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Note

An easy producible new oral hydrocolloid drug delivery system with a late burst in the release profile☆

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Abstract

One of the main drawbacks of hydrocolloid matrices as oral controlled drug delivery systems is the often observed decreasing rate of drug release at the end of the release process. This study describes a new pH-controlled hydrocolloid drug delivery system consisting of a neutral cellulose ether as basis polymer and enteric coating materials as additives. The new dosage form is able to accelerate the drug release at a predetermined pH. In a typical example, methylhydroxy ethylcellulose, MHEC 10000 B, was used as the basis polymer and hydroxypropyl methylcellulose acetate succinate, HPMCAS HF, as release modifier. The new delivery system is characterized by its homogenous structure and easy production by direct compression of the components. The acceleration is well reproducible. Furthermore the new formulation shows high stability against hydrodynamic stress and tolerates ionic strengths up to 0.25 without any significant changes in the release profile. As mechanism of the final burst at pH values >5.7, enforced erosion of the gel layer surrounding the tablet core, could be identified.

Keywords: Burst effect; pH control; Drug delivery; Hydrocolloid tablets; pH-dependent solubility; Erosion; MHEC; HPMCAS HF

1. Introduction

The main drawback of diffusion controlled hydrocolloid tablets is the decreasing amount of released drug with time, resulting in incomplete absorption and therapeutically insufficient plasma levels at the end of the dose interval. For biopharmaceutical and chronopharmacological reasons even constant release rates of erosion controlled systems (Möckel and Lippold, 1993) are not always the ideal drug input functions. Therefore, it seems to be reasonable to accelerate the drug release of hydrocolloid matrices during the final release process. In a recently published paper (Freichel and Lippold, 2000), a hydrocolloid dosage form on the basis of polyvinyl alcohol is

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presented, showing a pH-independent, time controlled burst at the end of the release profile.

This paper describes the development of an oral controlled release dosage form on the basis of a hydrocolloid with a reproducible, pH-dependent final burst in the release profile. This burst should occur while the release medium exceeds a specific pH value in vitro or the tablet reaches the region of that specific pH during its gastro-intestinal transit.

Starting point of this development is the addition of acid polymers to an erosion controlled hydrocolloid slow release system with high release stability against hydrodynamic stress. As the latter MHEC 10000 B (Tylose MHB 10000, Clariant Frankfurt), a methylhydroxy ethylcellulose recently described by Zuleger and Lippold, (2001), is used. As additive different enteric coating materials are screened. HPMCAS HF (Aqoat, Shin-Etsu/Syntapharm, Tokyo/Mühlheim), a hydroxy-

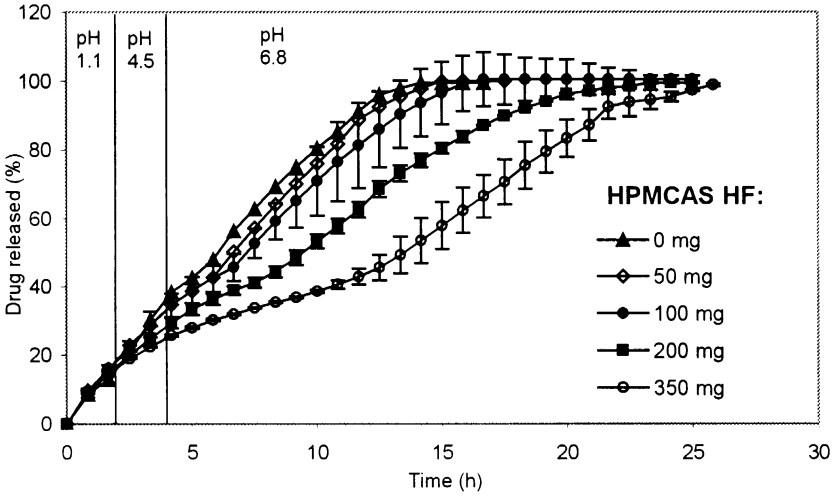

Fig. 1. Drug release from tablets with MHEC 10000 B: $700 - x$ mg, HPMCAS HF: x mg, Pentoxifylline: 100 mg

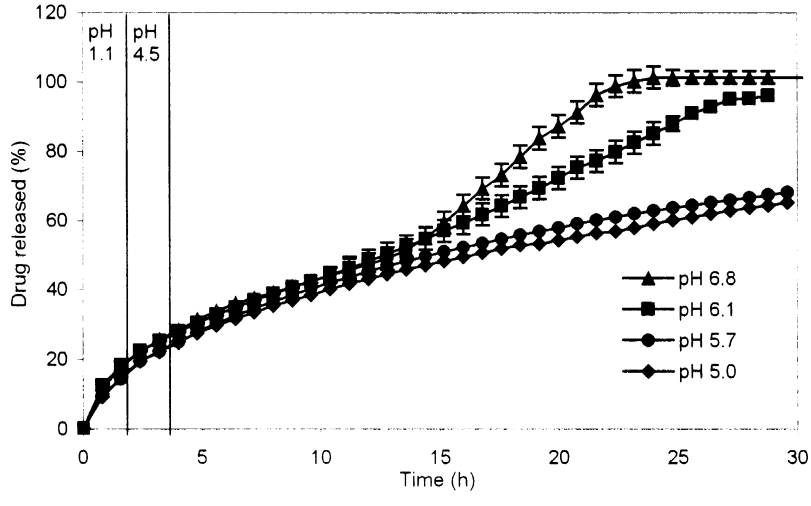

Fig. 2. Drug release as a function of pH from tablets with MHEC 10000 B: 350 mg, HPMCAS HF: 350 mg, Pentoxifylline: 100 mg

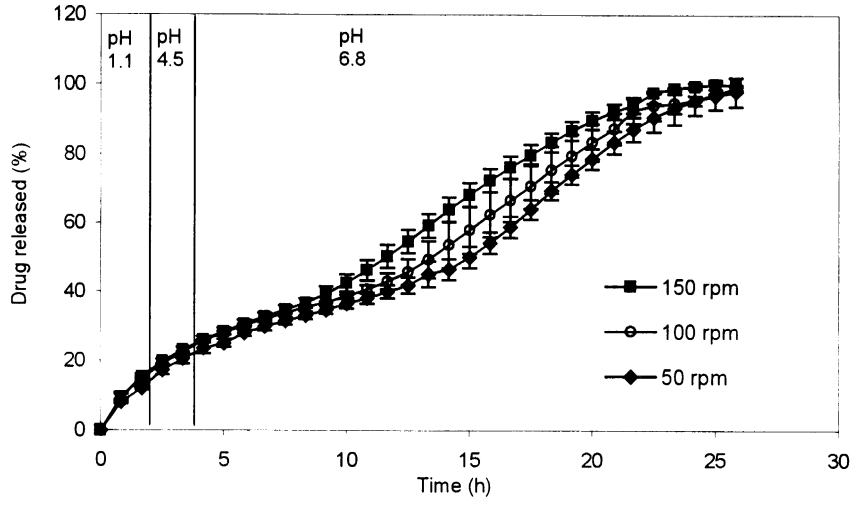

Fig. 3. Drug release as a function of the stirring speed from tablets with MHEC 10000 B: 350 mg, HPMCAS HF: 350 mg, Pentoxifylline: 100 mg

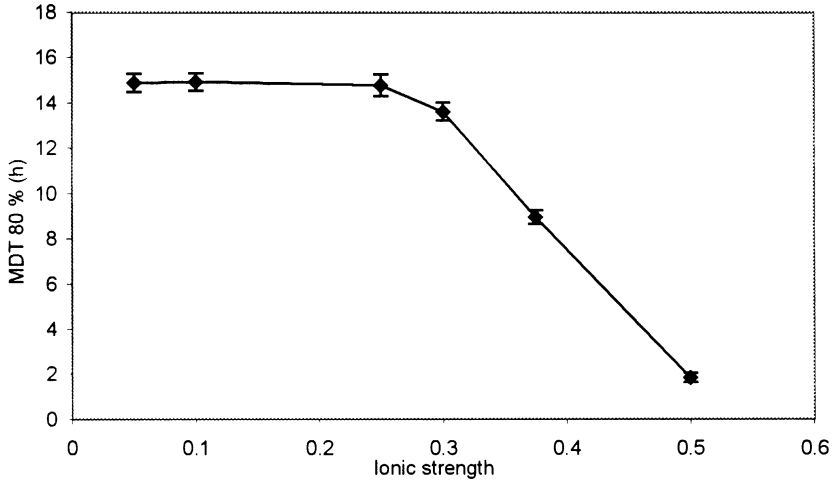

Fig. 4. Mean dissolution times for 80% release (MDT 80%) as a function of the ionic strength of the release media (adjusted with NaCl) of tablets with MHEC 10000 B: 350 mg, HPMCAS HF: 350 mg, Pentoxifylline: 100 mg

propyl methylcellulose acetate succinate, proves to be the most potent additive. As model drug Pentoxifylline (Hoechst AG, Frankfurt, Germany) is used.

Eight hundred milligram tablets, each containing 100 mg of Pentoxifylline (for detailed composition, see legends of Figs. 1–4) are prepared by direct compression of the powdered components using a hand-hydraulic KBr press (Perkin Elmer) at a compression force of 20 kN. All tablets are initially approximately 5 mm thick and have a diameter of 13 mm. The paddle apparatus Ph. Eur. 1997 is used with 1000 ml of different media at a temperature of 37 ± 0.5°C for the release studies. The stirring speed is 100 rpm to prevent sticking of the tablets to the vessel. Different media for the individual release studies are used: 0.1 N-HCl, pH 1.1, and phosphate buffers for pH

values between 4.5 and 6.8. The ionic strength is adjusted to ≈ 0.1. The release studies are carried out either at a defined pH value during the entire test or a pH gradient is implemented by transferring the tablets after predetermined time periods from one medium to the next one. All experiments are repeated at least three times. The concentration of the drug in the medium is determined by continuous UV-absorption measurements in a flow-through cell.

Fig. 1 shows the accelerated release of Pentoxyfylline from hydrocolloid matrices which are simple mixtures of MHEC 10000 B as basis polymer and increasing fractions of HPMCAS HF as additive. Increasing amounts of HPMCAS HF in the tablet lead to a later but also to a more pronounced progression of release. In acid media (pH 1.1 and pH 4.5), the release at early times proceeds mainly diffusion controlled. HPMCAS HF is insoluble at these pH values, but visibly tends to form a stable matrix. After transferring the tablets in the dissolution media of pH 6.8, HPMCAS HF begins to dissolve from the gel layer. As HPMCAS HF is dissolving, the stability of the gel layer decreases. An accelerated erosion of the gel forming MHEC 10000 B results. Finally, loss of structural integrity of the gel layer and subsequently enforced erosion occur.

The erosion of the gel layer leads to an accelerated release for two reasons (Freichel and Lippold, 2000):

1. The release of the drug still incorporated in the gel layer is enhanced by the accelerated erosion.
2. The reduction of the gel layer shortens the diffusion way for the remaining drug in the tablet.

As seen in Fig. 2, the burst effect only occurs if the pH value exceeds a certain number. Remarkably, the required pH value for accelerated release is higher than pH = 5.7, the dissolution pH determined for the used additive HPMCAS HF (Schmidt-Mende et al., 1998). Supposedly, there is a pH value in the interior of the swollen hydrocolloid dosage form lower than that in the surrounding dissolution medium, which is caused by the acid properties of the enteric coating material. Only a further increase of the pH value leads to the dissolution of the enteric coating material. In vivo this should guarantee the occurrence of the final burst effect not before the tablet has reached the lower gastro-intestinal region.

As shown in Fig. 3, the formulation is characterized by a satisfying stability against hydrodynamic stress. Referring to the standard stirring speed of 100 rpm, 50 rpm result in a slight decrease in the release rate, whereas 150 rpm induce a slight increase. The relatively high stability of the drug delivery system against hydrodynamic stress in acid milieu is due to the matrix forming properties of the insoluble HPMCAS HF. This leads to a high structural stability of the dosage form and switches the erosion controlled release of MHEC 10000 B alone to diffusion control in presence of HPMCAS HF. The hydrodynamic stability in the second phase of the dissolution process is caused by the polymer particle erosion mechanism of methylhydroxy ethylcelluloses which was first mentioned by Lindner and Lippold (1995) and described in detail by Zuleger and Lippold, (2001).

The new formulation also excels due to low susceptibility of the release against different ionic strengths (Fig. 4). Up to an ionic strength of 0.25 no significant change in the release profile is observed. Only an ionic strength higher than 0.25 increases the erosion process due to dehydration of the polymer chains in the gel layer. As in the gastro-intestinal tract ionic strengths only up to 0.17 are found (Johnson et al., 1993), the obtained release profiles should not be altered in vivo.

Hydrocolloid matrices consisting of MHEC 10000 B and HPMCAS HF in ratios of 1:0.16 to 1:1 lead to drug release profiles with a final burst. This new hydrocolloid drug delivery system seems promising as an alternative to more complicated coat-core systems already on the market (Heilmann, 1991). Further investigations concentrate on the mechanism of the burst in the release profile in detail.

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