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Polymer particle erosion controlling drug release. I. Factors influencing drug release and characterization of the release mechanism

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Abstract

The present study deals with controlled drug delivery from hydrocolloid tablets by polymer particle erosion. The influence of excipients and formulation factors on the dissolution behaviour of the methyl hydroxyethyl cellulose (MHEC)-tablets is investigated. Linear drug release with low susceptibility to hydrodynamic stress is obtained. The use of drugs with higher solubility leads to a slight acceleration of the release due to the contribution of diffusion to the release process. Higher drug loading and consequently lower polymer content expedites dissolution as well as changes in the tablets' geometry resulting in enlarged release surfaces. Furthermore, alterations of the composition of the dissolution medium affect drug release. However, neither viscosity grade nor the particle size of the polymer or compaction pressure has a marked impact on the dissolution. Investigations to clarify the mechanism of polymer particle erosion include erosion studies and the comparison of different batches of MHEC, of products from different manufacturers and of fibrous trial products. There is evidence that the insoluble fibres within the water soluble MHEC are responsible for the occurrence of polymer particle erosion by disturbing swelling and formation of a thick coherent gel layer and thus, causing erosion of the hydrocolloid tablet with synchronous drug release.

Keywords: Controlled drug delivery; Hydrocolloid tablets; Methyl hydroxyethyl cellulose (MHEC); Polymer particle erosion; Zero-order release; Hydrodynamic stress

1. Introduction

Several controlled release principles have been developed and established within the past years in order to increase safety, efficacy and convenience in oral drug delivery.

The most popular concepts for controlled drug delivery are coated systems, such as diffusion pellets, matrix tablets, eroding tablets and oral osmotic therapeutic systems (OROS®-tablets). Drug release from diffusion pellets and matrix tablets strongly depends on drug solubility. In the case of poorly soluble drugs, only insufficient

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release rates are obtained. Since the majority of the new potent drugs have only a very limited water solubility, systems such as eroding embeddings and OROS®-tablets, suitable for the release of these poorly soluble drugs, are of great interest.

Erosion controlled systems are prepared by simply incorporating the drug in water soluble polymeric carriers (hydrocolloids) which are available in a broad variety at low costs. In contact with the dissolution medium, the hydrophilic carrier starts to swell and a gel layer is formed. Depending on the strength of the gel layer formed, drug release is controlled by different mechanisms with diverging kinetics: Using gelling agents of low viscosity grades, erosion of the swollen polymer represents the release mechanism and leads to zero-order kinetic of the drug release. If polymers of high viscosity grades are applied as the embedding material, a stable matrix is formed and polymer dissolution is negligible. The drug is released from the swollen matrix predominantly by Fickian diffusion through the stable gel layer following $\sqrt{t}$-kinetic. Often, both processes — diffusion and erosion — contribute to the release of the incorporated drug. This transition between the two mechanisms results in a kinetic in-between $\sqrt{t}$ and zero-order, equivalent to the kinetic of 'anomalous transport', a term used for drug release with contribution of both diffusion and relaxation (Korsmeyer and Peppas, 1984). In accordance with other authors (Lindner and Lippold, 1995; Yang and Fassihi, 1996; Sujja-areevath et al., 1998), in the following the use of the term anomalous transport will be expanded to processes with this intermediate kinetic caused by a combination of erosion and diffusion.

Lindner et al. found a special type of erosion controlled drug delivery with low susceptibility to agitation for tablets with Tylose MH 10 000 B, a methyl hydroxyethyl cellulose (Lindner and Lippold, 1995). This mechanism termed as 'polymer particle erosion' is characterized by erosion of partially swollen polymer particles. In contrast to classical eroding tablets, which dissolve completely during the dissolution test, a turbid solution or suspension is formed during the release of tablets showing polymer particle erosion.

The present work focuses on hydrocolloid tablets with drug release by polymer particle erosion in order to elucidate this release mechanism. The aim of this study is the determination of polymer properties that are required to obtain this release mechanism. The dependence of the release on agitation is a significant disadvantage of tablets with release by classical erosion. Therefore, the achievement and proof of robustness for delivery systems showing polymer particle erosion is a major target of this work.

Furthermore, the evaluation of other factors including excipients and formulation variables, which may possibly affect the drug release, belongs to the objectives of this study.

2. Materials and methods

2.1. Materials

Methyl hydroxyethyl cellulose of different viscosity grades and degrees of substitution (Table 1) were used in this study: MHEC 3000 B (Tylopur® MHB 3000 P2), MHEC 10 000 B (Tylose® MHB 10 000 P2), MHEC 30 000 B (Tylose® MHB 30 000 P2), MHEC 15 000 P6 (Tylose® MH 15 000 P6), MHEC 60 000 P4 (Tylose® MH 60 000 P4) (Clariant GmbH, Wiesbaden, Germany), Metolose® SEB 04T, SEB 15T and SEB 30T and Metolose® SNB 30T and SNB 60T (Syntaphar/Shin-Etsu, Mühlheim-Ruhr, Germany). To distinguish between the two different batches of some MHEC-products, which have been used in this study, the suffix No. 1 (Batch No. 1) or No. 2 (Batch No. 2) was added to the names of these products.

Special trial products of MHEC (MHEC DS 0934/11 and MHEC DS 0935/10), made of flax and containing a higher amount of fibres than commercially available products, were kindly provided by Clariant GmbH.

Two powder celluloses, Elcema (Degussa AG, Frankfurt, Germany) and Sanacel 40 (Cellulose-Füllstoff-Fabrik, Mönchengladbach, Germany), were used as insoluble additives with $d_{99\%} < 125$ μm and $d_{98\%} < 40$ μm, respectively.

The reference systems with diffusion and classical erosion controlled release were made of a high and a low viscosity grade MHPC, respectively: Metolose® 90SH 100 000SR (MHPC 100 000) and Pharmacoat 606 (Syntapharm).

Proxyphylline (Knoll AG, Ludwigshafen, Germany, donated by Trommsdorff GmbH and Co., Alsdorf, Germany) was used as the freely soluble model drug ($c_s > 700$ g l^{-1} in 0.1 mol l^{-1} HCl at 37°C) while acetophenetidin (Bayer AG, Leverkusen) represents the poorly soluble model drug ($c_s = 1.37$ g l^{-1} in 0.1 mol l^{-1} HCl at 37°C).

2.2. Methods

2.2.1. Viscosity

The viscosity at 20°C of 2% aqueous solutions of the polymers was determined using the rotational viscosimeter (RV 20 combined with Rheocontroller RC20, Haake, Karlruhe Germany). The measurement was performed with the cone-plate-probe PK45/4 at $D = 1$ s^{-1} for 1 min, except the analysis of the low viscosity grade MHPC Pharmacoat 606, which required the use of the coaxial-cylinder-probe ME45 at $D = 50$ s^{-1} for 1 min.

2.2.2. Tablet preparation

Single unit tablets containing 5 or 30% of the freely or poorly soluble model drug and 95%, respectively 70% of polymer were prepared by direct compression of the powder mixture in flat-faced punches (diameter 13 mm) at 2 tons (≈ 20 kN) for 10 s using a manual hydraulic press for KBr discs (Perkin–Elmer, Überlingen, Germany). The tablet weight was either 300 ± 3 or 800 ± 3 mg with a corresponding tablet thickness of ≈ 2 and 5 mm, respectively.

Multiple unit mini tablets (diameter 3 mm, thickness ≈ 2 mm) with a weight of 20 ± 2 mg consisting of 5% drug and 95% polymer were compressed in flat faced punches of an excenter press (Frogerais Type 0A, Parmentier, Frankfurt, Germany).

Table 1
Properties of the polymers used in this study

Polymer	Substitution[a]		Viscosity[b] (mPa·s)	Comments
	DS	MS		
MHEC 3000 B No. 1	1.8–2.2	0.1–0.2	5022	
MHEC 3000 B No. 2	1.8–2.2	0.1–0.2	6529	
MHEC 10 000 B No. 1	1.8–2.2	0.1–0.2	14 338	
MHEC 10 000 B No. 2	1.8–2.2	0.1–0.2	18 009	
MHEC 30 000 B	1.8–2.2	0.1–0.2	39 201	
MHEC 15 000 P6 No. 1	1.4–1.7	0.1–0.2	25 154	Very fine powder
MHEC 15 000 P6 No. 2	1.4–1.7	0.1–0.2	27 553	Very fine powder
MHEC 60 000 P4 No. 1	1.4–1.7	0.1–0.2	66 192	Fine powder
MHEC 60 000 P4 No. 2	1.4–1.7	0.1–0.2	79 681	Fine powder
Metolose SEB 04T	1.4	0.2	5735	
Metolose SEB 15T	1.4	0.2	18 500	
Metolose SEB 30T	1.4	0.2	28 443	
Metolose SNB 30T	1.4	0.35	35 758	
Metolose SNB 60T	1.4	0.35	62 905	
MHEC DS 0934/11	Not determined	Not determined	36 576	Trial product
MHEC DS 0935/10	Not determined	Not determined	47 906	Trial product
MHPC 100 000	1.4	0.2	54 697	Type 2208 USP
Pharmacoat 606	1.9	0.25	5	Type 2910 USP

[a] Degree of substitution as declared by the manufacturers.
[b] Viscosity of 2% solutions.

2.2.3. Dissolution studies

The dissolution tests were carried out in the USP paddle apparatus (Erweka, Heusenstamm, Germany) at 37 ± 0.5°C using 0.1 mol l^{-1} HCl as the dissolution medium. The drug release was determined by UV-spectroscopy at 266 nm for proxyphylline and 216 nm for acetophenetidin. To investigate the impact of hydrodynamic stress on the drug release characteristics, the studies were performed at different stirring speeds (SS) of the paddle (50, 100 and 200 rpm).

2.2.4. Erosion studies

Dissolution tests were performed as described before at 100 rpm. The residues of the tablets were removed from the dissolution medium at time points equivalent to 30 and 70% drug release. After drying the residues over P_2O_5 under vacuum at room temperature, the polymer erosion was determined by difference in weight, taking the amount of the drug release into account.

2.2.5. Quantification of insoluble polymer components

Two alternative methods were applied to determine the amount of insoluble fibres in the polymers: gravimetric analysis after ultracentrifugation and Coulter–Counter analysis. For both methods, test solutions of 0.5% polymer in water are applied.

Ultracentrifugation of 20 g of the aqueous solutions at 25 000 rpm over a period of 90 min was performed under vacuum at 22°C in the centrifuge L7-65 with the rotor 70 Ti (Beckmann Coulter GmbH, Unterschleissheim, Germany). Subsequently, the amount of polymer dissolved in the clear supernatant was determined after drying 10 g of the solutions at 60°C for 48 h. Finally, the amount of insoluble fibres was calculated by difference in weight.

Coulter–Counter analysis carried out with the Multisizer II (Coulter Electronics GmbH, Krefeld, Germany) requires the dilution of the test solutions with a filtered electrolyte solution (Isoton II, Coulter Electronics GmbH) to ensure conductivity of the sample. The capillary (∅ 140 μm, length 105 μm) allows the analysis of particles in the range of 2.8–80 μm. During the test, a definite volume of 2000 μl of the sample was pumped through the orifice of the capillary. All particles were counted and registered by size in 64 channels.

2.3. Characterization of the release profiles

The common exponential equation of Korsmeyer and Peppas (Korsmeyer et al., 1983), extended by the term b to take a possible burst effect into account (Lindner and Lippold, 1995), was applied to describe the release profiles:

$$Q/Q_\infty = k \cdot t^n + b \quad (1)$$

where Q is the amount released at time t, Q_∞ the overall released amount, k the release constant of the n^{th} order and n, a dimensionless number. The exponent n describes the kinetic and thus the release mechanism and depends on the geometry of the system (Ritger and Peppas, 1987a,b). For a slab, $\sqrt{t}$-kinetic according to Fickian diffusion is defined by $n = 0.5$, zero-order release due to erosion or relaxation by $n = 1.0$ and anomalous transport is indicated by values between 0.5 and 1.0, while in the case of a cylinder, values of 0.45, 0.89 and 0.45 to 0.89, respectively are obtained (Peppas, 1985; Ritger and Peppas, 1987b). The geometry of a planar tablet differs from both models as drug release takes place at both the two planar faces and the lateral cylindrical surface. Regarding the two extremes, a very thin tablet and a rod-shape tablet, the models of the slab and the cylinder may be applied as the release area of the lateral surface (thin tablet) and the bases (rod) may be neglected. In between these two extremes, the relation between diameter and height of the tablet influences the values of the release exponent. For a certain geometry of a tablet, the values of the release exponent can be determined graphically (Ritger and Peppas, 1987a) as performed for the tablets used in this study, results are given in Table 2.

The mean dissolution time determined for drug release up to 80% (MDT-80%) is applied to compare dissolution rates regardless of release kinetics (Voegele et al., 1985).

To evaluate the susceptibility to hydrodynamic stress, the MDT-80%$_{200/100}$-quotient is calculated

Table 2
Release exponents n corresponding to different release mechanisms in dependence of the tablet geometry

Release exponents		Kinetic and release mechanism
300 mg-tablets ($\varnothing = 13$ mm, h = 2 mm)	800 mg-tablets ($\varnothing = 13$ mm, h = 5 mm)	
0.465	0.435	$\sqrt{t}$-kinetics: Fickian diffusion (Case I)
$0.465 < n < 0.930$	$0.435 < n < 0.870$	Anomalous transport
0.930	0.870	Zero-order kinetics: erosion or relaxation control (Case II)

by MDT-80%$_{200}$/MDT-80%$_{100}$ for stirring speeds (ss) during the dissolution tests of 200 and 100 rpm, respectively (Lindner and Lippold, 1995).

3. Results and discussion

3.1. Selection of polymers

Several polymers, including galactomannans, polyvinyl alcohol, povidone, and various cellulose ethers have been investigated. The desired nearly linear, erosion controlled release with a high stability to variations in hydrodynamic conditions was only obtained for some high viscosity grade MHECs (Table 3). During the dissolution tests of tablets with these MHECs, erosion of partially swollen polymer particles occurred and the formation of the characteristic turbidity was observed.

3.2. Dissolution studies

3.2.1. MHEC-tablets with polymer particle erosion

The parameters calculated from the release profiles of 300 mg-tablets of the different MHECs containing 5% acetophenetidin are presented in Table 3 in comparison to Pharmacoat 606-tablets, the classical erosion controlled system and MHPC 100 000-tablets, the diffusion matrix.

Almost linear drug release over a period of 4–10 h is observed for the five different MHEC-tablets (Fig. 1 and Table 3). The release exponents $n = 0.85$–1.14 indicate erosion controlled drug delivery with zero-order kinetic. The visual observation of the dissolution process reveals that tablets with MHEC 3000 B No. 1 and 10000 B No. 1 show the lowest extent of swelling and the highest turbidity in the medium. Tablets of MHEC 15 000 P6 No. 1, MHEC 60 000 P4 No. 1 and especially MHEC 30 000 B exhibit more pronounced swelling, yet even those do not form thick, stable gel bodies like the high viscosity grade MHPC. Increasing the stirring speed causes faster drug release for all investigated polymers. However, compared to the classical erosion controlled system made of the low viscosity grade MHPC Pharmacoat 606, the particle erosion controlled delivery from the MHEC-tablets is much more resistant to changes in agitation, as indicated by the significantly higher MDT-quotients. Especially MHEC 3000 B No. 1- and MHEC 10 000 B No. 1-compacts exhibit a satisfactory stability to agitation. Furthermore, the MHEC-tablets excel due to a stronger retardation of the drug release. The dissolution of short chain Pharmacoat 606 is strongly susceptible to hydrodynamics and proceeds too fast to achieve sufficient prolongation of the drug release.

Despite the very high viscosity grade of MHPC 100 000, even this diffusion matrix exhibits a noticeable degree of erosion when the poorly soluble acetophenetidin is incorporated. The release exponents of $n = 0.74$ and 0.78 markedly exceed the value of 0.465, expected for diffusion controlled release and indicate significant contribution of erosion. If the freely soluble proxyphylline is embedded in MHPC 100 000, the release from these tablets is dominated by diffusion with an exponent of $n = 0.55$. As described by several authors (Ford et al. 1987; Ranga Rao et al., 1990; Talukdar et al., 1996; Kim, 1998), the reduced water solubility of the embedded drug leads to a decrease in release rates (MDT-80% = 2.33 h for the

Table 3
Release exponents n, MDT-80% values and MDT-80%-quotients for the release of acetophenetidin from different cellulose ether tablets (300 mg), drug content 5% (mean ± S.D., $n = 3$–6)

Polymer	SS (rpm)	Release exponent n	MDT-80% (h)	MDT-80%$_{200/100}$-quotient
MHEC 3000 B No.1	100	1.03 ± 0.01	2.90 ± 0.07	0.83
	200	1.05 ± 0.03	2.42 ± 0.07	
MHEC 10 000 B No. 1	100	1.14 ± 0.03	2.38 ± 0.12	0.83
	200	1.12 ± 0.05	1.97 ± 0.02	
MHEC 30 000 B	100	0.85 ± 0.01	4.03 ± 0.23	0.82
	200	0.88 ± 0.03	3.28 ± 0.11	
MHEC 15 000 P6 No. 1	100	0.93 ± 0.02	3.72 ± 0.14	0.82
	200	0.92 ± 0.01	3.05 ± 0.08	
MHEC 60 000 P4 No. 1	100	0.94 ± 0.03	3.26 ± 0.13	0.74
	200	1.01 ± 0.02	2.42 ± 0.03	
Pharmacoat 606	100	0.98 ± 0.03	1.28 ± 0.09	0.69
	200	1.27 ± 0.07	0.83 ± 0.07	
MHPC 100 000	100	0.74 ± 0.03	6.98 ± 0.31	0.85
	200	0.78 ± 0.06	5.92 ± 0.45	

release of proxyphylline and MDT-80% = 6.98 for acetophenetidin at 100 rpm) and additionally, causes a change in the release mechanism towards an increased contribution of erosion (Ford et al. 1987; Bonferoni et al., 1995; Tahara et al. 1995). As a result of the long dissolution time because of the low diffusion rate of the poorly soluble acetophenetidin, even these stable gel bodies begin to show relevant polymer erosion. Due to the contribution of erosion, the release of the poorly soluble drug is less stable to agitation than the diffusion controlled release of the freely soluble drug, as proven by the $MDT_{200/100}$-quotient of 0.85 for acetophenetidin in comparison to a $MDT_{200/100}$-quotient of 1.0 for the proxyphylline release.

3.2.2. Viscosity grade and degree of substitution

Regarding the effect of the viscosity grade, only MHECs with the same degree of substitution may be compared: An increase in the molecular weight of the polymer is followed by an increase in the drug release rate and in the release exponent (Table 3 and Fig. 1).

The impact of the viscosity grade on the dissolution rate has been studied intensively for MHPC. In the case of MHPC of low or intermediate molecular weight, an increase in the viscosity leads to stronger polymer entanglement, slower polymer erosion and subsequently, to a decrease in the drug release rate (Salomon et al., 1979; Lindner and Lippold, 1995; Kim and Fassihi, 1997; Reynolds et al. 1998). Yet similar release profiles are obtained for matrices made of high viscosity grade MHPC (Ford et al., 1985a,b; Bettini et al., 1994): From a certain threshold, a further increase in polymer chain length does not slow down drug release significantly anymore as

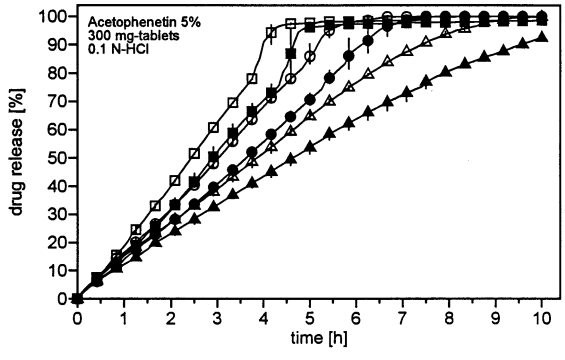

Fig. 1. Drug release by polymer particle erosion (mean ± S.D., $n = 3$). Closed symbols: 100 rpm, open symbols: 200 rpm. ●○, MHEC 3000 B No. 1; ■□, MHEC 10 000 B No. 1; ▲△, MHEC 15 000 P6 No. 1.

stable matrices are formed and drug release is primarily diffusion controlled. The increase in the release exponent and acceleration of the drug release with increasing viscosity grade of the MHECs is surprising as stronger entanglement and reduced polymer dissolution rates at increasing molecular weight should decelerate the drug release. Furthermore, it is striking that this high viscosity grade MHECs actually exhibit intensive polymer erosion while diffusion matrices are formed using similar polymers like MHPC and other cellulose ethers of equivalent viscosity grades.

MHEC 3000 B No. 1 and MHEC 10 000 B No. 1 are selected for further studies, as tablets with these two polymers show the most pronounced erosion and turbidity in the dissolution medium and highest stability to hydrodynamics.

3.2.3. Particle size of the polymer

To investigate the influence of the particle size of the polymer on the dissolution behaviour, tablets prepared of four sieve fractions (<45, 45–100, 100–140, 140–200 μm) are compared to tablets made of the raw material (<315 μm). The study is carried out with 300 mg-tablets of MHEC 3000 B No. 1/acetophenetidin and MHEC 10 000 B No. 1/proxyphylline with a drug content of 5%. In both cases, almost identical release profiles up to 70% drug release are obtained for the fractions with particle sizes >45 μm. Only at the very end of the dissolution test, the coarse fractions (100–140 and 140–200 μm) exhibit faster disintegration of the tablets. Due to the smaller surface area of coarse material, there is less contact between the particles and the cohesion is reduced, which leads to faster disintegration of the tablets (Mitchell et al., 1993; Dabbagh et al., 1996). As a result of the strong cohesion between the fine particles (<45 μm), significantly slower drug release is observed for these tablets at 100 rpm. Nevertheless, at an increased hydrodynamic stress of 200 rpm, the release from tablets of this fine material is comparable to tablets of coarse and unsieved material. These results indicate that variations in polymer particle size do not have a marked effect on drug release of matrices with a high polymer content (Mitchell et al., 1993; Campos and Villafuerte, 1995).

3.2.4. Compaction pressure

The same two systems MHEC 3000 B No. 1/acetophenetidin and MHEC 10 000 B No. 1/proxyphylline were studied with regard to the robustness of the release by polymer particle erosion to variations in compaction pressure which may occur during the industrial production of tablets. An extreme increase in the load applied during compaction from 2 to 5 tons did not cause a noticeable change in the dissolution profiles or in the calculated release parameters.

3.2.5. Tablet size — multiple units

An increase in the mass of MHEC 3000 B No. 1-tablets from 300 to 800 mg at a constant drug loading of 5% causes a marked prolongation of the drug release (Table 4). Because the same punches are used for both masses, a geometric change only occurs in tablet height. While the mass of the tablet and of the incorporated drug increases by $\approx 170\%$, the surface area of the 800 mg-tablet is enlarged by only 35%. Therefore, the drug release rate is significantly reduced compared to the 300 mg-tablet.

As expected, drug release is accelerated dramatically if multiple units (15 tablets with a weight of 20 mg each) are applied instead of a single unit 300 mg-tablet. This effect again has to be ascribed to the change in the release area of the tablets. The release exponents of the three tablet sizes are almost identical. Because of the large surface of the multiple units, no adequate retardation of the drug release is obtained, the drug release is completed within ≈ 2.5 h (MDT-80% = 1.08 to 1.2 h, Table 4). Comparable results are found for MHEC 10 000 B No. 1.

3.2.6. Drug solubility

If the freely soluble proxyphylline is embedded instead of the poorly soluble acetophenetidin, drug release proceeds somewhat faster (Fig. 2). Looking at the release exponents presented in Table 4 for MHEC 3000 B No. 1, it becomes obvious that the higher solubility of the drug also alters the release mechanism. At 5% drug loading, release exponents of $n \approx 1$ indicating zero-order release (erosion control) are derived from the dissolution profiles of the sparingly soluble drug,

Table 4
Influence of tablets size, drug solubility and drug loading on release parameters of MHEC 3000 B No. 1-tablets (mean ± S.D., $n = 3$)

	SS (rpm)	Release exponent n	MDT-80% (h)	MDT-80%$_{200/100}$-quotient
Mini-tablets:				
Acetophen 5%	100	1.08 ± 0.07	1.20 ± 0.04	0.90
	200	1.05 ± 0.04	1.08 ± 0.00	
300 mg-tablets:				
Acetophen 5%	100	1.03 ± 0.01	2.90 ± 0.07	0.83
	200	1.05 ± 0.03	2.42 ± 0.07	
800 mg-tablets				
Acetophen 5%	50	1.14 ± 0.04	7.03 ± 0.18	0.81
	100	1.03 ± 0.02	6.30 ± 0.13	
	200	0.99 ± 0.01	5.50 ± 0.10	
Acetophen 30%	50	1.37 ± 0.02	5.97 ± 0.27	0.76
	100	1.26 ± 0.02	5.17 ± 0.10	
	200	1.16 ± 0.03	3.95 ± 0.23	
Proxyphyll 5%	50	0.77 ± 0.02	5.06 ± 0.15	0.80
	100	0.76 ± 0.02	4.53 ± 0.07	
	200	0.77 ± 0.03	3.63 ± 0.24	
Proxyphyll 30%	50	0.78 ± 0.02	4.27 ± 0.14	0.81
	100	0.78 ± 0.00	3.60 ± 0.05	
	200	0.82 ± 0.01	2.92 ± 0.03	

while in the case of the freely soluble proxyphylline anomalous transport with exponents of $n = 0.76–0.77$ is observed. Because of the high diffusion rate of the freely water soluble drug, the release is no longer exclusively erosion controlled, but diffusion contributes noticeably. Independent of the solubility of the incorporated substance, drug release is affected only moderately by agitation.

3.2.7. Drug loading

As expected, an increase in drug loading from 5 to 30% is followed by an acceleration of the drug release (Table 4). For the tablets investigated in this study, which do not contain any other excipients than drug and polymer, changes in the drug content are always linked to alterations of the amount of polymer. Early investigations with MHPC-tablets prove an increase of the dissolution rates with decreasing polymer content (Huber et al., 1966). This finding has since been confirmed in many studies mainly on diffusion controlled systems.

The comparison of matrices with the two drugs with different water solubility reveals a difference in the effect of an increase in the drug loading. Throughout the whole dissolution test, proxyphylline release is faster for the tablets with the

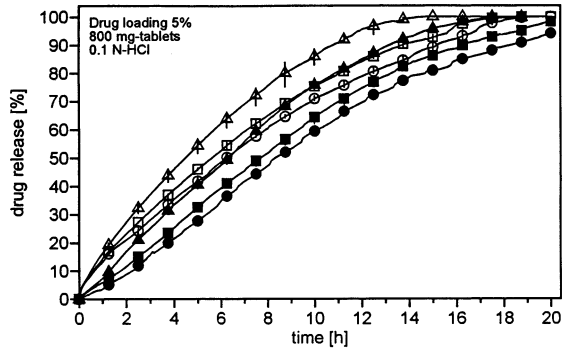

Fig. 2. Influence of drug solubility on the release from MHEC 3000 B-tablets (mean ± S.D., $n = 3$). Closed symbols: acetophenetidin, open symbols: proxyphylline. ●○, 50 rpm; ■□, 100 rpm; ▲△, 200 rpm.

higher drug loading and consequently, reduced polymer content. Regardless of the drug content, release exponents of $n \approx 0.78$ are calculated for proxyphylline tablets, whereas rising the acetophenetidin loading causes a significant increase in the release exponent. The exponents of the drug release from tablets with 30% drug content ($n = 1.16–1.37$) strongly exceed the values of $n = 0.87$ expected for erosion controlled, zero-order release. Drug release profiles with lower release rates at the beginning and increasing rates during the test are obtained. This phenomenon of release exponents exceeding the theoretical value has been described several times, especially for the erosion controlled release of poorly soluble drugs (Lindner and Lippold, 1995; Kim and Fassihi, 1997; Kim, 1998; Talukdar et al., 1998). This may, on the one hand, be a result of an increasing release area due to erosion and disintegration of the tablet and on the other hand, be caused by a delayed hydration of the tablets because of the poor water solubility and the hydrophobicity of the incorporated drug. Actually, looking at the results of the present study, the latter explanation seems to be more reasonable, as the effect is much more pronounced for tablets with high drug loading (Section 3.2.1). Although the overall drug release is faster at high loading, the opposite is observed during the first hours of the dissolution test. Apparently, the high amount of the poorly soluble, hydrophobic drug impedes hydration and delays drug release.

3.2.8. Dissolution medium

Surprisingly, the use of phosphate buffer pH 6.8 as the dissolution medium instead of hydrochloric acid leads to a marked increase in the acetophenetidin release rates. Drug release acceleration is even more pronounced if a pH-change is induced during the dissolution test by the addition of 13.0 g of sodium acetate $\cdot$ $3H_2O$ after 2 h (increase to pH 4.5) and 10.8 g of $Na_3PO_4 \cdot 12H_2O$ after another 2 h (increase to pH 6.8). The high dehydrating capacity of the salts used to modify pH may impede the formation of a protective gel layer and may subsequently enforce polymer erosion.

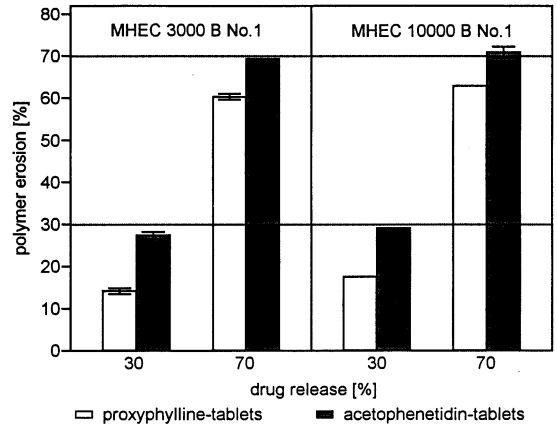

Fig. 3. Polymer erosion versus drug release for MHEC-tablets (800 mg) with a drug content of 5% (mean $\pm$ S.D., $n = 3–6$).

3.3. Erosion studies

To substantiate the conclusions drawn from the dissolution studies concerning the release mechanism, erosion studies were carried out. The results for MHEC 3000 B No. 1 and MHEC 10 000 B No. 1 are presented in Fig. 3, which shows polymer erosion versus drug release at the investigated time points equivalent to 30 and 70% drug release. These two MHEC-systems show rather good agreement between drug release and polymer erosion similar to Pharmacoat-tablets, the model for classical erosion. The best correspondence of drug release and polymer erosion is found when the poorly soluble acetophenetidin is embedded. Proxyphylline tablets, however, exhibit higher drug release than polymer erosion at the investigated time points. At 30% proxyphylline release, only 15% MHEC 3000 B and 17% MHEC 10 000 B have eroded and at 70% proxyphylline release it is $\approx 60\%$ polymer erosion. Obviously, a considerable amount of the highly soluble drug is not released by erosion of the polymer, but by diffusion through the gel layer.

Polymer erosion is less evident for tablets of MHEC 15 000 P6 No. 1, MHEC 60 000 P4 No. 1 and MHEC 30 000 B, which even show a slight discrepancy (up to 10%) between polymer erosion and drug release, when the sparingly soluble acetophenetidin is incorporated. This finding sup-

ports the suggestion that the contribution of diffusion is more pronounced for these tablets as concluded from the release profiles.

MHPC 100 000-tablets (model for diffusion controlled release) exhibit very little polymer erosion when the highly soluble drug is embedded: At 30% proxyphylline release, only 4.6% polymer have dissolved and even at 70% proxyphylline release, polymer erosion does not exceed 20%. However, polymer erosion is approximately doubled, if the poorly soluble model drug acetophenetidin is embedded.

The erosion studies prove in good agreement with the mathematical analysis of the release profiles, that a change in the drug solubility alters the release mechanism. For MHPC-tablets, a shift from diffusion control to anomalous transport is recorded when drug solubility is reduced. Devices with completely erosion-controlled release of poorly soluble drugs (e.g. MHEC 3000 B-, MHEC 10 000 B No. 1- and Pharmacoat-tablets) will release by anomalous transport when the diffusion rate increases due to the incorporation of a freely soluble drug.

3.4. The role of insoluble polymer components

An explanation has yet to be found for the finding that high viscosity grade MHECs do not form stable gel bodies but erode, while very similar polymers like MHPC of the same viscosity grades swell to coherent diffusion matrices. The turbidity of the solutions, also described by the manufacturer, led to further investigations. Unsubstituted cellulose fibres or fibres with a very low degree of substitution are claimed to be responsible for the occurrence of the opalescence of the solutions. These fibres representing by-products from the production process may swell when suspended in water but do not dissolve due to a too low degree of substitution (Stawitz and Kage, 1959; Grosse and Klaus, 1972).

As the content of insoluble fibres is not specified by the manufacturers, variations between products and batches are conceivable, which may affect the dissolution behaviour. Therefore, products from another manufacturer, as well as second batches of the products investigated so far, are included in the study to see if any differences in the release profiles can be detected.

3.4.1. Products from different manufacturers

Significant differences are observed in the drug release when comparing MHEC 15 000 P6 No. 1 and MHEC 60 000 P4 No. 1 to products with the same degree of substitution and similar viscosity grades but obtained from another manufacturer (Fig. 4a). In contrast to the MHECs supplied by Clariant, the Metoloses® (MHECs provided by Shin-Etsu) show pronounced swelling and only little erosion, even when the poorly soluble drug is embedded. A thick, coherent gel body is formed and drug release is distinctly prolonged. The release exponents of $n \approx 0.78$ are comparable to the data of MHPC 100 000-tablets and much smaller than the ones of the MHECs with purely erosion controlled release ($n > 1$). In the visual analysis, both dissolution media and Metolose solutions appear to be less turbid.

3.4.2. Batch to batch variations

The impression that variations in the amount of insoluble components of MHEC from the two manufacturers may be responsible for differences in the drug release is confirmed by the results of the study with different batches of the Clariant MHEC. While tablets with the two batches No. 1 and No. 2 of MHEC 3000 B and MHEC 10 000 B were almost identical in their release behaviour, extreme differences are observed for the batches No. 1 and No. 2 of MHEC 15 000 P6 and MHEC 60 000 P4. The release from MHEC 15 000 P6 No. 2-tablets proceeds much faster than from MHEC 15 000 P6 No. 1-compacts, while the opposite is detected for MHEC 60 000 P4 (Fig. 4b). Release from tablets of batch No. 2 of this product is comparable to the profiles of the high viscosity grade Metoloses. The high turbidity of MHEC 15 000 P6 No. 2 solutions and the almost clear solutions of MHEC 60 000 P4 No. 2 once more suggest that the amount of insoluble fibres is of great importance for the mechanism and rate of drug release. Therefore, further studies were performed to quantify the fibre content of the polymers.

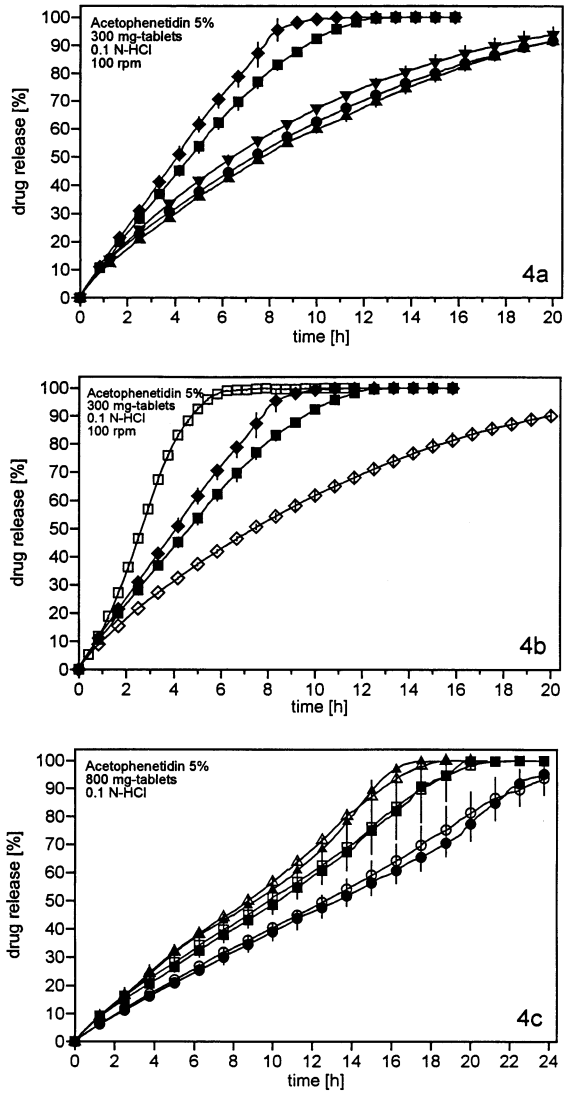

Fig. 4. Influence of insoluble fibres on the drug release from MHEC-tablets (mean ± S.D., $n = 3$): (a) Products from different manufacturers. ■, MHEC 15 000 P6 No. 1; ◆, MHEC 60 000 P4 No. 1; ▼, Metolose SEB 04T; ●, Metolose SEB 15T; ▲, Metolose SEB 30T. (b) Batch to batch variations. Open symbols: Batch No. 1, closed symbols: Batch No. 2. ■□, MHEC 15 000 P6; ◆◇, MHEC 60 000 P4. (c) Trial products with a high fibre content. Closed symbols: MHEC DS 0934/11, open symbols: MHEC DS 0935/10. ●○, 50 rpm; ■□, 100 rpm; ▲△, 200 rpm.

3.4.3. Determination of insoluble components in the MHECs

The amount of insoluble fibres is quantified both by gravimetric analysis after ultracentrifugation of the polymer solution and by Coulter–Counter analysis. Turbidity measurement of polymer solutions turned out to be an inappropriate method (Zuleger, 2000).

3.4.3.1. Ultracentrifugation and Coulter–Counter analysis. The results of the ultracentrifugation study show that the commercially available MHECs and MHPCs contain an amount of insoluble fibres ranging from 0.3 to ≈5% (Table 5). Low contents (≈1–1.5%) of insoluble fibres are found in products like MHPC 100 000, the embedding material for diffusion matrices, and in most of the Metoloses, which also exhibit marked swelling and limited erosion during the dissolu-

Table 5
Amount of insoluble components determined gravimetrically after ultracentrifugation (mean ± S.D., $n = 6$–8) and number of particles according to Coulter–Counter analysis (mean ± S.D., $n = 3$–6) of different MHECs and MHPCs

Polymer	Insoluble fibres (%)	Number of particles per gram of polymer powder (10^8/g)
MHEC 3000 B No. 1	2.7 ± 0.5	1.2586 ± 0.0404
MHEC 3000 B No. 2	3.2 ± 1.5	1.5691 ± 0.0862
MHEC 15 000 P6 No. 1	2.9 ± 0.6	1.4851 ± 0.0850
MHEC 15 000 P6 No. 2	4.6 ± 0.4	2.5410 ± 0.0663
MHEC 60 000 P4 No. 1	2.4 ± 0.4	1.0102 ± 0.0278
MHEC 60 000 P4 No. 2	0.3 ± 0.4	0.6008 ± 0.0355
MHEC DS 0934/11	17.9 ± 0.6	3.2510 ± 0.2371
MHEC DS 0935/10	11.1 ± 1.4	2.9955 ± 0.0776
Metolose SEB 04T	1.1 ± 0.4	1.0035 ± 0.0502
Metolose SEB 15T	1.6 ± 0.4	0.9695 ± 0.0193
Metolose SEB 30T	3.7 ± 1.2	2.8876 ± 0.0759
Metolose SNB 30T	0.6 ± 0.5	0.4325 ± 0.0166
Metolose SNB 60T	3.9 ± 0.6	2.2731 ± 0.0447
MHPC 100 000	1.5 ± 1.0	3.4681 ± 0.0747

tion test. On the other hand, high amounts of insoluble components are detected in MHEC 3000 B and MHEC 10 000 B, the two polymers with the most evident polymer erosion in the release studies. Obviously, unimpeded swelling and formation of stable gel bodies is only possible if few insoluble fibres are present in the matrix, while a higher concentration of insoluble fibres disturbs swelling and causes attrition of polymer material.

Batch to batch variations in the release which occurred in the case of MHEC 15 000 P6 and MHEC 60 000 P4, may also be related to differences in the fibre content: Release is accelerated for tablets of batch No. 2 of MHEC 15 000 P6 containing a significantly higher amount of insoluble components (4.6%) than batch No. 1 (2.9%) characterized by slower release of its tablets. In the case of MHEC 60 000 P4, an intermediate amount of fibres is found in batch No. 1 (2.4%) corresponding to less erosion of the tablets compared to MHEC 3000 B- and MHEC 10 000 B-tablets. Batch No. 2 is a very pure product, containing only 0.3% of insoluble cellulose fibres. Therefore, unhindered polymer swelling with only little polymer erosion occurs resulting in drug release comparable to MHPC 100 000-tablets with diffusion controlled release of the freely soluble drug and anomalous transport, if a poorly soluble substance is embedded.

Only the high amount of particles found in the high viscosity grade Metolose SEB 30T and Metolose SNB 60T do not correspond to the mainly diffusion controlled release from matrices with these polymers.

3.4.3.2. Coulter–Counter analysis. The findings of the gravimetric study are supported by the results of the Coulter–Counter analysis (Table 5). However, there are some differences. A high number of particle were counted in solutions of MHPC 100 000, which yields only a low content of 1.5% (w/w) of insoluble fibres in the gravimetric analysis, because MHPC 100 000 contains a larger fraction of fine particles (0.05% >40 μm, 50% <3.5 μm) compared to most of the other polymers (1% >40 μm, 50% <4 μm). Apparently, fine particles are better tolerated than bigger particles and can be present in the matrix in a high number without causing significant attrition of the polymer during the release process.

Obviously, the insoluble components like un- or low-substituted cellulose fibres, by-products of the synthesis of the polymer, strongly influence the release behaviour of hydrocolloid tablets. During the swelling of the tablets, they observably disturb the gelling, inhibit the formation of a coherent gel layer and act like a disintegrant. Thus, polymer erosion occurs and turbidity, caused by the insoluble fibres, becomes visible in the dissolution medium. To get a better insight in this phenomenon of polymer particle erosion, various swelling studies were performed and will be discussed in a following publication.

3.4.4. Trial products with a high fibre content

There are no commercial products available with a very high content of insoluble components, as these fibres cause unwanted turbidity of the polymer solution and have to be regarded as impurities. Therefore, special trial products with a very high content of fibres were investigated (Fig. 4c). Linear release profiles over a period of 18–24 h are obtained. To some extent the high viscosity grade of the polymer helps to withstand the strong tendency to erode caused by the insoluble fibres. Furthermore, the different nature of the trial products, which are made of flax instead of wood or cotton linters like the commercial products, definitely influences the release. The products do not look like real powders, but are rather felty products with strong coherence of the single particles, which helps to maintain integrity of the tablet and slows erosion.

3.4.5. Cellulose as additive to provoke particle erosion

Two powder celluloses of different particle size, Elcema F150 and Sanacel 40, are used as additives and mixed with Metolose SNB 30T in the ratio 1:9. Indeed, in both cases higher drug release rates and a slight increase in polymer erosion are observed. However, erosion is not as pronounced as in the case of MHEC 3000 B- and MHEC 10 000 B-tablets, release does not strictly follow zero-order kinetics and, above all, the systems with admixture of cellulose are more dependent

on agitation. Apparently, the physical mixture of a water soluble polymer and insoluble cellulose fibres cannot replace the insoluble fibres within the polymer.

4. Conclusion

Slow zero-order drug release by polymer particle erosion with high stability to hydrodynamic stress is found for tablets made of some types of high viscosity grade MHEC. These tablets do not form a thick stable gel layer but erode to a turbid dispersion with insoluble fibres.

Specific release profiles may be achieved by selective use of polymers with a certain high amount of insoluble components. Thus, the content of insoluble fibres should be included in the specifications of the polymer.

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