers, K15M) as a rate-limiting polymer. In vitro dissolution studies of the tablets indicated initial burst, followed by a sustained drug release pattern. Application of barrier membrane (BM) coating, using aqueous ethylcellulose dispersion (Surelease® aqueous ethylcellulose dispersion, E-7-19010) with a pore-former (Opadry® complete film coating system), resulted in elimination of the burst effect, followed by near zero order release. The findings of the study indicated robust and consistent drug release when the BM coated matrices were exposed to bio-relevant media and different agitation rates.

Introduction

Hydrophilic matrix systems are the most popular technology used in oral extended release drug delivery. For the purpose of achieving extended release of a high dose and highly water soluble drug, such as metoprolol tartrate, rapid hydration and strong gel layer formation of the rate controlling polymer are essential. Generally a high viscosity grade of hypromellose is used. However, the highly soluble drug available at and adjacent to the surface of the matrix dissolves immediately upon contact with the dissolution media and released, prior to formation of the gel layer. This gives rise to an initial burst release followed by controlled release of the drug.[1]

It has been reported that BM coating of matrices may help to suppress the initial burst release.[2] Hence, the objective of this investigation was to eliminate burst release from the hydrophilic matrices of metoprolol tartrate (MT), as a very soluble model drug (~1000 mg/mL), using a suitable combination of BM (Surelease) and a pore-former (Opadry). In addition, the robustness and consistency of drug release from BM coated matrices, exposed to different media; agitation rates and type of agitation were also investigated to simulate in vivo conditions.

Experimental Methods

High Shear Granulation and Tablet Preparation

The formulation of metoprolol tartrate ER matrices is shown in Table 1. The milled drug was dry blended with half the hypromellose and half quantity of filler (microcrystalline cellulose (MCC), or Starch 1500® partially pregelatinized maize starch), then granulated in a high shear granulator (Diosna P/VAC 10, Germany). Water was used as the granulating liquid, sprayed at 35g/min. The resulting granules were dried in an oven at 45-50ºC, to ~5% of LOD, then milled (Quadro Comil, Quadro Engineering, Canada) using a 1.18 mm grated screen. The milled granules were blended with the remainder of the hypromellose and filler, fumed silica, then blended for 10 minutes (twin shell blender, Patterson Kelly, USA). The resulting blends were lubricated with magnesium stearate for 3 minutes and compressed on an instrumented rotary press (Piccola, Riva, Argentina) using 9.5 mm standard concave tooling, to a target tablet weight and dose level of 400 and 200 mg, respectively.

Application of Barrier Membrane Coating

The tablets were coated using Surelease E-7-19010 with an HPMC based Opadry film coating system as pore-former, weight ratio of 85:15 w/w. Prior to BM application, the coating dispersions were prepared in water at 10% w/w solids content; tablets were then coated to 2-8% weight gain (WG). Typical coating processing parameters were used for application of BM coating.[3]

Dissolution Studies

In vitro dissolution studies of uncoated and BM coated matrices were conducted using the following methods:

1. Compendial Media:

Dissolution testing was carried out using Apparatus II (paddles) with sinkers in 900 mL of specified dissolution media at 37°C. Tablets were first placed in pH 4.5 acetate buffer for 4 hours (50, 100 and 150 rpm), followed by pH 6.8 phosphate buffer (100 rpm) for the remaining 12 hours. Drug release was determined spectrophotometrically at a wavelength of 275 nm.

2. Biorelevant Media:

Dissolution testing was carried out using Apparatus III (reciprocating cylinder) and fasted or fed dissolution media at 37°C. The reciprocating cylinder was operated at 10 dips per minute (DPM) with multiple steps of media changeover to simulate the human gastrointestinal environment. The dissolved drug was measured using HPLC.

The drug release profiles were compared using similarity factors (f_2).

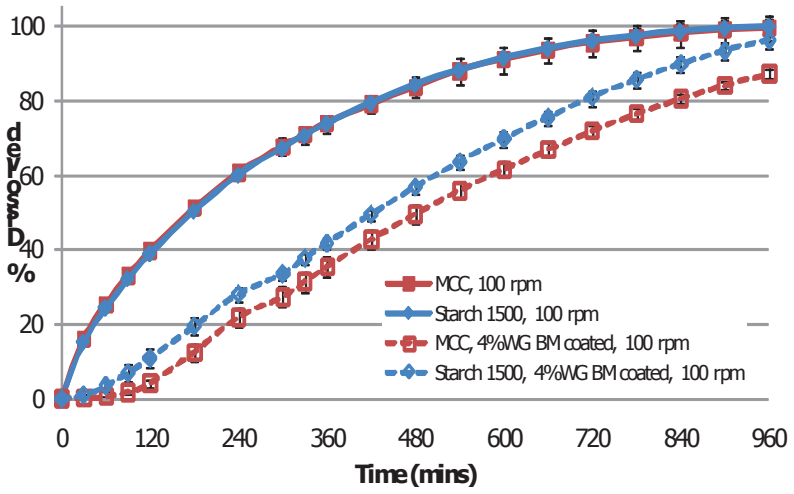
Table 1. Extended Release Matrix Formulations

Ingredients	Concentration (%w/w)
Metoprolol Tartrate (Polydrug Pvt. Ltd., India)	50
Hypromellose (METHOCEL™ K15M Premium, IFF., USA)	30
Partially pregelatinized starch (Starch 1500®, Colorcon, USA) **or** **Microcrystalline Cellulose (MCC)** (JRS Pharma, USA)	19
Fumed silica (CAB-O-Sil M5P, Cabot Corp., USA)	0.5
Magnesium Stearate (Mallinckrodt, USA)	0.5
Total	100

Results and Discussion

All formulations resulted in tablets with acceptable mechanical strength [(hardness>12kP (2.8 MPa)]. Figure 1 shows that drug release from uncoated matrices, containing different fillers, was similar with f_2 values >90. Both matrices showed the initial burst release of about 40% drug release within the first 2 hours of dissolution.

Figure 1. Dissolution Profiles of Uncoated and BM Coated MT Matrices with Starch 1500 or MCC as Filler (Compendial Media)



Application of BM coating at 4% WG resulted in elimination of burst release with a lag phase in drug release profile. Near zero order release was obtained for both fillers with f_2=56 at 100 rpm. This was achieved through rupture of BM coating around the belly band area of the matrix tablets, while the ruptured coating remained intact on tablet surfaces. Increasing the coating weight gain resulted in reduction of drug release rate from BM coated matrices.

The same phenomenon (consistent coating rupture and similar drug release) was observed when dissolution testing was performed at varied agitation rates of 50, 100 and 150 rpm in pH 4.5 for 4 hours, followed by pH 6.8 phosphate buffer at 100 rpm (data not shown). The consistency of drug release from BM coated matrices was further evaluated using USP Apparatus III (reciprocating cylinder) and biorelevant media. Results showed that drug release had minimal sensitivity to the biorelevant media and the reciprocating motion of the dosage form within the Apparatus III (Figures 2 & 3). Table 2 summarizes the f_2 values when different dissolution conditions are used.

Figure 2. Dissolution Profiles of BM Coated MT Matrices with Starch 1500 or MCC at 4% WG of BM Coating (Biorelevant Fasted Media)

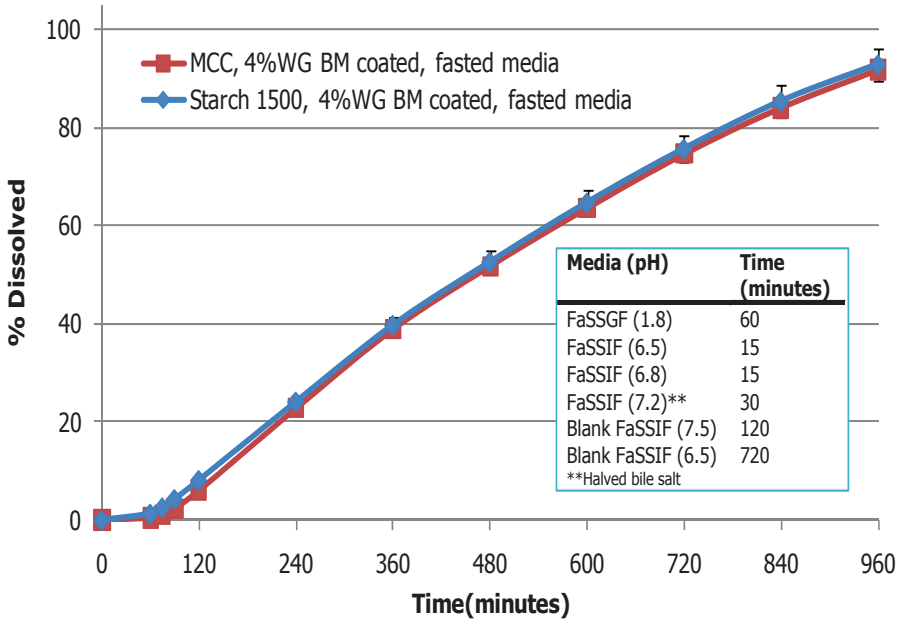


Figure 3. Dissolution Profiles of BM Coated MT Matrices with Starch 1500 or MCC at 4% WG of BM Coating (Biorelevant Fed Media)

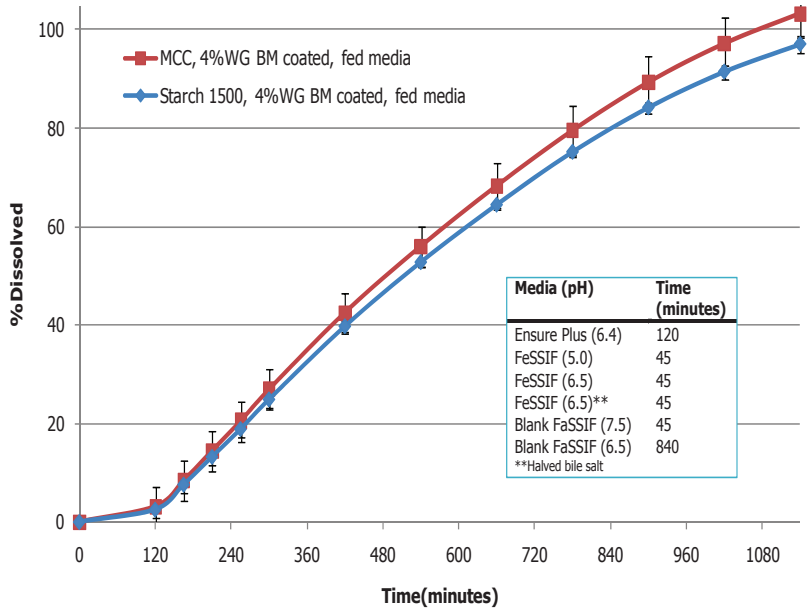


Table 2. Comparison of Similarity Factors (f_2) for BM Coated MT Matrices

Type of Filler	Dissolution Methods			
	FeSSIF vs FaSSIF	50 rpm vs 100 rpm	150 rpm vs 100 rpm	50 rpm vs 150 rpm
MCC	76	88	68	75
Starch 1500	60	72	74	84

Conclusions

The application of a barrier membrane coating, Surelease/Opadry combination, eliminated the burst release from hydrophilic matrices of metoprolol tartrate, a very soluble model drug. Consistent drug release from BM coated matrices was obtained when exposed to biorelevant media and different agitation rates, simulating the gastrointestinal conditions. This approach may provide further options when formulating drugs susceptible to burst release, where zero order release is targeted.

References

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