Barrier Membrane Coated Hydrophilic Matrices: Robustness of Metoprolol Tartrate Release under Biorelevant Test Conditions – Impact of Media Composition

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Introduction

Hydrophilic matrix systems are the most popular technology used in oral extended release (ER) drug delivery. For the purpose of achieving extended release of a high dose and highly water soluble drug, rapid hydration and strong gel layer formation of the rate controlling polymer are essential. For this purpose, generally a high viscosity grade of hypromellose is used in the manufacture of such matrix formulations. However, the highly soluble drug available at and adjacent to the surface of ER the tablet dissolves immediately upon contact with the dissolution media, 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 barrier membrane (BM) coating of matrices may help to suppress the initial burst release[2]. The aim of the present study was to investigate the robustness of *in-vitro* drug release from BM-coated hydrophilic matrix tablets of metoprolol tartrate, a BCS class I drug, in media representing typical physicochemical properties of fasted and fed state gastrointestinal fluids.

Methods

Formulation and Tablet Preparation

Extended release hydrophilic matrix tablets of metoprolol tartrate (see table 1 for composition) were formulated using high viscosity hypromellose as a rate-limiting polymer. The BM coating consisting of aqueous ethylcellulose dispersion (Surelease E-7-19010) and an HPMC-based Opadry™ system, as pore former (85:15 w/w), was applied onto the matrices at 4% w/w weight gain to eliminate a burst release from uncoated matrices, generally observed for highly soluble drugs.

Table 1: Composition of metoprolol tartrate ER hydrophilic matrix tablets

Ingredients	w/w	Amount per Tablet
Metoprolol Tartrate, Polydrug Pvt. Ltd., India	50 %	200 mg
Hypromellose (METHOCEL™ K15M Premium), IFF., USA	30 %	120 mg
Partially pregelatinized starch (Starch 1500®), Colorcon, USA	19 %	76 mg
Colloidal Silicon Dioxide (CAB-O-Sil M5P), Cabot Corp., USA	0.5 %	2 mg
Magnesium stearate, Mallinckrodt, USA	0.5 %	2 mg
Total	100 %	400 mg

Dissolution Studies

Uncoated and BM-coated matrices were subjected to various dissolution studies. Initially, drug release from BM-coated matrices was evaluated in USP apparatus III (RRT 10, Erweka, Heusenstamm, Germany, Figure 1) simulating the pH gradient during a fasted and fed state passage through the human gastrointestinal (GI) tract (Tables 2-3). Subsequently, experiments were performed in the Mini-Paddle apparatus (DT 600, Erweka, Heusenstamm, Germany) using 200 mL of medium and a stirring speed of 100 rpm . To simulate additional relevant physiological changes of the GI fluid composition, particularly the increase in osmolality and the decrease in surface tension after food intake, the osmolality or the surface tension of the media was varied by applying different concentrations of NaCl or sucrose or different concentrations of SLS or Tween 80, respectively, while the pH was kept constant (Blank FaSSIF pH 6.8). The magnitude of variation in osmolality and surface tension was according to the physiological relevance of human gastrointestinal tract under fed and fasted conditions. All experiments were run in triplicate. Samples were taken at predetermined time points and after appropriate dilution were analyzed at 272nm using a UV-spectrophotometer (U 2000, Hitachi Ltd, Tokyo, Japan).

Table 2: Simulation of a fasted state GI passage (USP apparatus III)

GI segment	Medium	Residence time
Stomach	SGFsp pH 1.8	60 min
Proximal jejunum	Blank FaSSIF pH 6.5	60 min
Distal jejunum	Blank FaSSIF pH 6.8	60 min
Proximal ileum	Blank FaSSIF pH 7.2	60 min
Distal ileum	Blank FaSSIF pH 7.5	60 min
Proximal colon	SCoF pH 5.8	300 min
Colon	Blank FaSSIF pH 6.5	360 min
Colon	Blank FaSSIF pH 6.8	480 min

Table 3: Simulation of a fed state GI passage (USP apparatus III)

GI segment	Medium	Residence time
Stomach	Blank FeSSIF pH 5.0	120 min
Stomach	SGFsp pH 2.0	120 min
Proximal jejunum	Blank FeSSIF pH 5.0	60 min
Distal jejunum	Blank FeSSIF pH 6.5	60 min
Proximal ileum	Blank FeSSIF pH 6.8	60 min
Distal ileum	Blank FeSSIF pH 7.5	60 min
Proximal Colon	SCoF pH 5.8	240 min
Colon	Blank FaSSIF pH 6.5	240 min
Colon	Blank FaSSIF pH 6.8	480 min

Results

Impact of pH variations on drug release

Figures 1 and 2 show drug release for BM-coated hydrophilic metoprolol tartrate (MPT) matrices under pH-conditions of a simulated fasted and fed state GI passage. It is evident that pH variation within the physiological range in the GI tract did not affect drug release.

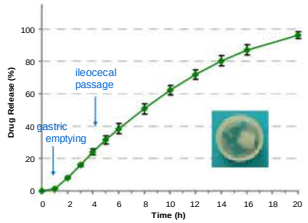

Fig. 1: Drug release (mean of n=3 ± SD) from BM-coated MPT matrices in a fasted pH gradient: 200 mL/vessel, 10 dpm

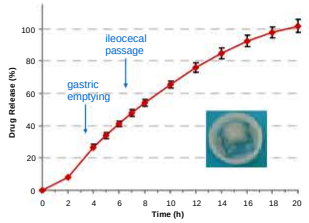

Fig. 2: Drug release (mean of n=3 ± SD) from BM-coated MPT matrices in a fed state pH gradient: 200 mL/vessel, 10 dpm

Impact of osmolality and surface tension on drug release

Figures 3 and 4 show drug release for BM-coated und uncoated MPT matrices in Blank FaSSIF pH 6.8 adjusted to physiologically relevant osmolalities of 100 to 600 mOsmol/kg and with 0.001 to 0.1 % surfactant added.

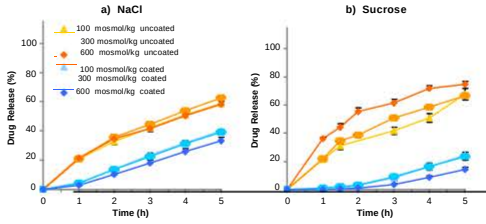

Fig. 3: Drug release (mean of n=3 ± SD) from BM-coated and uncoated MPT matrices in Blank FaSSIF pH 6.8 adjusted to 100 - 600 mOsmol/kg

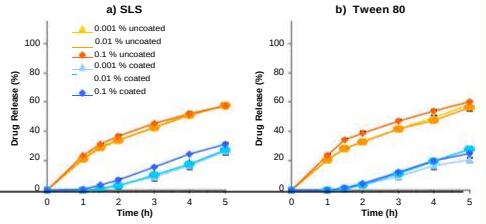

Fig. 4: Drug release (mean of n=3 ± SD) from BM-coated and uncoated MPT matrices in Blank FaSSIF pH 6.8 containing 0,001 - 0.1 % surfactant

The release profiles presented in Figures 3 and 4 indicate that drug release from both uncoated and BM-coated matrices is controlled and independent of the osmolality and the concentration of surfactants. In addition, the impact of the BM-coating becomes visible in a reliable and highly controlled release profile which even under worst conditions (very high/low osmolality and very high concentrations of surfactants) prevents a burst release.

Conclusion

BM-coated hydrophilic matrices represent a very promising approach for obtaining a controlled and robust release of metoprolol tartrate by eliminating the observed burst release. In future experiments it needs to be shown, if the same approach would offer similar advantages for other BCS class I drugs and, even more interesting, if it is also applicable to BCS class II compounds.

References

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