ELSEVIER

International Journal of Pharmaceutics 247 (2002) 23–37

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Polymer particle erosion controlling drug release. II. Swelling investigations to clarify the release mechanism

Susanne Zuleger [a], Reza Fassihi [b], Bernhard C. Lippold [a,*]

[a] *Institut für Pharmazeutische Technologie, Heinrich-Heine-Universität, Universitätsstr. 1, D-40225, Düsseldorf, Germany*
[b] *School of Pharmacy, Temple University, 3307 North Broad Street, Philadelphia, PA 19140, USA*

Received 7 January 2002; received in revised form 21 June 2002; accepted 21 June 2002

Abstract

The aim of the study was a comprehensive swelling investigation of hydrocolloid tablets with drug release by diffusion, erosion and polymer particle erosion, respectively, in order to reveal differences in the swelling behaviour responsible for the diverging drug release mechanisms. Four different methods were applied to study swelling of the tablets: determination of the expansion factor, texture analysis, visual swelling observation of dye containing tablets sandwiched between plexiglas® discs and photomicroscopy. Altogether they allowed the investigation of dimensional changes, swelling velocity, thickness, appearance and strength of the gel layer and front movements. However, none of the methods included a determination of all these factors. A combination of the different techniques proved to be helpful to provide information necessary for a broad understanding of the complex phenomenon of swelling. Intensive swelling was observed for matrices with diffusion controlled release (e.g. MHPC 100000), while erosion controlled systems (e.g. Pharmacoat 606) were characterized by limited swelling and fast polymer erosion. In the case of tablets exhibiting polymer particle erosion (e.g. MHEC 10000 B) the importance of the amount of insoluble fibres was confirmed. Insoluble fibres were clearly visible in the swelling zone of these tablets. They impeded the swelling, weakened the gel layer and caused attrition of polymer material, thus only a thin gel layer was formed. Synchronization of the movement of swelling and erosion fronts occurred during the swelling of tablets with a high content of insoluble fibres. The freely soluble drug proxyphylline was found to promote swelling while the poorly soluble acetophenetidin hindered the hydration of the tablet. Furthermore, the swelling study confirmed the low robustness to hydrodynamic stress of tablets with erosion control compared to tables with polymer particle erosion.

Keywords: Methyl hydroxyethyl cellulose; Polymer particle erosion; Swelling; Gel structure; Texture analysis; Photomicroscopy

1. Introduction

Different high viscosity grade methyl hydroxyethyl celluloses (MHEC) proved to be suitable embedding material for drug release by polymer particle erosion. Drug release from methyl hydro-

* Corresponding author. Tel.: +49-211-811-4220; fax: +49-211-811-4251
E-mail address: lippold@uni-duesseldorf.de (B.C. Lippold).

0378-5173/02/$ - see front matter
PII: S0378-5173(02)00362-9

xyethyl cellulose tablets by polymer particle erosion has been studied intensively and results were presented in a recent publication (Zuleger and Lippold, 2001). Based on this mechanisms, which is characterized by erosion of only partially swollen polymer particles, the development of tablets exhibiting almost linear drug release profiles with low susceptibility to hydrodynamic stress is feasible regardless of drug solubility. Further investigations have provided evidence that the occurrence of polymer particle erosion is related to the presence of insoluble fibres within the water soluble cellulose ether. Although expected to release the active by diffusion, tablets made of high viscosity grade MHEC showed erosion, when containing a significant amount of insoluble fibres in the polymer. MHEC products with a high amount of insoluble fibres were found to release the poorly soluble drug acetophenetidin purely by erosion at appropriate release rates. Insoluble fibres were assumed to interrupt the swelling and disturb the formation of a thick coherent gel layer. As a result, erosion of swollen polymer material and the release of embedded drug occurred synchronously. By contrast, tablets of MHEC with a very low content of insoluble components exhibited only little polymer erosion. Extensive swelling of the embedding during the dissolution test was observed and drug release was mainly diffusion controlled. In the case of poorly soluble drugs the release rate decreased dramatically.

To substantiate the supposition of insoluble fibres and their effect on swelling being decisive for drug release by polymer particle erosion, swelling needed to be studied in detail.

Regardless of the drug release mechanism, hydration of the tablet is imperative for drug release. Hydration and subsequent dissolution of the drug in the dissolution medium are prerequisites for diffusion to take place, and erosion requires sufficient hydration of the polymer chains to reach the disentanglement concentration (Ju et al., 1995) at which the macromolecules begin to detach from the swollen matrix.

Because of the important role of swelling for drug release from hydrocolloid tablets, many approaches have been made and different methods were developed to investigate processes taking place during hydration of the tablet. A simple way to study swelling is to register changes in size of the embedding during hydration as performed by Heyd et al. (1969), Kim and Fassihi (1997a), Lindner and Lippold (1995), Panomsuk et al. (1995), Talukdar and Kinget (1995) and others. Some authors use photo or video equipment and image analysis to document dimensional changes (Le Néel et al., 1997; Martini et al., 1995; Papadimitriou et al., 1993; Talukdar et al., 1998). In microscopical studies in the 1960s already, carbon black was used to visualize hydration and front movements in polystyrole films (Ueberreiter, 1968). Nowadays, photomicroscopy is still very helpful for the understanding of drug delivery (Colombo et al., 1995; Kim and Fassihi, 1997a; Pham and Lee, 1994). Incorporation of coloured drugs (Colombo et al., 1995; Pham and Lee, 1994) or additives (Freichel and Lippold, 2000) in the tablet, respectively dying the swelling medium (Sujja-areevath et al., 1998; Ferrero et al., 2000), facilitates the detection of movements of erosion, diffusion and swelling front. For better observation, tablets are often fixed between Plexiglas® discs permitting water uptake only from the lateral surface and preventing both the formation of a gel layer and the expansion in the axial direction (Bettini et al., 1994).

Furthermore, different techniques based on measuring the penetration of a probe in the gel layer of a swollen tablet have been applied to investigate gel layer thickness by determination of the position of swelling and erosion fronts (Colombo et al., 1987; Konrad et al., 1998; Mitchell et al., 1993a; Yang et al., 1998). Some of these represent methods of gel structure analysis, which provide information not only on gel layer thickness but also on the texture (strength) of the gel.

In this study several methods were selected to investigate swelling of MHEC- and methyl hydroxypropyl cellulose (MHPC)-tablets with different release mechanisms. Combining methods measuring different parameters (like volume expansion, front movement, gel layer thickness and texture, and swelling velocity) in a swelling study is necessary to comprehensively describe and understand this complex phenomenon. Focus was put on clarifying the role of insoluble fibres in the

water soluble cellulose ether for polymer swelling and drug release and on distinguishing polymer particle erosion from other release mechanisms.

2. Materials and methods

2.1. Materials

The cellulose ethers, MHEC and MHPC, and drugs used in this study are identical to the materials described in part I of this publication (Zuleger and Lippold, 2001).

2.2. Methods

2.2.1. Tablet preparation

As described in the previous publication (Zuleger and Lippold, 2001) tables were prepared by direct compression in flat-faced punches (diameter 13 mm) using a manual hydraulic press (Perkin Elmer, Überlingen, Germany). Additionally, tablets with a diameter of 10 mm (mass 600 ± 3 mg) manufactured by direct compression using the Carver Press (Model C, Fred S. Carver Inc., Wabash, USA) at 2 tons (≈ 20 kN) for 10 s were applied in the gel structure analysis. The same press was used to compress thin slabs (diameter 7 mm, 100 ± 3 mg) of pure polymer for the microscopy studies.

2.2.2. Axial expansion and expansion factor

Tablets (300 mg, drug 5%) were positioned in scaled, flat-bottomed test tubes (diameter 14 mm). After adding 5 ml of swelling medium the tubes were positioned in a water bath at 37 ± 0.5 °C. Axial expansion was measured and the expansion factor was determined by calculating the quotient of the heights of the swollen and the dry tablets.

2.2.3. Gel structure analysis

Covering one planar base of the tablets with an organic water insoluble coating (60 g Eudragit® RS in a mixture of 50 ml acetone and 50 ml isopropanol) the tablets were glued to petri dishes. The petri dishes were positioned in the dissolution vessels filled with 900 ml of deionized water and swelling was performed at 37 ± 0.5 °C in the USP paddle apparatus at 100 rpm. The petri dishes with the swollen embeddings were removed from the medium at predetermined times over a period of 8 h and subjected to texture analysis. Expansion of the tablets and development of gel layer thickness during the swelling process were investigated using the Texture Analyser (TA.XT2, Stable Micro Systems, Goldalming, UK) (Yang et al., 1998). At a test speed of 0.2 mm s^{-1} the penetration of a flat-tipped cylindrical steel probe (diameter 2 mm, height 3 cm) under increasing load (max. 700 g) was measured and data acquisition and analysis was performed using a computer equipped with the TEXTURE EXPERT® software.

2.2.4. Swelling of dye containing tablets sandwiched between Plexiglas® discs

To visualize the water uptake, tablets (diameter 13 mm, 800 mg, 30% drug) containing 2 mg methylene blue per tablet as a dye were used. Fixing these tablets between two Plexiglas® discs (6×6 cm^2) joined by 4 stainless steel screws (Fig. 7) water uptake and swelling were restricted to the lateral surface of the compact. The tablets sandwiched between the discs were inserted into the USP paddle apparatus (Erweka, Heusenstamm, Germany), dissolution was carried out in deionized water at 37 ± 0.5 °C and 200 rpm. The mountings were removed from the dissolution tester at 2, 4, 8 and 32 h and the swollen tablets were photographed through the Plexiglas® using a digital camera (Canon Powershot 600, Tokyo, Japan).

2.2.5. Photomicroscopy

Swelling of the thin polymer slabs in deionized water at 37 ± 0.5 °C was carried out both under static conditions in a petri dish and at 100 rpm in the USP paddle apparatus. Swelling was analyzed by photomicrography with a microscope (Olympus SHZ 10, Tokyo, Japan) connected to a digital camera (Sony DKC 5000, Tokyo, Japan).

3. Results and discussion

3.1. Axial expansion and expansion factor

Since expansion during swelling of hydrocolloid tablets is much more pronounced in the axial direction than in the radial (Gao and Meury, 1996, Kim and Fassihi, 1997a,b; Mitchell et al., 1993a; Papadimitriou et al., 1993; Rajabi-Siahboomi et al., 1994; Sujja-areevath et al., 1998), focus was put on changes in tablet height and radial expansion was suppressed by insertion of the compacts into tight fitting vials. Thus, according to Eq. (1), the expansion factor EF_t, as a measure of change in volume caused by swelling for a certain time t can simply be calculated by determining the quotient of the height of the swollen tablet (h_t) and of the dry compact ($h_o = 2$ mm) Fig. 4.

$$EF_t = h_t/h_o \quad (1)$$

Fig. 1 depicts the increase in tablet height of proxyphylline tablets with different cellulose ethers during swelling in 0.1 mol l^{-1} HCl. In the first 8 h MHEC 3000 B No. 1- and MHEC 10000 B No. 1 -tablets swell much faster than the reference systems for diffusion controlled release based on the high viscosity grade MHPC 100000 and the low viscosity grade MHPC Pharmacoat 606-tablets with erosion controlled drug release (Fig. 1a). In contrast to the MHPC-tablets, which already formed a coherent gel body during these first hours, no coherent gel layer was formed in the case of the MHEC-tablets. Swelling of the MHEC-tablets led to a loose, fluffy sediment on top of the tablets, which were sitting at the bottom of the vials. Thus, for the MHEC-tablets the height presented in Fig. 1 consists of tablet height and height of the sediment formed during swelling. The expansion factor of Pharmacoat 606-tablets was approximately 2 during the first 8 h, while swelling of tablets made of the high viscosity grade MHPC 100000 was a little more pronounced resulting in an expansion factor of 2.7 after 8 h (Table 1). Distinctively higher expansion factors of 3.2–5.0 were calculated for tablets with MHEC 3000 B No. 1, MHEC 10000 B No. 1, MHEC 15000 P6 No. 1 and MHEC 60000 P4 No. 1, which all initially did not form a gel layer but the described

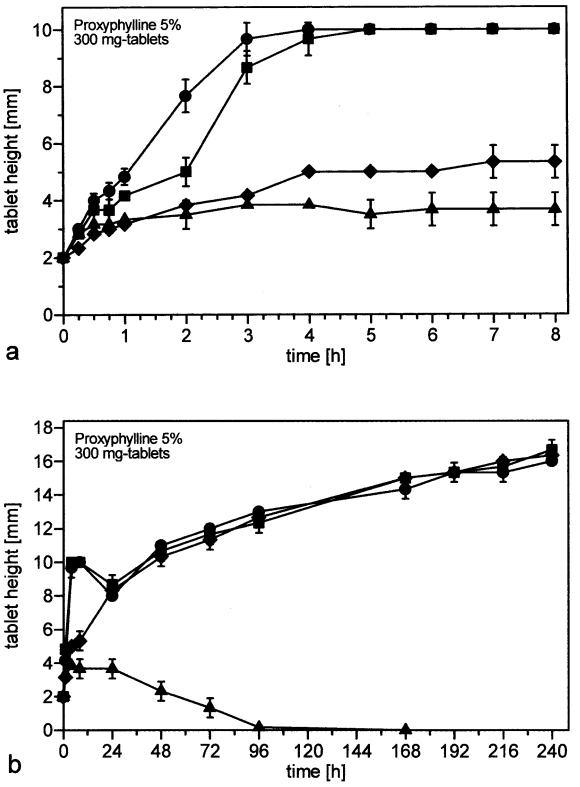


Fig. 1. Swelling of proxyphylline tablets in 0.1 mol l^{-1} HCl (mean ± S.D., $n = 3$). (a) initial swelling (8 h). (b) Long term swelling (240 h). MHEC 3000 B No. 1 (■); MHEC 10000 B No. 1 (●); MHPC 100000 (◆); Pharmacoat 606 (▲).

Table 1
Expansion factors of proxyphylline-tablets (300 mg, drug content 5%) after swelling in 0.1 mol l^{-1} HCl for 4, 8 and 240 h, (mean ± S.D., $n = 3$)

Polymer	Expansion factor		
	$t = 4$ h	$t = 8$ h	$t = 240$ h
MHEC 3000 B No. 1	4.8[a] ± 0.2	5.0[a] ± 0.0	8.0 ± 0.0
MHEC 10000 B No. 1	5.0[a] ± 0.0	5.0[a] ± 0.0	8.3 ± 0.2
MHEC 15000 P6 No. 1	3.3[a] ± 0.2	4.7[a] ± 0.2	8.2 ± 0.2
MHEC 60000 P4 No. 1	3.0[a] ± 0.0	3.2[a] ± 0.2	7.8 ± 0.2
MHPC 100000	2.5 ± 0.0	2.7 ± 0.2	8.2 ± 0.2
Pharmacoat 606	1.9 ± 0.1	1.8 ± 0.2	dissolved

[a] fluffy sediment.

fluffy sediment. All these polymers showed drug release by polymer particle erosion and contained significant amounts of insoluble fibres. This ob-

servation supports the theory that insoluble fibres disturb the gelling of the tablet and lead to detachment of polymer particles from the embedding as assumed in the previous publication (Zuleger and Lippold, 2001).

The rapid initial 'swelling' of the MHEC-tablets, which is actually rather a partial disintegration of the tablet, was followed by a gelling period, in which the fluffy sediment subsided and gradually thickened, thus, after 24 h a coherent gel body had developed. Under the static conditions in the test tube penetration and interdiffusion of the polymer chains finally occurred, allowing interaction between the chains necessary for gel formation. According to studies of Stawitz and Kage (1959), swelling of low-substituted cellulose fibres, which were found to represent the insoluble components within water soluble cellulose ethers, was much slower and often terminates at a lower degree of hydration compared to sufficiently substituted fibres. Therefore only long term swelling allowed gradual hydration of the slow hydrating fibres and finally gel formation. After swelling for 24 h, differences between high viscosity grade MHPC and MHEC had equalled out and a synchronous course of swelling was recorded over 10 days (Fig. 1b). Swelling of the low viscosity grade Pharmacoat 606 was at its maximum after approximately 12–24 h. Afterwards dissolution dominated and tablets height slowly decreased, until the tablets had finally dissolved completely after a couple of days.

The early period up to 8 h was decisive to distinguish between tablets showing polymer particle erosion and systems with diffusion or erosion controlled release. On the other hand longer observation of the swelling was necessary to differentiate between diffusion and erosion control of the release, as dissolution of the tablet with erosion controlled release was very slow under the static conditions in the swelling tube.

3.1.1. Drug solubility

When the poorly soluble acetophenetidin was incorporated instead of the freely soluble proxyphylline, expansion factors measured at 4 and 8 h increased for all tablets which did not form a coherent gel but a fluffy sediment (Table 2). A reason may be the impeded hydration and swelling at incorporation of the hydrophobic drug, which hinders the formation of a protective gel layer. Thus, there is less resistance to the disintegrative activity of the insoluble fibres and the detachment of polymer particles is enforced resulting in an increased sediment volume and therefore higher expansion factor. Swelling of the MHPC-tablets, which formed a coherent gel body, was not distinctively affected by the nature of the drug.

Table 2
Expansion factors of acetophenetidin-tablets (300 mg, drug content 5%) after swelling in 0.1 mol l^{-1} HCl for 4, 8 and 240 h, (mean ± S.D., $n = 3$)

Polymer	Expansion factor		
	$t = 4$ h	$t = 8$ h	$t = 240$ h
MHEC 3000 B No. 1	5.5[a] ± 0.2	5.5[a] ± 0.0	7.5 ± 0.0
MHEC 3000 B No. 2	4.7[a] ± 0.2	4.5[a] ± 0.0	7.5 ± 0.0
MHEC 10000 B No. 1	6.7[a] ± 0.0	6.5[a] ± 0.4	8.0 ± 0.0
MHEC 10000 B No. 2	7.5[a] ± 0.0	7.2[a] ± 0.2	7.5 ± 0.0
MHEC 15000 P6 No. 1	4.8[a] ± 0.5	5.2[a] ± 0.6	7.8 ± 0.2
MHEC 15000 P6 No. 2	9.5[a] ± 0.4	10.2[a] ± 0.2	9.0 ± 0.0
MHEC 60000 P4 No. 1	4.3[a] ± 0.2	4.0[a] ± 0.0	8.3 ± 0.2
MHEC 60000 P4 No. 2	2.6 ± 0.2	2.8 ± 0.2	7.8 ± 0.2
Metolose SEB 04T	2.3 ± 0.2	2.4 ± 0.1	7.2 ± 0.2
Metolose SEB 15T	2.5 ± 0.2	2.7 ± 0.2	7.7 ± 0.2
Metolose SEB 30T	2.5 ± 0.0	2.7 ± 0.1	7.8 ± 0.2
Metolose SNB 30T	2.4 ± 0.1	2.8 ± 0.2	7.5 ± 0.0
Metolose SNB 60T	2.6 ± 0.1	2.8 ± 0.2	7.8 ± 0.2
MHPC 90SH 100000SR	2.5 ± 0.0	2.8 ± 0.1	8.2 ± 0.2
Pharmacoat 606	1.9 ± 0.1	1.8 ± 0.2	dissolved

[a] fluffy sediment.

3.1.2. Swelling medium

In order to explain the significant impact of the dissolution medium on the drug release from MHEC tablets showing polymer particle erosion (Zuleger and Lippold, 2001), the swelling experiment with acetophenetidin tablets was repeated using phosphate buffer pH 6.8 as the swelling medium The swelling of the gel forming Pharmacoat 606- and MHPC 100000-tablets was not affected by the swelling medium. However, a distinctive change in swelling behaviour was observed in the case of MHEC-tablets, as depicted for MHEC 3000 B No. 1 and MHEC 10000 B No. 1 in Fig. 2.

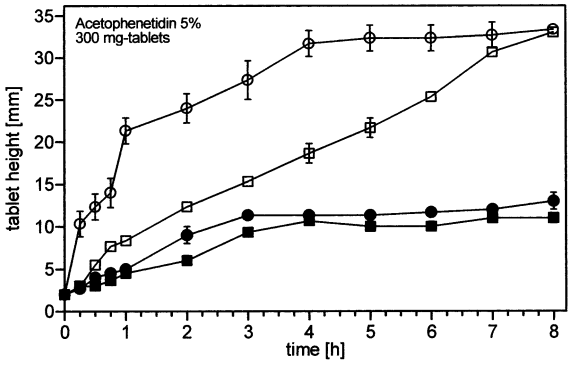


Fig. 2. Influence of the swelling medium on the swelling of acetophenetidin tablets mean ± S.D., $n = 3$). Closed symbols: 0.1 mol l^{-1} HCl, open symbols: phosphate buffer pH 6.8. MHEC 3000 B No. 1 (■□); MHEC 10000 B (●○).

Corresponding to the accelerated erosion and drug release when using phosphate buffer as dissolution medium, faster expansion of the tablets was observed in the swelling study. Again, no coherent gel body was formed, but the tablets partially disintegrated and a voluminous sediment was formed. The results of the swelling investigation substantiate the assumption that polymer erosion is intensified and drug release is accelerated due to the higher dehydrating capacity of the buffer ions, which impedes swelling and formation of a protective gel layer. Reduced gel formation at the presence of dehydrating salts clearly promotes the disintegration induced by the insoluble polymer fibres.

3.1.3. *Insoluble fibres*

The determination of the expansion factor had proved a simple and useful tool to distinguish between tablets exhibiting drug release by polymer particle erosion and the reference systems with diffusion (MHPC 100000) or erosion (Pharmacoat 606) controlled release. It was claimed that insoluble fibres are responsible for differences in the swelling behaviour. In order to find out if the determination of the expansion factor can be applied to distinguish between products with different fibre contents and therefore diverging drug release mechanisms, MHEC from different batches and manufacturers, which vary in their content of insoluble fibres, were included in the swelling study. In fact, differences in the content of insoluble fibres and drug release mechanism were reflected in the swelling performance: High expansion factors at 4 and 8 h as a result of disintegration and formation of a loose, voluminous sediment were calculated for all MHECs, which show polymer particle erosion and contain significant amounts of insoluble components. Significant batch to batch variations concerning the insoluble fibres as in the case of MHEC 15000 P6 and MHEC 60000 P4 may also be detected by determination of the expansion factor: After 8 h of swelling MHEC 15000 P6 No. 1 which contains 2.9% of insoluble fibres had an expansion factor of 5.2 while the second batch, MHEC 15000 P6 No. 2, which contains 4.6% was characterized by an expansion factor of 10.2. The only MHEC from this manufacturer which did not form a fluffy sediment was the very pure MHEC 60000 P4 No. 2 (insoluble fibres 0.3%). Tablets of this product as well as all Metolose-compacts did not release the drug by polymer particle erosion but formed a coherent gel layer both in the dissolution and the swelling study, resulting in expansion factors of approximately 2.5 at 4 and 8 h, which match the values obtained for the high viscosity grade MHPC. As described before, in the long run all MHEC finally formed a coherent gel body in the vial with comparable expansion factors at 240 h. Again the first 8 h of swelling experiment were most decisive for the differentiation of the polymers.

3.2. *Gel structure analysis*

According to the investigations of Yang et al. (1998) the Texture Analyser was used to examine the gel structure and to determine gel layer thickness and axial expansion of the tablet during swelling. With the Texture Analyser the force necessary for penetration of a cylindrical probe into the swollen tablet is measured precisely. Movement of the probe is microprocessor controlled. At contact of the probe with the surface of the swollen tablet (erosion front) data acquisition is initiated when reaching a threshold load necessary for penetration into the gel layer. At the beginning of the tests only low forces are necessary

to penetrate the swollen gel layer. A sharp increase in the load required for further penetration indicates the position of the boundary between gel layer and dry core (swelling front) of the tablet. Once the maximum force is reached, reverse movement starts withdrawing the probe from the swollen tablet. Examples of resulting penetration profiles are given in Fig. 3.

Gel layer thickness was obtained calculating the difference between the maximum penetration distance of the swollen and the dry tablets. Furthermore axial expansion of the tablet may be analyzed, as the apparatus gauges tablet height. In contrast to alternative penetration methods like TMA, penetrometer and consistometer measurements, which simply base on the determination of the penetration distance at a distinct force, the Texture Analyser also provides information on gel structure, as complete force–distance-diagrams are recorded during the penetration process.

3.2.1. Pure polymer tablets

The penetration profiles of MHPC 100000 tablets, the matrices with diffusion controlled release used as reference systems, show a strong increase in the penetration distance with swelling time, indicating a distinct increase in gel layer thickness during swelling.

Looking at single penetration profiles provides information on the gel texture. After swelling for 1 h, a load of $\approx$100 g was sufficient to penetrate about 1.2 mm in the outer gel layer. For further penetration of 0.6 mm an increase to a load of 400 g was necessary due to the less hydrated, denser structure of the gel in the inner area. Subsequently, a sharp increase in the load was detected, similar to the profile of the dry compact, indicating that the probe had reached the dry core of the tablet. During the swelling of the tablets a gradient in hydration of the gel layer had developed, which determined the structure of the gel. Due to strong hydration and therefore low polymer concentration, outer areas are characterized by lower gel strength and less resistance to penetration while inner, less hydrated areas of more dense gel structure require higher loads for penetration. Finally, the dry core does not allow further penetration of the probe. Comparing the 8 h swelling profile to the profile after 1 h swelling discussed above, it becomes obvious that prolonged swelling time did not only lead to an increase in the maximum penetration distance but also significantly altered the forces needed for penetration. For a penetration distance of about 1 mm, which required a load of almost 100 g after swelling for 1 h, a load as small as 10 g was sufficient in the case of the tablets swollen for 8 h. Applying the same load of 100 g after swelling for 8 h, the probe penetrated much further (2.6 mm) in the tablets because of stronger hydration and lower gel strength. Comparing the results of the polymers included in this study, significant differences in gel layer thickness and axial expansion are observed (Fig. 4). The high viscosity grade MHPC 100000 exhibited extensive swelling. After 8 h a gel layer of 4 mm had formed, although swelling was not even at equilibrium yet, and tablet height was almost doubled.

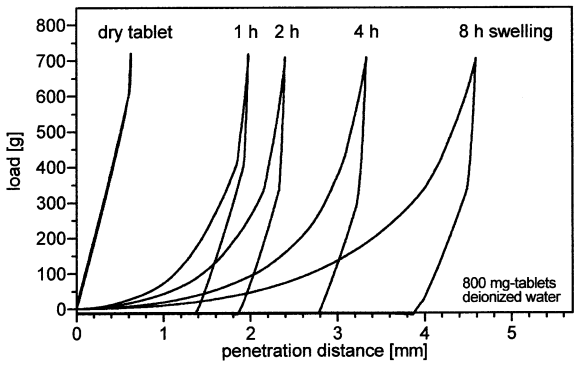


Fig. 3. Typical penetration profiles of dry and swollen MHPC 100000-tablets.

Tablets made of low viscosity grade MHPC, Pharmacoat 606, showed only little swelling. Tablet height gradually decreased due to erosion of the gel. After about 5 h in the dissolution bath, the tablets had dissolved completely.

Only moderate swelling was found in the case of tablets exhibiting polymer particle erosion like MHEC 3000 B No. 1 and MHEC 10000 B No. 1 tablets. In the initial phase the course of swelling was similar to tablets made of the high viscosity grade MHPC 100000. However, after 2 h, when a gel layer with a thickness of approximately 2 mm had formed, no further increase in the gel layer

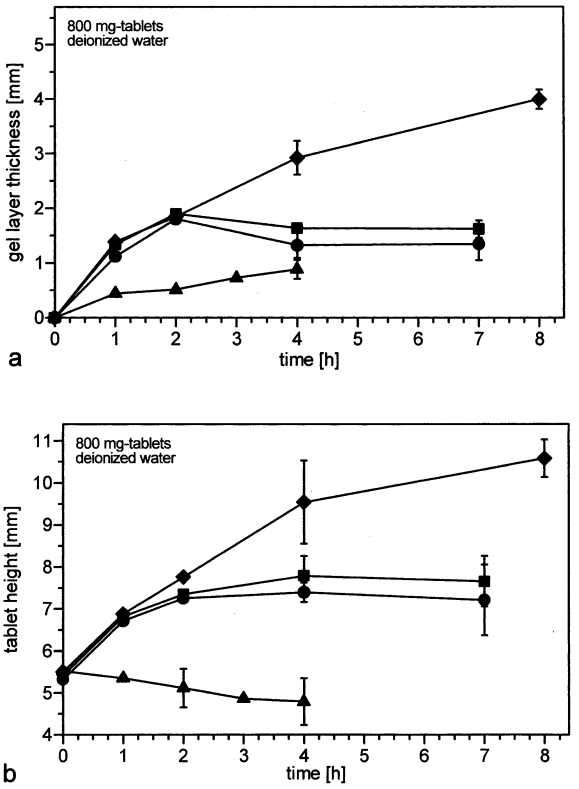


Fig. 4. Swelling of hydrocolloid tablets (mean ± S.D., $n = 3$). (a) Gel layer thickness. (b) Axial expansion. MHEC 3000 B No. 1 (■); MHEC 10000 B No. 1 (●); MHPC 100000 (◆); Pharmacoat 606 (▲).

thickness was observed indicating synchronization of the movement of swelling and erosion fronts. After an increase in the initial swelling phase, tablet height of the MHEC tablets remained fairly constant, although polymer erosion took place. This may be explained by an axial expansion of the drug core as described by Rajabi-Siahboomi et al. (1994), and Gao and Meury (1996). The results of the texture analysis study clearly prove that a thin gel layer of constant thickness is formed during dissolution of MHEC tablets. Depending on its solubility, the drug is released either by diffusion through a gel layer of constant thickness or as particles as a consequence of polymer erosion. Regardless of drug solubility, appropriate release rates were obtained using these MHEC which show polymer particle erosion due to the high content of insoluble fibres (Zuleger and Lippold, 2001).

On the other hand, the increasing diffusional pathway due to extreme swelling of MHPC 100000 was responsible for very low release rates of poorly soluble drugs like acetophenetidin from these tablets, while in the case of Pharmacoat 606-tablets fast polymer dissolution caused rapid release of the drug, inappropriate for controlled release devices. By use of the Texture Analyser it is possible to differentiate between tablets with drug release by diffusion, erosion or polymer particle erosion.

Further experiments with different batches of MHEC and MHEC products from different manufacturers were performed, looking for a correlation between fibre content, swelling behaviour and drug release. In fact, the expected influence of insoluble fibres on the swelling behaviour can easily be detected looking at the swelling profiles of different batches of MHEC 15000 P6 and MHEC 60000 P4 given in Fig. 5. Tablets with MHEC 15000 P6 No. 2, a product with a very high fibre content of 4.6%, were characterized by intensive polymer erosion and low gel layer thickness. On the other hand, MHEC 60000 P4 No. 2, a very pure product with a fibre content $< 1\%$, resembled MHPC 100000 in swelling behaviour. At this low level of insoluble fibres a thick gel layer was formed as a result of

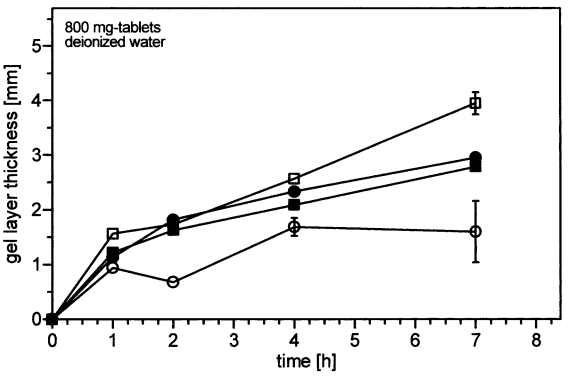


Fig. 5. Effect of batch to batch variations of MHEC-products on gel layer thickness during swelling of MHEC-tablets (mean ± S.D., $n = 3$). MHEC 15000 P6 No. 1 (●); MHEC 15000 P6 No. 2 (○); MHEC 60000 P4 No. 1 (■); MHEC 60000 P4 No. 2 (□).

unimpeded swelling with little polymer erosion. After 8 h gel layer thickness was almost 4 mm and swelling was not at equilibrium yet, MHEC 15000 P6 No. 1 and MHEC 60000 P4 No. 1 containing 2.9, respectively 2.4% of insoluble fibres showed an intermediate degree of swelling. In contrast to MHEC 3000 B No. 1 and MHEC 10000 B No. 1 tablets, synchronization of the movement of swelling and erosion fronts did not occur despite a similar content of fibres. This may be explained by the higher gel strength of these high viscosity grade polymers counteracting the disintegrative activity of the insoluble components. Front synchronization was observed only in the case of the fibre-rich MHEC 15000 P6 No. 2.

As expected because of similar behaviour in the dissolution studies, intensive swelling with profiles identical to the ones of MHEC 60000 P4 No. 2- and MHPC 100000-tablets was observed for tablets made of Metolose SEB and SNB (MHEC with low fibre content, Zuleger and Lippold, 2001). The even greater extent of swelling of tablets made of Metolose SNB compared to SEB may be related to the higher degree of substitution with hydrophilic hydroxyethoxy-groups, which facilitates the water uptake.

3.2.2. *Influence of drug solubility*

To evaluate the influence of drug solubility on the swelling behaviour of hydrocolloid matrices, tablets containing 30% of proxyphylline or acetophenetidin as the freely, respectively poorly soluble model drug were included in the study and results were compared to the drug-free compacts. Results for MHPC 100000- and MHEC 10000 B No. 1-tablets are presented in Fig. 6. Incorporating the freely soluble proxyphylline, swelling was intensified for both polymers. Despite the reduced polymer content in the matrix an increase in the thickness of the gel layer formed during swelling of the tablet was observed. In contrast gel layer thickness was reduced slightly, if the poorly soluble acetophenetidin was embedded.

For both polymers rapid swelling occurred in the first hour, regardless of drug solubility. In the following hours the increase in gel layer thickness was more distinctive, when proxyphylline was embedded. In the case of MHPC 100000-tablets

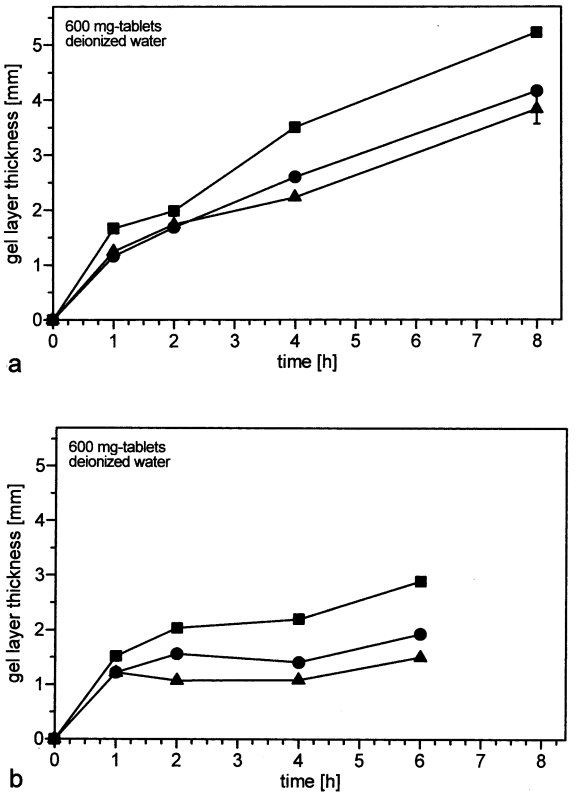


Fig. 6. Influence of drug solubility on gel layer thickness during swelling of hydrocolloid tablets (mean ± S.D., $n = 3$). (a) MHPC 100000-tablets. (b) MHEC 10000 B No. 1-tablets. without drug (●); 30% proxyphylline (■); 30% acetophenetidin (▲).

gel layer thickness after 8 h was 5.2 mm, when proxyphylline was incorporated and 3.8 mm for acetophenetidin tablets, compared to 4.1 mm of the tablets without drug. Regardless of drug incorporation, front synchronization appears after 2 h during the swelling of MHEC 10000 B No. 1 tablets. After 6 h gel layer thickness was 1.5, 1.9 and 2.9 mm for tablets with acetophenetidin, without drug, or with proxyphylline, respectively. In accordance with the results of this study, Conte et al. (1988), Konrad et al. (1998) and Mitchell et al. (1993b) report stronger swelling at the incorporation of freely soluble drugs compared to poorly soluble actives. Water uptake and swelling are intensified by freely soluble drugs due to their osmotic pressure, while poorly soluble drugs, which mainly are not dissolved in the hydrated layer, impede water uptake and even promote

erosion (Bettini et al., 2001). Panomsuk et al. (1995) describe reduced expansion of hydrocolloid tablets when increasing the loading with a sparingly soluble active, related to the decreasing polymer content in the matrix. Furthermore the hydrophobic nature of many poorly soluble drugs is responsible for reduced hydration as in the case of acetophenetidin tablets used in this study. The increased hydration at the incorporation of proxyphylline did not only compensate the effect of the reduced polymer content of the tablets at a drug loading of 30%, but even led to an increase in gel layer thickness compared to compacts of pure polymer. In contrast Mitchell et al. (1993b) report a reduced degree of swelling for both poorly and freely soluble drugs compared to the drug-free reference. Obviously, the promoting effect on hydration of propranolol HCl used as freely soluble model drug is not sufficient to compensate the impact on swelling resulting from the reduction in polymer content at the high drug loading of 50% in that study. It may be concluded that swelling and gel layer thickness are influenced by drug and polymer characteristics as well as drug loading. Likewise additives used for tabletting may also have an impact on swelling behaviour.

3.3. Visual swelling study of dye containing tablets

To visualize movements of swelling as well as diffusion and erosion fronts, tablets were sandwiched between two Plexiglas® discs and fixed with screws as described by Bettini et al. (1994). Instead of selecting a coloured drug for these experiments as performed by Bettini et al. (1994), Colombo et al. (1995) and Pham and Lee (1994), the same, white coloured model drugs, proxyphylline and acetophenetidin, also used in the other studies, were chosen. Additionally a small amount of methylene blue, a freely water soluble dye, was incorporated in the tablets. Before starting the swelling experiment, methylene blue was visible as little dark spots in the dry, white tablet. At contact with water the dye dissolved immediately dying the swelling zone blue. A sharp line between the blue hydrated area and the white dry core indicated the position of the swelling front (Fig. 7). Usually, the position of the diffusion front within the blue

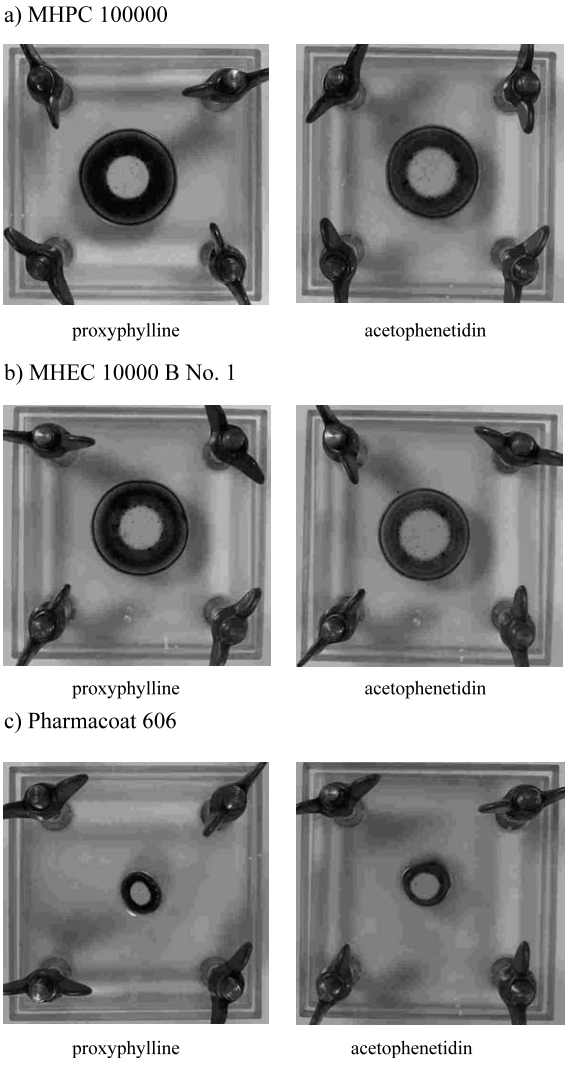


Fig. 7. Influence of drug solubility—Photographs of dye containing tablets sandwiched between Plexiglas® discs and swollen for 8 h in deionized water.

hydrated area is marked as a borderline between a transparent area with dissolved drug and a non-transparent area carrying drug particles. The boundary of the tablet represents the erosion front.

Fixing the tablets between the discs, only the lateral surface got in contact with the swelling medium. Due to this restriction of the area available for water-uptake, swelling and drug release was much slower compared to dissolution

tests under standard conditions. Furthermore the discs shielded the tablets from hydrodynamic stress in the dissolution medium.

Tablets made of the high viscosity grade MHPC 100000 exhibited intensive swelling compared to the limited degree of swelling of the Pharmacoat 606-tablets, which only formed a very thin gel layer. The photographs presented in Fig. 7 clearly allow to distinguish between tablets loaded with drug of different solubility. Hydration was faster and more distinct for proxyphylline tablets compared to compacts containing the poorly soluble acetophenetidin. Because of its very high water solubility, proxyphylline immediately dissolved upon hydration of the embedding. Thus, in the case of MHPC-tablets, the gel layer formed was clear and intensively blue coloured, due to the simultaneous dissolution of the dye. For this freely soluble active the diffusion front was identical to the swelling front. The fast dissolution of proxyphylline observed upon hydration of the MHPC tablets proves that the non-transparent zone, visible in swollen MHEC 10000 B No. 1 may not be related to undissolved drug. The turbidity of the gel layer is rather caused by insoluble or slowly hydrating polymer components.

When the poorly soluble acetophenetidin was embedded, the diffusion front could be detected within the blue, hydrated zone indicating the position of the drug particles. However, in the case of MHEC 10000 B No. 1-tablets it was not possible to differentiate between drug particles and incompletely hydrated polymer fibres. The limited degree of polymer erosion in this swelling study, despite the presence of insoluble polymer fibres in the MHEC 10000 B No. 1-tablets, is ascribed to the shielded position of the tablet in the Plexiglas® device. At the reduced hydrodynamic stress the strength of the gel formed is sufficient to resist polymer erosion. Therefore diffusion controls drug release as in the case of MHPC 100000-tablets resulting in extremely low release rates for the poorly soluble drug. The concurrently performed determination of drug release from the sandwiched tablets proved that less than 10% of acetophenetidin have been released after 8 h.

The significant changes in release conditions (surface area, contact with the swelling medium, hydrodynamics) involved with sandwiching the tablets caused differences between this swelling investigation and standard dissolution tests. Thus transference of results obtained with this swelling method to performance in dissolution tests was difficult. Nevertheless, important differences in swelling behaviour related to polymer and drug characteristics could be identified with these swelling investigations.

3.4. Photomicroscopical studies

Photomicroscopy was another method tested to study the swelling of hydrocolloid tablets and to identify differences in the gel layer of tablets characterized by different drug release mechanisms.

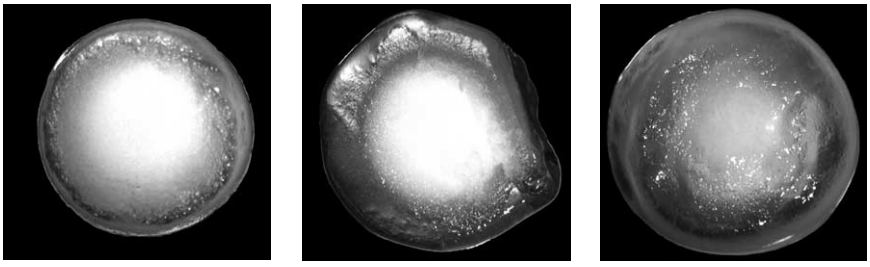
In order to study swelling under conditions similar to the ones in the dissolution test and to avoid artificial restriction of swelling to one direction, no mountings were used to fix the tablets. As gel layers of comparable thickness are formed in the axial and radial direction (Gao and Meury, 1996; Rajabi-Siahboomi et al., 1994) only the radial swelling of very thin compacts of pure polymer was investigated. To obtain sharp pictures of the swollen tablet, it was necessary to remove the axial swelling zone on the top side of the tablet by a radial cut.

3.4.1. Swelling under static conditions

The photomicrographs of tablets swollen under static conditions, displayed in Fig. 8, reveal significant differences in gel layer thickness, gel structure and polymer erosion. Pronounced swelling of MHPC 100000-tablets led to formation of a big, translucent gel body (Fig. 8a). While after 2 h of swelling a big, dry core existed, surrounded by a clear gel layer, the size of this dry core had diminished distinctly and a large gel body was formed after 6 h. As the hydration was impeded by the gel layer, it took more than 24 h, until the dry core had disappeared and a completely translucent gel body was formed.

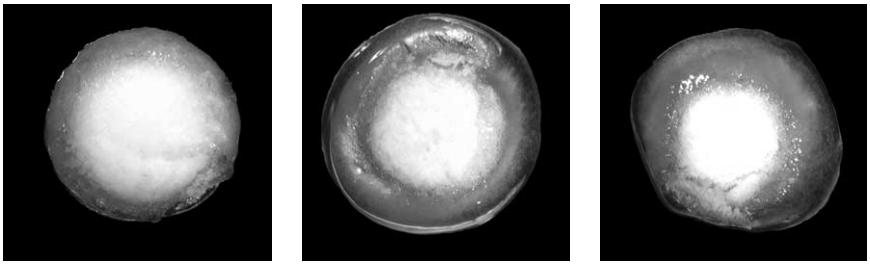
By contrast, during 2 h of swelling of MHEC 10000 B No. 1, no clear gel layer was formed. The hydrated zone visible as the dark area surrounding the white dry core was only slightly swollen and

a) MHPC 100000



2 h 4 h 6 h

b) MHEC 10000 B No. 1



2 h 4 h 6 h

c) Pharmacoat 606

2 h 4 h 6 h

Fig. 8. Photomicrographs of tablets after swelling under static conditions in deionized water.

did not have consistency of a gel but a rather crumbly texture. In the petri dish the tablet was surrounded by eroded, undissolved polymer particles. After 4 and 6 h of swelling the core was embedded in a soft, weak gel layer containing insoluble components as shown in Fig. 8b. This weak gel layer stuck to the compact when swelling was performed without agitation in the swelling medium. Only slight hydrodynamic stress was required for detachment of this swollen material.

In accordance with the results of the texture analysis, the photomicroscopic study proved that only a thin gel layer is formed during swelling of Pharmacoat tablets (Fig. 8c). Erosion of this short chain polymer was very fast. After 6 h the size of the embedding had decreased dramatically and the

dry core had disappeared. The tablets was swollen completely with many little air bubbles entrapped in the gel which were responsible for the not totally translucent appearance of the gel body. Shortly after, the tablet had dissolved completely.

3.4.2. Influence of hydrodynamics

The photomicroscopy experiments were repeated performing the swelling in the paddle apparatus at 100 rpm to evaluate the influence of hydrodynamics. Results after 2 h of swelling without and with agitation of 100 rpm are compared in Fig. 9. Susceptibility of the investigated tablets to hydrodynamics stress differs significantly: Changes in hydrodynamic conditions showed no effect on swelling of MHPC 100000-tablets due to the high stability of the gel body. Pictures of the tablet swollen under static conditions and in the dissolution bath are almost identical (Fig. 9a).

MHEC 10000 B No. 1 tablets also exhibited low susceptibility to hydrodynamic stress. Regardless of the swelling conditions, the formation of a partially hydrated zone of crumbly texture was observed (Fig. 9b). The sizes of tablets swollen for 2 h were comparable indicating a similar degree of erosion despite the differences in agitation. As described before, after swelling for 4 h in the petri dish, the tablet was surrounded by a weak gel layer. Formation of such a gel layer did not occur in the paddle apparatus. After 4 h in the dissolution bath the tablets dissolved completely. However hydrodynamic stress is not the only reason for faster polymer erosion in the dissolution bath. The significant increase in the contact area between tablet and swelling medium in the dissolution bath compared to the limited contact area of the tablet sticking to the bottom of the petri dish accelerates swelling and erosion of the tablet.

While erosion of MHEC 10000 B No. 1-tablets proved to be only moderately influenced by hydrodynamic stress, a strong influence of agitation on erosion of Pharmacoat 606-tablets was observed. Performing the swelling under static conditions, tablet size had decreased only slightly and a thin gel layer was formed after 2 h (Fig. 9c). During the same period of time in the dissolution bath at 100 rpm the tablet had almost dissolved.

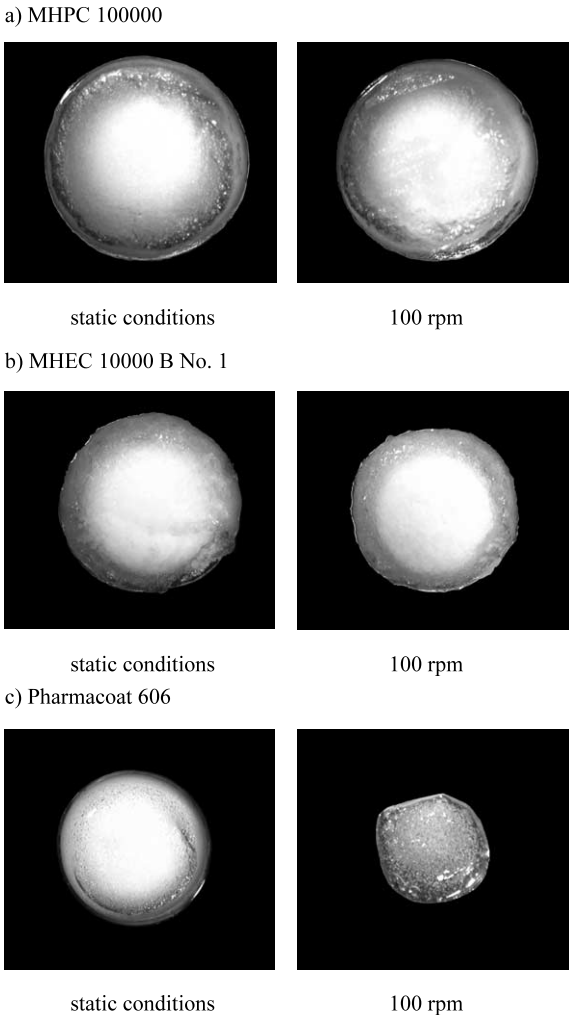


Fig. 9. Influence of hydrodynamics—Photomicrographs of tablets after swelling for 2 h in deionized water.

The strength of the gel formed after swelling of these short chain molecules is not sufficient to resist the hydrodynamic stress in the dissolution bath. Thus polymer erosion proceeds very quickly and adequate retardation of drug release can not be achieved.

The photomicroscopic documentation of the swelling process did not only give information about the gel layer thickness of swollen hydrocolloid tablets but also provided the possibility to investigate the appearance of the swelling zone and allowed visualization of undissolved particles in

the swollen layer. Photomicroscopy turned out to be a very helpful tool to prove the existence of insoluble or incompletely hydrated polymer particles in the swelling zone of tablets showing polymer particle erosion. These fibres impede the formation of a stable, translucent gel layer and lead to erosion of partially swollen polymer material even at minimal hydrodynamic stress. Furthermore, by means of photomicroscopy, it is possible to clearly show differences in susceptibility to hydrodynamics: it could be confirmed that erosion based on the low viscosity grade of the embedding material is strongly influenced by agitation while polymer particle erosion is only moderately affected by hydrodynamic stress.

4. Conclusion

This swelling study, which combined four different methods applied to characterize swelling of hydrocolloid tablets, provided insight in processes involved with hydration during the dissolution of hydrocolloid tablets. Several factors like axial expansion, gel layer thickness, swelling velocity, front movement and gel texture were determined in these investigations. As none of the four methods gives information on all these factors, a combination of different methods is recommended. Good correspondence was found in the results obtained with the different experiments, and each method contributed to a comprehensive understanding of the swelling process and its effect on drug release. The swelling investigations allow the characterization and differentiation of different mechanisms of drug release from hydrocolloid tablets and the evaluation of the influences of hydrodynamics on drug release.

Acknowledgements

We gratefully acknowledge the companies which provided the materials used in this study.

References

Bettini, R., Colombo, P., Massimo, G., Catellani, P.L., Vitali, T., 1994. Swelling and drug release in hydrogel matrices: polymer viscosity and matrix porosity effects. Eur. J. Pharm. Sci. 2, 213–219.

Bettini, R., Catellani, P.L., Santi, P., Massimo, G., Peppas, N.A., Colombo, P., 2001. Translocation of drug particles in HPMC matrix gel layer: effect of drug solubility and influence on release rate. J. Controlled Release 70, 383–391.

Colombo, P., Gazzaniga, A., Caramella, C., Conte, U., La Manna, A., 1987. In vitro programmable zero-order release drug delivery system. Acta Pharm. Technol. 33, 15–20.

Colombo, P., Bettini, R., Massimo, G., Catellani, P.L., Santi, P., Peppas, N.A., 1995. Drug diffusion front movement is important in drug release control from swellable matrix tablets. J. Pharm. Sci. 84, 991–997.

Conte, U., Colombo, P., Gazzaniga, A., Sangalli, M.E., La Manna, A., 1988. Swelling-activated drug delivery systems. Biomaterials 9, 489–493.

Ferrero, C., Munoz-Ruiz, A., Jiménez-Castellanos, M.R., 2000. Fronts movement as a useful tool for hydrophilic matrix release mechanism elucidation. Int. J. Pharm. 202, 21–28.

Freichel, O.L., Lippold, B.C., 2000. A new oral erosion controlled drug delivery system with a late burst in the release profile. Eur. J. Pharm. Biopharm. 50, 345–351.

Gao, P., Meury, R.H., 1996. Swelling of hydroxypropyl methylcellulose matrix tablets. 1. Characterization of swelling using a novel optical imaging method. J. Pharm. Sci. 85, 725–731.

Heyd, A., Kildsig, D.O., Banker, G.S., 1969. Dissolution of macromolecules I: surface phenomena associated with polymer dissolution. J. Pharm. Sci. 58, 586–588.

Ju, R.T.C., Nixon, P.R., Patel, M.V., 1995. Drug release from hydrophilic matrices. 1. New scaling laws for predicting polymer and drug release based on the polymer disentanglement concentration and the diffusion layer. J. Pharm. Sci. 84, 1455–1463.

Kim, H., Fassihi, R., 1997a. A new ternary polymeric matrix system for controlled drug delivery of highly soluble drugs: I. Diltiazem hydrochloride. Pharm. Res. 14, 1415–1421.

Kim, H., Fassihi, R., 1997b. Application of a binary polymer system in drug release rate modulation. 1. Characterization of release mechanism. J. Pharm. Sci. 86, 316–322.

Konrad, R., Christ, A., Zessin, G., Cobet, U., 1998. The use of ultrasound and penetrometer to characterize the advancement of swelling and eroding fronts in HPMC matrices. Int. J. Pharm. 163, 123–131.

Le Néel, T., Morlet-Renaud, C., Lipart, C., Gouyette, A., Truchaud, A., Merle, C., 1997. Image analysis as a new technique for the study of water uptake in tablets. S.T.P. Pharmac. Sci. 7, 117–122.

Lindner, W.D., Lippold, B.C., 1995. Drug release from hydrocolloid embeddings with high or low susceptibility to hydrodynamic stress. Pharm. Res. 12, 1781–1785.

Martini, L.G.A., Collett, J.H., Attwood, D., 1995. The release of 5-Fluorouracil from a swellable matrix of a triblock

copolymer of ε-caprolactone and ethylene oxide. Pharm. Res. 12, 1786–1790.

Mitchell, K., Ford, J.L., Armstrong, D.J., Elliott, P.N.C., Hogan, J.E., Rostron, C., 1993a. The influence of substitution type on the performance of methylcellulose and hydroxypropylmethylcellulose in gels and matrices. Int. J. Pharm. 100, 143–154.

Mitchell, K., Ford, J.L., Armstrong, D.J., Elliott, P.N.C., Hogan, J.E., Rostron, C., 1993b. The influence of drugs on the properties of gels and swelling characteristics of matrices containing methylcellulose or hydroxypropylmethylcellulose. Int. J. Pharm. 100, 165–173.

Panomsuk, S.P., Hatanaka, T., Aiba, T., Katayama, K., Koizumi, T., 1995. A study of the hydrophilic cellulose matrix: effect of indomethacin and a water-soluble additive on swelling properties. Int. J. Pharm. 126, 147–153.

Papadimitriou, L., Buckton, G., Efentakis, M., 1993. Probing the mechanism of swelling of hydroxypropylmethylcellulose matrices. Int. J. Pharm. 98, 57–62.

Pham, A.T., Lee, P.I., 1994. Probing the mechanism of drug release of hydroxypropylmethyl cellulose matrices. Pharm. Res. 11, 1379–1384.

Rajabi-Siahboomi, A.R., Bowtell, R.W., Mansfield, P., Henderson, A., Davies, M.C., Melia, C.D., 1994. Structure and behaviour in hydrophilic matrix sustained release dosage forms: 2. NMR-imaging studies of dimensional changes in the gel layer and core of HPMC tablets undergoing hydration. J. Controlled Release 31, 121–128.

Stawitz, J., Kage, M.P., 1959. Über die Quellungsstadien der wasserlöslichen Celluloseäther und die übermolekulare Struktur der Cellulose. Das Papier 13, 567–572.

Sujja-areevath, J., Munday, D.L., Cox, P.J., Khan, K.A., 1998. Relationship between swelling, erosion and drug release in hydrophilic natural gum mini-matrix formulations. Eur. J. Pharm. Sci. 6, 207–217.

Talukdar, M.M., Kinget, R., 1995. Swelling and drug release behaviour of xanthan gum matrix tablet. Int. J. Pharm. 120, 63–72.

Talukdar, M.M., Rombaut, P., Kinget, R., 1998. The release mechanism of an oral controlled-release delivery system for indomethacin. Pharm. Dev. Technol. 3, 1–6.

Ueberreiter, K., 1968. The solution process. In: Crank, J., Park, G.S. (Eds.), Diffusion in Polymers. Academic Press, New York, pp. 219–257.

Yang, L., Johnson, B., Fassihi, R., 1998. Determination of continuous changes in the gel layer thickness of poly (ethylene oxide) and HPMC tablets undergoing hydration: a texture analysis study. Pharm. Res. 15, 1902–1906.

Zuleger, S., Lippold, B.C., 2001. Polymer particle erosion controlling drug release. I. Factors influencing drug release and characterization of the release mechanism. Int. J. Pharm. 217, 139–152.