Barrier Membrane Coated Hydrophilic Matrices: Robustness of Metoprolol Tartrate Release under Biorelevant Test Conditions – Impact of pH and Mechanical Stress

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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, 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 the ER 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 drug release from BM-coated ER tablets of metoprolol tartrate, as a model drug, by *in-vitro* testing simulating fasted and fed pH conditions and mechanical stress in the human gastrointestinal (GI) tract.

Methods

Formulation and Tablet Preparation

Extended release hydrophilic matrix tablets of metoprolol tartrate 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 the burst release from uncoated matrices, generally observed for highly soluble drugs.

Dissolution Studies

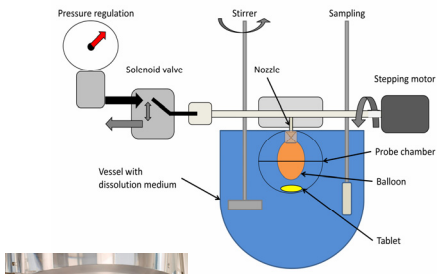
Uncoated and BM-coated matrices were subjected to various dissolution studies. Initially, experiments were performed using the USP apparatus III (RRT 10, Erweka, Heusenstamm, Germany). Biorelevant pH gradients and simplified pH gradients (Tables 1 & 2) simulating fasting and fed state pH-conditions along the human GI tract were applied to determine drug release[3]. Subsequently, media volumes and the agitation speeds (dip rates) were varied to evaluate the impact of inter- and intra-individual variations of such parameters on dissolution of metoprolol tartrate. Finally, a biorelevant stress test apparatus (Figure 1) was used to screen the impact of mechanical stress applied on the dosage form during gastric emptying, ileocecal passage and transport in the GI tract, on drug release[4]. All experiments were run in triplicate and samples were analyzed at 272 nm using a UV-spectrophotometer (U 2000, Hitachi Ltd, Tokyo, Japan).

Table1: Simulation of a fasted state GI passage

GI segment	Medium – setups 1-2	Medium – setup 3	Medium – setup 4	Residence time
Stomach	SGFsp pH 1.8	SGFsp pH 1.8	SGFsp pH 1.8	60 min
Proximal jejunum	Blank FaSSIF pH 6.5	Blank FaSSIF pH 6.8	Carbonate buffer pH 6.8	60 min
Distal jejunum	Blank FaSSIF pH 6.8	Blank FaSSIF pH 6.8	Carbonate buffer pH 6.8	60 min
Proximal ileum	Blank FaSSIF pH 7.2	Blank FaSSIF pH 6.8	Carbonate buffer pH 6.8	60 min
Distal ileum	Blank FaSSIF pH 7.5	Blank FaSSIF pH 6.8	Carbonate buffer pH 6.8	60 min
Proximal colon	SCoF pH 5.8	SCoF pH 5.8	SCoF pH 5.8	300 min
Colon	Blank FaSSIF pH 6.5	SCoF pH 5.8	SCoF pH 5.8	360 min
Colon	Blank FaSSIF pH 6.8	SCoF pH 5.8	SCoF pH 5.8	480 min

Table 2: Simulation of a fed state GI passage

GI segment	Medium – setups 1-2	Medium – setup 3	Medium – setup 4	Residence time
Stomach	Blank FeSSIF pH 5.0	Blank FeSSIF pH 5.0	Blank FeSSIF pH 5.0	120 min
Stomach	SGFsp pH 2.0	Blank FeSSIF pH 5.0	Blank FeSSIF pH 5.0	120 min
Proximal jejunum	Blank FeSSIF pH 5.0	Blank FeSSIF pH 6.8	Carbonate buffer pH 6.8	60 min
Distal jejunum	Blank FeSSIF pH 6.5	Blank FeSSIF pH 6.8	Carbonate buffer pH 6.8	60 min
Proximal ileum	Blank FeSSIF pH 6.8	Blank FeSSIF pH 6.8	Carbonate buffer pH 6.8	60 min
Distal ileum	Blank FeSSIF pH 7.5	Blank FeSSIF pH 6.8	Carbonate buffer pH 6.8	60 min
Proximal Colon	SCoF pH 5.8	SCoF pH 5.8	SCoF pH 5.8	240 min
Colon	Blank FaSSIF pH 6.5	SCoF pH 5.8	SCoF pH 5.8	240 min
Colon	Blank FaSSIF pH 6.8	SCoF pH 5.8	SCoF pH 5.8	480 min



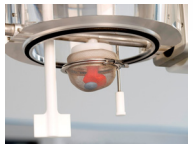


Fig. 1: Biorelevant stress test apparatus (©Physiolution GmbH)

Results

Impact of pH variations on drug release

Figures 2 and 3 show drug release from BM-coated hydrophilic metoprolol tartrate (MPT) matrices under pH-conditions of a simulated fasted and fed state GI passage. Neither variation of the pH within the physiological gastrointestinal pH range, nor the agitation speed or the media volume affect drug release.

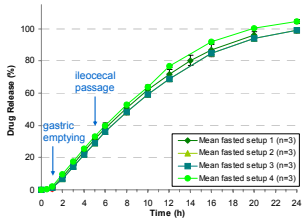


Fig. 2: Drug release (mean of n=3 ± SD) from BM-coated MPT matrices in a fasted pH gradient: Setup 1 ,3,4 (2): 200 mL (100 mL) /vessel, 10 (5) dpm

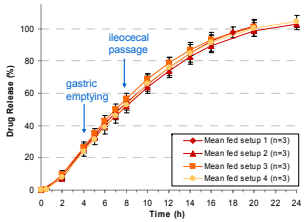


Fig. 3: Drug release (mean of n=3 ± SD) from BM-coated MPT matrices in a fed state pH gradient: Setup 1,3,4 (2): 200 mL (100 mL) /vessel, 10 (5) dpm

Impact of mechanical stress on drug release

Figure 4 shows drug release from BM-coated matrices under conditions of a simulated fasted and fed state GI passage in the stress test device. For the fed state the intensity of mechanical forces was varied to simulate high and low gastric "grinding" and transport activity representing a best-and worst case scenario for the dosage form.

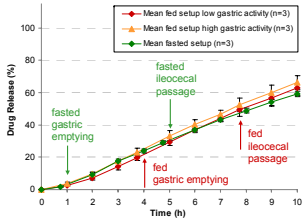


Fig. 4: Drug release (mean of n=3 ± SD) from BM-coated MPT matrices under fasted and fed state stress conditions

Release profiles from the fasted and fed state stress test experiments were superimposable, indicating a similar drug release ate and the absence of burst release. These results exhibit a robust dosage form with drug release unaffected even when high mechanical stress, i.e. pressure (up to 300 mbar) is applied on the dosage form during simulated gastric emptying and rotational/shear forces simulating transport events in the human gastrointestinal tract. Based on the obtained i*n-vitro* results, it is unlikely for the drug release from BM-coated metoprolol matrices to be prone to physiological changes in the media composition and to mechanical stress events in the GI tract *in vivo*.

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.

Acknowledgement

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References

1 S.B. Tiwari *et al.*, Modulation of drug release from hydrophilic matrices. Pharm. Technol. 2008
2 V.D. Dias *et al.*, Modulation of drug release from HPMC matrices. AAPS meeting, San Antonio, TX, November 2006 (Poster)
3 S. Klein S. Predicting food effects on drug release from extended-release oral dosage forms. Dissol Technol. 2009
4 G. Garbacz *et al.*, A biorelevant dissolution stress test device – background and experiences. Expert Opin Drug Deliv. 2010