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Research paper

Artificially induced polymer particle erosion of oral hydrocolloid systems by the addition of insoluble cellulose fibres to fibre-free methylhydroxy ethylcellulose (MHEC)

Oliver L. Freichel, Bernhard C. Lippold*,[1]

Institut für Pharmazeutische Technologie, Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany

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Abstract

The erosion-controlled drug release from different methylhydroxy ethylcellulose (MHEC) hydrocolloid tablets was examined. The special polymer particle erosion mechanism, which is nearly independent from the hydrodynamic conditions in the dissolution medium, could be attributed to the existence of insoluble fibres within the polymer material. They could be identified via microscopic analysis. The study presents a precipitation method, which guarantees an appropriate incorporation of insoluble microcrystalline cellulose fibres into fibre-free MHEC material. This method leads to a manufacturing process for polymer particle erosion-controlled hydrocolloid systems with the possibility to adjust the drug release rate.

Keywords: Cellulose fibres; Erosion control; Hydrodynamic influence; Methylhydroxy ethylcellulose; Polymer particle erosion; Precipitation

1. Introduction

Hydrocolloid embeddings as drug delivery systems are well-known devices for the extended release of orally administered drugs [1–3]. If constant release of the incorporated ingredient is requested, not diffusion but erosion-controlled hydrocolloid systems based on many different polymers and mixtures of polymers can be used [4,5]. The main drawback of these erosion-controlled systems is their high dependency on hydrodynamic influences, which results in a more or less varying dissolution process. However, Lindner and Lippold [6] and Zuleger et al. [7,8] described a hydrocolloid carrier on the basis of methylhydroxy ethylcellulose (MHEC) type 10000 B which releases the incorporated drug nearly unaffected by the rotation speed of the paddle in the dissolution apparatus. Zuleger and Lippold [7] traced this polymer particle erosion process back to the fact of incorporated insoluble fibres in the used MHEC which remain in the polymer after the manufacturing process due to an incomplete chemical derivatization process.

These insoluble fibres impede the swelling of the respective tablets, weaken the gel layer and cause attrition of the polymer material, thus only a thin gel layer is formed. During swelling of the tablet and release of the drug, synchronisation of the movement of swelling and erosion front occurs.

One aim of this work is to further clarify the necessity of the presence and the influence of the insoluble fibres on the erosion process and the releasing behaviour of MHEC type 10000 B based hydrocolloid systems.

Furthermore the manufacturing process of the MHEC type 10000 B cannot guarantee for a homogenous content of insoluble fibres in different batches of the polymer. This lack of reproducibility leads to a more or less pronounced erosion behaviour of hydrocolloid tablets produced from different batches, which is responsible for the observed varying release processes [7].

This study therefore also provides a method to incorporate insoluble fibres to fibre-free methylhydroxy ethylcellulose in a reproducible manner to control the release process. Pentoxifylline is used as a model drug.

* Corresponding author. Address: Institut für Pharmazeutische Technologie, Heinrich-Heine-Universität Düsseldorf, Universitätsstr. 1, D-40225 Düsseldorf, Germany. Tel.: +49-8652-5643; fax: +49-8652-977567.
E-mail address: lippold.b@t-online.de (B.C. Lippold).
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2. Materials and methods

2.1. Materials

Fibre-containing methylhydroxy ethylcellulose MHEC, Tylose® MHB 10000 B P2 (powder) was provided by Clariant AG (Wiesbaden, Germany). Nearly fibre-free methylhydroxy propylcellulose MHPC, Metolose® 65 SH 50 as well as nearly fibre-free methylhydroxy ethylcellulose MHEC Metolose® SNB 30 T and nearly fibre-free methylhydroxy ethylcellulose MHEC Metolose® SEB 04 T were a gift from Shin-Etsu (Syntapharm, Mühlheim, Germany/Shin-Etsu, Tokyo, Japan). Insoluble cellulose fibres Elcema® type P 050 and type F 150 as well as Sanacel® 150 were from Cellulose-Füllstoff-Fabrik (Mönchengladbach, Germany). Insoluble fibres Lattice® type NT-006 and Avicel® RC-581 were provided by Lehmann and Voss (Hamburg, Germany/FMC Corp., Philadelphia, USA). Heweten® 99, Vivapur® 99 and 102, other insoluble cellulose fibres, were a gift from J. Rettenmaier & Söhne GmbH & Co. KG (Rosenberg, Germany). Pentoxifylline was obtained from Hoechst AG (Frankfurt, Germany).

2.2. Methods

2.2.1. Microscopic analysis of the components

The microscopic analysis of the celluloseethers and cellulose powders was performed using a LEICA DS 100 light microscope (Leica Camera AG, Solms, Germany). The resulting images were transmitted and saved on an IBM-compatible PC with an appropriate software (Leica QWin, Leica Camera AG).

2.2.2. Separation of fibres from fibre-containing polymers

In the literature the amount of insoluble fibres from a solution of MHEC type 10000 B is determined using ultracentrifugation resulting in a value of 4.1 ± 0.8% [7]. The separation of the insoluble fibres in the following study is performed using a common laboratory centrifuge. This method resulted in an average fibre content of 3.5 ± 1.0%. Also it was not possible to separate the fibres in the same extent as with the ultracentrifuge, the use of the laboratory centrifuge was time-saving and allowed the extraction of larger quantities of insoluble fibres and soluble polymer in the supernatant. The supernatant and the sediment containing the insoluble fibres were separated from each other, dried at 100 °C, milled and subsequently sieved to gain fractions with different particle sizes.

2.2.3. Incorporation of insoluble fibres in nearly fibre-free MHEC

For the following studies the MHEC 10000 B-like MHEC SNB 30 T served as embedding material which has the very low fibre content of approximately 0.6 ± 0.5% as determined by Zuleger and Lippold [7] by ultracentrifugation. This low fibre content results, in contrast to MHEC 10000 B, in a diffusion-controlled release of the incorporated drug with an intact gel structure of the tablet up to the end of the dissolution process. It was used to clarify whether the addition of insoluble fibres causes erosion control.

2.2.3.1. Manual blending. Incorporation of 10% insoluble cellulose fibres to the fibre-free MHEC SNB 30 T material was first carried out by simple mixing of the two pure components in a plastic bowl with a pestle.

2.2.3.2. Spray-drying of a suspension. The 10% insoluble cellulose fibres were dispersed in a MHEC SNB 30 T sol for 24 h using a glass stirrer with a stirring speed of 250 rpm at ambient temperature. During the subsequent spray-drying process the suspension was stirred with a magnetic stirrer to avoid sedimentation of the insoluble fibres. The spray-drying process was carried out with a Mini Spray Dryer 190 (Büchi Laboratoriums-Technik GmbH, Eislingen-Fils, Germany) with inlet temperatures between 125 and 145 °C, outlet temperatures from 80 to 110 °C, an aspirator level of 90–100%, a pumping level of 10% and an airflow of approximately 30–60 litres/min.

2.2.3.3. Temperature-induced precipitation of a suspension. The 10% insoluble cellulose fibres were dispersed in a MHEC SNB 30 T sol as described in Section 2.2.3.2. The resulting suspension was heated above a temperature of 70 °C under constant stirring. At a specific temperature dehydratisation of the polymer chains occurred which leaded to the precipitation of the former soluble polymer. The precipitated polymer with the incorporated insoluble fibres was then separated from the remaining water by filtration through a paper filter and dried at 100 °C in a drying oven. After 24 h the polymer was milled and sieved to particle sizes between 45 and 200 μm for the following studies.

2.2.4. Dissolution studies

Eight hundred milligram-tablets were prepared by direct compression of a mixture of the powdered MHEC SNB 30 T cellulose components and pentoxifylline as model drug using a hand-hydraulic KBr press at a compression force of 20 kN. All tablets were initially approximately 4.4 mm thick and had a diameter of 13 mm. The paddle apparatus Ph. Eur. 1997 (Erweka DT6, Erweka Apparatebau, Heusenstamm, Germany) with 1000 ml 0.1 N-HCl as dissolution medium at a temperature of 37 ± 0.5 °C was used for the dissolution studies. The stirring speed was 100 rpm to prevent sticking of the tablets to the vessel. All experiments were repeated at least three times. The concentration of the drug in the medium was determined by continuous UV-absorption measurements (Lambda 2, Perkin Elmer, Überlingen, Germany) at 246 nm.

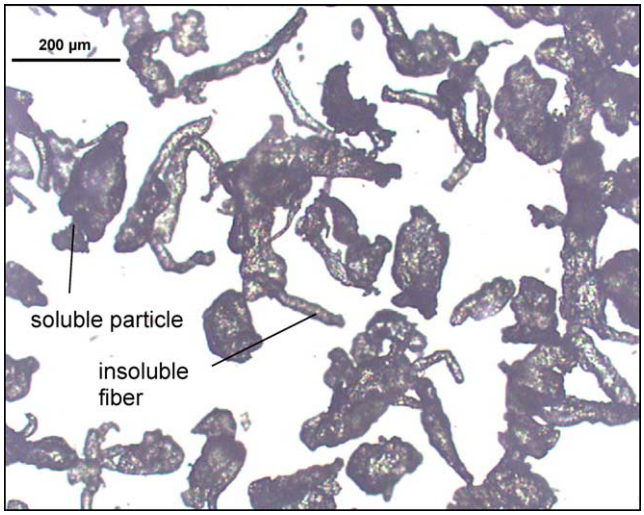

Fig. 1. Microscopic picture of a MHEC 10000 B powder, particle size: 100–200 µm.

3. Results and discussion

3.1. Microscopic analysis

3.1.1. Microscopic analysis of methylhydroxy ethylcelluloses

Fig. 1 shows the microscopic structure of an original MHEC type 10000 B powder with a particle size between 100 and 200 µm. Two different components become visible: the soluble fraction, which can be dissolved by adding a drop of water on the microscopic slide, and the insoluble fibre-like fraction. The fibres have a length up to 300 µm for the examined particle size of the MHEC 10000 B powder. In sieve fractions with smaller particle sizes there were also a lot of very small fibres in a range below 20 µm. In most cases there is a tight junction between the soluble particles and the insoluble fibres, a circumstance, which supports the thesis of an incomplete chemical reaction during the polymer derivatization process. This specific structure of the powder results in a very homogenous distribution of the fibres within the powder particles. Therefore the addition of insoluble fibres to fibre-free polymer material by manual blending might not be sufficient to realize hydrocolloid systems that can guarantee for an erosion-controlled release process. The nearly fibre-free MHEC SNB 30 T shows by microscopic analysis only a very low fibre content.

3.1.2. Microscopic analysis of insoluble fibres

3.1.2.1. Original fibres. Fig. 2 shows microscopic pictures of insoluble fibres, gained during the separation process of the MHEC 10000 B powder by centrifugation. The appearance of the fibres is as described in the literature for original, non-derivatized cellulose fibres.

3.1.2.2. Fibres used as additive. The cellulose types available on the market can be divided into two groups [9]. On the one hand there are pulverized celluloses, also known as native celluloses, which are obtained from cotton [10], characterized by an alternating structure of crystalline and amorphous segments. On the other hand, after acidic treatment of raw cellulose, so-called microcrystalline cellulose (MCC) results with a crystallinity up to 75–80% and a lower degree of polymerisation. Table 1 gives a survey over the celluloses used within this study. Besides native and microcrystalline celluloses, Avicel® RC-581 and Avicel® CL-611, two spray-dried microcrystalline cellulose products which were co-processed with different amounts of sodium carboxymethylcellulose (NaCMC) are used as additives to fibre-free polymers.

Fig. 3 shows microscopic images from milled, native celluloses with a fibre-like structure. The manufacturers declaration of the length of the fibres from these group of celluloses often differs considerably from the microscopically determined sizes. Moreover a broad particle size distribution is detected. Cellulose type Sanacel® 150, e.g. contains fibres in a range from 10 to 400 µm. A more homogenous appearance is observed for the microcrystalline celluloses, for example microcrystalline cellulose

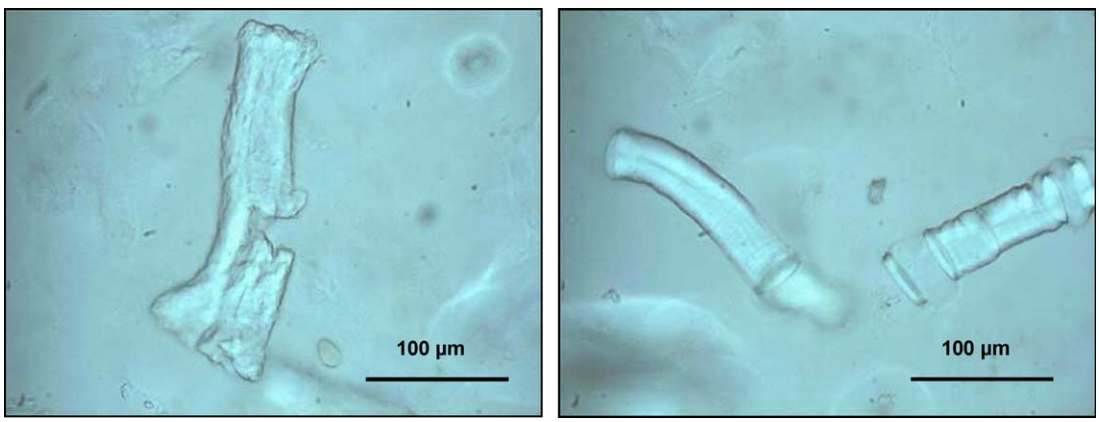

Fig. 2. Microscopic picture of insoluble fibres separated from MHEC 10000 B as described in the text.

Table 1
Celluloses used as additive

Type	Description	Average fibre length ca. (μm)
Elcema® P 050	Native	40[a]
Elcema® F 150	Native	120[a]
Sanacel® 150	Native	150[a]
Lattice® NT-006	Microcrystalline	6–10[a]
Heweten® 99	Microcrystalline	12[a]
Vivapur® 99	Microcrystalline	12[a]
Vivapur® 102	Microcrystalline	90[a]
Avicel® RC-581	MCC + NaCMC (8–13%)[a]	50[b]

[a] Manufacturers declaration.
[b] Microscopic analysis.

Heweten 99® with an indicated average fibre length of 12 μm (Fig. 4).

3.2. Dissolution studies of fibre-containing and fibre-free MHEC 10000 B carriers

To clarify the necessity of the presence of insoluble fibres for the occurrence of an erosion-controlled release mechanism, pentoxifylline tablets with original fibre containing as well as with fibre-free MHEC 10000 B are produced and subsequently subjected to a dissolution process in 0.1 N-HCl. The fibre-containing systems show polymer particle erosion with a nearly zero order release of the incorporated drug over a period of approximately 10 h (Fig. 5).

In contrast, the fibre-free tablets form a compact gel matrix during the whole dissolution process, which induces a slower, diffusion-controlled $\sqrt{t}$-release process of the drug (Fig. 5). Merely at the end of the release process a moderate erosion of the polymer system is observed macroscopically.

3.3. Dissolution studies with delivery systems after the addition of insoluble fibres to fibre-free polymer material

Due to the necessity of the presence of insoluble fibres to obtain erosion-controlled release systems, insoluble fibres are used as additive to fibre-free resp. fibre-cleared polymer material to artificially induce the intended release behaviour in the following experiments. The attempt to incorporate insoluble fibres by spray-drying a respective suspension failed. A significant amount of the insoluble fibres was deposited on the wall of the spray-drying apparatus during the drying process [11].

3.3.1. Addition by manual blending

In a first attempt 10% different insoluble fibres, pentoxifylline and fibre-free MHEC SNB 30 T, similar to the fibre-cleared MHEC 10000 B, were physically mixed and subsequently pressed to 800 mg tablets.

In addition to the additives used in the preceding experiments, Avicel® RC-581, a microcrystalline cellulose which is co-processed with sodium carboxymethylcellulose (NaCMC) as well as Lattice® NT-006, a very fine pulverized microcrystalline cellulose were applied as insoluble fibre material. Avicel® RC-581 contains approximately 8–13% NaCMC, which leads to strongly increased swelling of the cellulose. Therefore an increased erosion tendency of the whole hydrocolloid carrier is expected. However, the dissolution process for all tablets with incorporated additives did not result in significant differences of the release profiles in comparison to that of the MHEC SNB 30 T without any additive (Fig. 6). Only in the case of Heweten® 99 and Lattice® NT-006, both very fine cellulose fibres, a slightly accelerated release occurred. This fact corresponded with a macroscopically observed increase of particle erosion at the end of the dissolution process.

Obviously it is impossible to achieve polymer particle erosion by simple blending the insoluble fibres with fibre-free polymer material. Moreover the microscopic characterization of the fibre-containing MHEC 10000 B showed

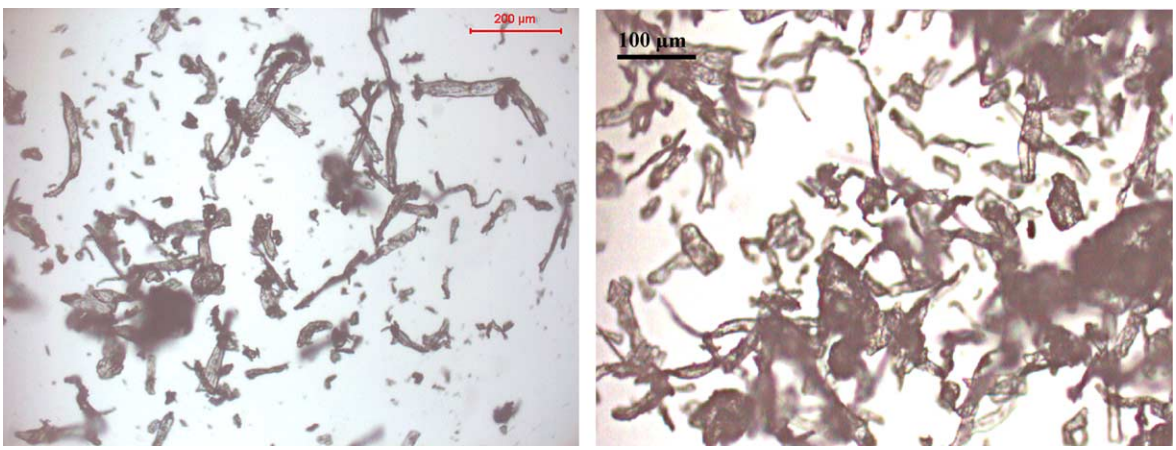

Fig. 3. Microscopic pictures of native celluloses type Sanacel® 150 (left hand) and Elcema® P 050 (right hand).

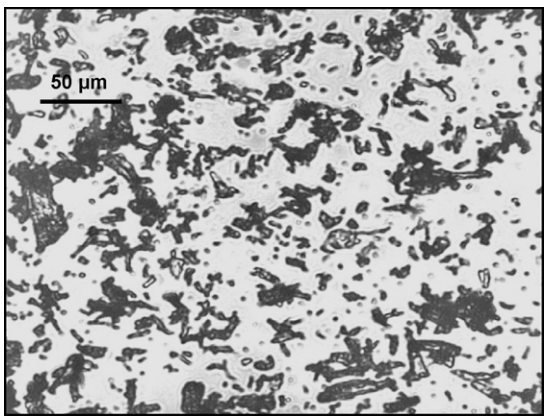

Fig. 4. Microscopic picture of microcrystalline cellulose type Heweten® 99.

a distinct connection between the insoluble fibres and the soluble polymer particles (Section 3.1.1), which could not be realised by physically mixing the components. Therefore the following methods tried to distribute the insoluble fibres within the soluble polymer material.

3.3.2. Freeze-dried suspension

A suspension was prepared from the fibre-free supernatant of the MHEC 10000 B resulting from the centrifugation process described in Section 2.2.2 and 10% of insoluble fibres (Elcema® P 050). This suspension was freeze-dried. However, the tablets manufactured from the resulting product showed accelerated but diffusion-controlled release behaviour (Fig. 7), probably due to the increased diffusional resistance caused by the incorporated insoluble fibres [12]. During the dissolution process a stable gel corpus was formed which released no polymer particles in the dissolution medium.

The microscopic analysis of the product exhibited a very voluminous structure, which differs substantially from that of the original products. There were hardly any particles with a distinct boundary to the surrounding but very fine fibrous structures wherein the added insoluble cellulose fibres are partially incorporated (Fig. 8).

Whereas the added insoluble fibres remain unchanged during the freeze-drying process, the structure of the soluble cellulose seems to change in a manner which leads to

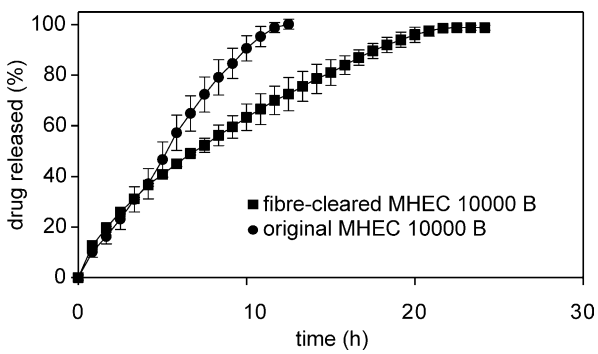

Fig. 5. Release of pentoxifylline 100 mg: MHEC 10000 B 700 mg with and without fibres ($\bar{x} \pm s$; $n = 3$).

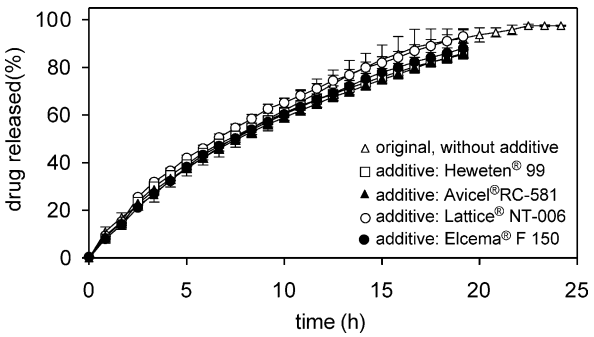

Fig. 6. Release of pentoxifylline 100 mg: MHEC type SNB 30 T, 700 resp. 635 mg, additive 0 resp. 65 mg ($\bar{x} \pm s$; $n = 3$).

a diffusion-controlled released process of the concerning tablets.

3.3.3. Temperature-induced precipitation of polymer suspensions

A suspension of insoluble cellulose fibres in a MHEC 10000 B polymer solution (10% insoluble fibres/soluble polymer) was heated slightly above 70 °C, which leads to the precipitation of the soluble MHEC due to the dehydratisation of the polymer chains. The suspended fibres should be distributed homogenous in the precipitated polymer because the suspension was stirred during

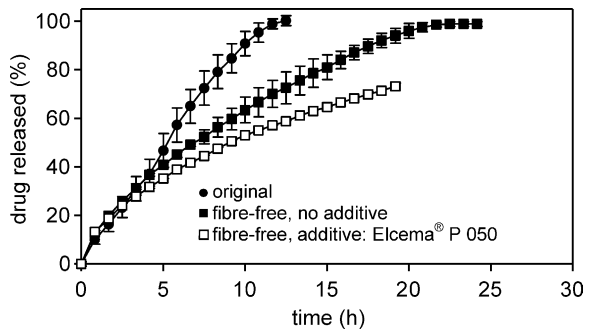

Fig. 7. Release of pentoxifylline 100 mg: freeze-dryed MHEC type 10000 B, 700 resp. 635 mg, additive 0 resp. 65 mg ($\bar{x} \pm s$; $n = 3$).

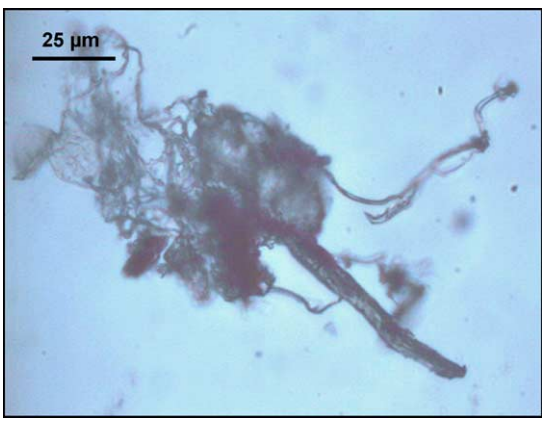

Fig. 8. Microscopic picture of a particle from a freeze-dried suspension from fibre-free MHEC type 10000 B 90%, Elcema® P 050 10%.

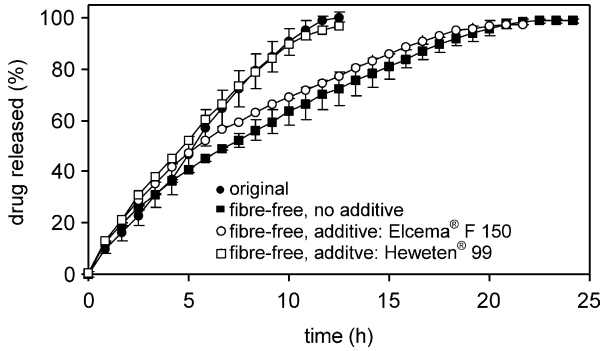

Fig. 9. Release of pentoxifylline 100 mg: precipitated MHEC type 10000 B, 700 resp. 635 mg, additive 0 resp. 65 mg ($\bar{x} \pm s$; $n = 3$).

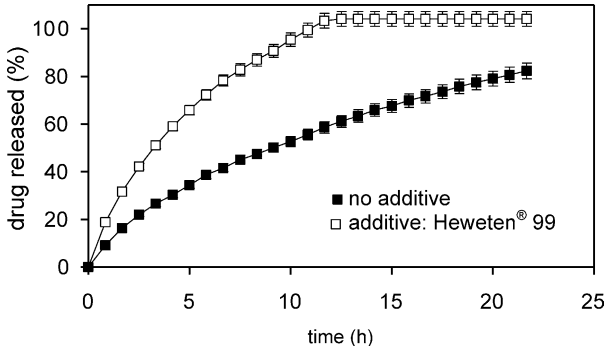

Fig. 10. Release of pentoxifylline 100 mg: MHEC type SEB 04 T 700 resp. 635 mg, additive 0 resp. 65 mg ($\bar{x} \pm s$; $n = 3$).

the heating process. The resulting polymer product was milled in a rotary knife cutter and sieved to obtain a particle size fraction from 45 to 200 μm. After adding pentoxifylline to the product the mixture was pressed to 800 mg tablets and subsequently subjected to a dissolution process in 0.1 N-HCl.

3.3.3.1. MHEC 10000 B. Using 10% Elcema® F 150 (average fibre length: 120 μm) as insoluble fibre additive, the resulting release profile does not differ from that of a fibre-free MHEC type 10000 B cellulose without additive (Fig. 9). In contrast to that, the addition of the fine pulverized microcrystalline cellulose Heweten® 99 (average fibre length: 12 μm) leads to a significant erosion of the tablet and therefore to an erosion-controlled release of the incorporated drug from the delivery system. The release process is very similar to that of a tablet manufactured from fibre-containing original MHEC type 10000 B polymer material. The erosion process can also be macroscopically observed in the dissolution medium. Obviously there are two major conditions to achieve erosion-controlled release behaviour from MHEC 10000 B systems:

1. Adequate process of incorporation of the insoluble fibres into the soluble polymer network.
2. Low particle size of the insoluble cellulose fibres used as additive.

3.3.3.2. MHEC, type SEB 04 T. In a final experiment another MHEC, the nearly fibre-free MHEC SEB 04 T was used to confirm the results. Without the addition of insoluble fibres, tablets with MHEC SEB 04 T as base polymer tended to a slight erosion but still released the incorporated drug mainly diffusion-controlled (Fig. 10). If 10% Heweten® 99 was used as insoluble additive, the precipitated product leads to tablets which also exhibit increased erosion and subsequently an accelerated release of pentoxifylline. The polymer particle erosion, however, is not as pronounced as observed with MHEC 10000 B as soluble polymer (Section 3.3.3.1).

4. Conclusion

It can be stated that it is necessary to incorporate the insoluble cellulose fibres within the network of the soluble polymer MHEC to achieve the desired erosion-controlled release. The results demonstrate that the heat precipitation method is appropriate in this respect. As insoluble cellulose fibres, small, microcrystalline cellulose products are suitable. It should be possible to optimise the presented method by variation of the process parameters of the precipitation as well as by the use of different types and particle sizes of the insoluble cellulose fibres.

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