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## Surfactants modify the release from tablets made of hydrophobically modified poly (acrylic acid)<sup>☆</sup>

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### ABSTRACT

Many novel pharmaceutically active substances are characterized by a high hydrophobicity and a low water solubility, which present challenges for their delivery as drugs. Tablets made from cross-linked hydrophobically modified poly (acrylic acid) (CLHMPAA), commercially available as Pemulen<sup>TM</sup>, have previously shown promising abilities to control the release of hydrophobic model substances. This study further investigates the possibility to use CLHMPAA in tablet formulations using ibuprofen as a model substance. Furthermore, surfactants were added to the dissolution medium in order to simulate the presence of bile salts in the intestine.

The release of ibuprofen is strongly affected by the presence of surfactant and/or buffer in the dissolution medium, which affect both the behaviour of CLHMPAA and the swelling of the gel layer that surrounds the disintegrating tablets. Two mechanisms of tablet disintegration were observed under shear, namely conventional dissolution of a soluble tablet matrix and erosion of swollen insoluble gel particles from the tablet. The effects of surfactant in the surrounding medium can be circumvented by addition of surfactant to the tablet. With added surfactant, tablets that may be unsusceptible to the differences in bile salt level between fasted or fed states have been produced, thus addressing a central problem in controlled delivery of hydrophobic drugs. In other words CLHMPAA is a potential candidate to be used in tablet formulations for controlled release with poorly soluble drugs.

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### 1. Introduction

A large amount of the novel pharmaceutically active substances can be characterized by a high hydrophobicity and a poor water solubility [1]. Various techniques to enhance the solubility or the dissolution of poorly water soluble active substances have been developed and include using solid dispersions [2–4], particle size reduction [5–7], amorphous substances [8] and solubilisation using surfactants [9] or complexes with, e.g., cyclodextrins [10]. However, there is still a pronounced need to develop formulation concepts that allow for controlled release of poorly soluble compounds. A common problem during formulation of a hydrophobic drug is also the differences in the intestinal fluid between fasted or fed state, which has been

shown to affect the dissolution [11,12]. Today there are few strategies that address these problematic food effects; examples of formulations of poorly soluble drugs that circumvent food effects include nano-particulate systems, e.g. with itraconazole [13,14]. In addition, lipids have been incorporated in the formulation to trigger fed state response [15–17], which then increased the solubility of the drug in the intestine and gave a higher bioavailability. Nevertheless, it is of importance that food effects are evaluated during development of new formulations.

Cross-linked poly (acrylic acid) (CLPAA), commercially available as Carbopol<sup>®</sup>, has been studied extensively for use in pharmaceutical formulations, frequently because of its bioadhesive properties and its ability to form gels. Much of the work has focused on its use as bioadhesive tablets [18–25], nasal applications [26–30], ocular delivery [31–33] and suppositories [34]. There has also been a considerable effort studying the application of CLPAA in tablets [35–38], which is approved for oral formulations. In this work the Carbopol used is Carbopol<sup>®</sup> 974P NF, which consist of poly (acrylic acid), cross-linked with allylpentaerythritol.

Pemulen<sup>TM</sup>, a commercially available cross-linked and hydrophobically modified PAA, (CLHMPAA) has been far less studied, mainly

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because it currently lacks a regulatory approval to be used in oral formulations. Most of the studies have focused on topical formulations [39] but some studies have evaluated its use in tablets [35,40,41]. Furthermore, a previous study showed that CLHMPAA could yield a way of controlling the release of poorly soluble compounds from tablet formulations [40]. The substance was assumed to be incorporated in hydrophobic domains formed by self-assembly of the hydrophobic substituents, the “hydrophobes”, of the polymer. The release was sustained via interactions between the hydrophobic substance and the hydrophobes of the polymer, which resulted in an almost ideal zero order release, which was not seen for a non-modified CLPAA. In this study, Pemulen™ TR2 NF is used. This polymer consists of poly (acrylic acid), cross-linked with allylpentaerytritol and is hydrophobically modified with grafted C10–C30 alkyl-chains.

Paulsson and Edsman [42–44] evaluated the release from CLPAA and CLHMPAA polymer gels, and saw that a higher hydrophobicity of the drug resulted in a higher probability of interaction with the hydrophobes on the polymer. The interaction between the two could decrease the rate of diffusion of the drug through the gel matrix, thus prolonging the release. They also saw that if surfactants were added to the system, the drug molecules would partition into the surfactant micelles to additionally slow down their diffusion. This suggests that the release from tablets made from CLHMPAAs could be affected by the presence of surfactant and provides a possible way to tune the release from tablets made of CLHMPAA. On the other hand, pronounced surfactant sensitivity could potentially aggravate problems with differences in drug absorption between the fasted and fed states.

The dissolution process for swellable matrix tablets is generally considered to involve solvent penetration, gel formation, swelling and disentanglement of the polymer chains [45,46]. Three different moving fronts have been established, i.e. the swelling front, the diffusion front and the erosion front, which determine the release rate. These fronts have been thoroughly studied [47–49] and the principles are summarized in a very recent review [50]. Recent studies on model tablets have shown that the rate of release of the polymer into the surrounding solution (the dissolution medium) depends on the viscosity of the so-called “gel layer” (the gelatinous semi-dilute polymer solution that surrounds the tablet) at the boundary to the dissolution medium [47,51]. It was shown that by altering the molecular weight of the polymer, and hence its efficiency to viscosify the gel layer, the dissolution rate of the polymer could be altered. The gel layer is generally considered to have two functions: it slows down the dissolution of the tablet itself and it works as a transport barrier for the drug. An increased thickness of the gel layer results in a slower dissolution of the tablet and a longer way for the drug to diffuse in order to be released, thus a slower drug release. In solutions of hydrophobically modified (HM) polymers the viscosity can be altered by addition of surfactant [52,53]. Moreover, added surfactant can solubilise such HM-polymers that, owing to extensive hydrophobic association, are not soluble in water [52,54]. These facts indicate that the release from HM-polymer tablets can be altered by the presence of surfactant.

This study further investigates the possibility to use CLHMPAA in tablet formulations manufactured by pharmaceutically relevant unit processes. Ibuprofen is used as a model drug substance due to its hydrophobic properties, in order to study the effects from hydrophobic interactions. Ibuprofen is not considered (during our experimental conditions) poorly soluble, which circumvents solubility issues.

The focus of this study is on the effects of adding surfactants, similar to the differences in the intestinal fluid between fasted or fed states. In the biological system the tablets might be affected by surface active compounds such as bile salts. In this work we have examined the effects from addition of different types of surfactants, which either are allowed for oral use or are endogenous substance from bile. A common model surfactant, sodium dodecyl sulfate (SDS), was chosen to further examine the general effects of surface active compounds.

**Table 1**

Compositions of tablets used in this study. The SDS content was varied and when SDS was added the corresponding amount of lactose (in weight percent) was removed. The amount of ibuprofen was chosen from an experimental perspective in order to the match detections levels of the UV spectrophotometer.

Ingredient	Amount (wt%)
Polymer	30
Ibuprofen	10
Lactose	58/56.75/54.25/50.5/45.5/33
Talc	1
Magnesium stearate	1
SDS	0/1.25/3.75/7.5/12.5/25

SDS is a well-known and studied anionic surfactant, which is also approved for oral formulations. Furthermore, SDS is also included in the tablet formulation in some experiments to elucidate whether this can be used to alter the drug release. The rheology of semi-dilute CLHMPAA solutions, and the solubility of the polymer in the various dissolution media, has also been studied to gain additional molecular insight into the release mechanisms.

## 2. Materials and methods

### 2.1. Materials

Pemulen™ TR2 NF (lot no. CC11MCU893) and Carbopol® 974P NF (lot no. CC23NAB431) were kindly provided by Lubrizol Chemicals. According to the supplier, both polymers consist of poly (acrylic acid), cross-linked with allylpentaerytritol, and contain 52–62% (Pemulen) or 56–68% (Carbopol) of COOH groups. Pemulen™ is also hydrophobically modified with grafted C10–C30 alkyl-chains via ester bonds. From recorded <sup>1</sup>H NMR intensities of the terminal methyl groups of the alkyl grafts we deduce that a 1 wt% CLHMPAA solution contains ca. 4 mM of alkyl grafts (hydrophobes).

Sodium dodecyl sulfate (SDS) was purchased from VWR International (Sweden), lot no. 8Z0007176. In addition, Tween80 (lot no. 93781) and crude bile salts (lot no. BCBJ8214V) were acquired from Fluka. The crude bile salt was a 50/50 mixture between sodium taurocholate and sodium deoxycholate. Ibuprofen sodium salt (lot nos. 038K0755 and 87H0764) was purchased from Sigma Aldrich and used as delivered. The CMC for SDS is 8.3 mM in pure water [55], and with a tensiometer and a de Noüy ring, we determined the CMC to 1.8 mM at 37 °C in 0.1 M phosphate buffered solution, pH 7.2. The CMC for Tween80 is equal to 0.02 mM at 25 °C [56,57]. Bile salts have poorly defined CMC values, which differs between different environments, nevertheless it is estimated to be between 0.5 and 2 g/L [58,59].

Lactose, talc and magnesium stearate were of analytical grade. For granulation fluid a (70:30) mixture of ethanol (99.5%) and 0.001 M aqueous HCl was used.

### 2.2. Tablet preparation

Tablets were prepared with compositions as specified in Table 1, and the manufacturing procedure was the same for all compositions. First, the dry ingredients, lactose, polymer and ibuprofen (and SDS, where applicable) were mixed in an intensive mixer (Kitchen Aid), for 5 min. The granulation process started with gently spraying granulation fluid over the powder, with interruptions to allow the fluid to absorb. The procedure was continued until the desired properties of the granulation were achieved. The granulation was then sieved through a 2 mm sieve, and if the particle size was too large, a food-processor was used to further reduce it. The granulation was then dried in an oven at 50 °C overnight and was afterwards sieved again through a 2 mm sieve. The dried granulation was mixed with talc and magnesium stearate in a cone blender for 2 min after each addition.

The tablets were manufactured with a single-punch tableting machine, Diaf (Denmark), to a weight around 400 mg. Appropriate settings were applied to ensure a good hardness and weight of the tablets. Hardness and friability were measured according to US Pharmacopeia methods. All tablets achieved a hardness over 5 kp and a friability less than 1%, except for those containing high amounts of SDS ( $\geq 10$  wt%), which were too soft (hardness  $< 5$  kp) and had a poor friability ( $> 1\%$ ).

### 2.3. Dissolution experiments

Dissolution experiments were carried out at 37 °C in a USP dissolution apparatus II (Prolabo Intelligent dissolution tester Novakemilab, Sweden) with a paddle speed of 100 rpm. Samples were continuously withdrawn and transferred by means of a pump to a spectrophotometer (Cary 50 Bio UV–visible, Varian, Australia) which measured the ibuprofen concentration in the vessels as the absorption at  $\lambda = 222$  nm. From the measured UV absorbance the concentration of ibuprofen and, hence, the fraction released in the dissolution medium, could be determined.

Each USP vessel was filled with 800 mL of dissolution medium. The media used were 0.1 M phosphate buffered solution, pH 7.2, and water deionised in a Milli-Q water apparatus. The pH of the water solution was not monitored during dissolution nevertheless it is likely that pH will change during dissolution. Tween80 and bile salts were added to buffered solution in the following concentrations 10 g/L and 7.14 g/L respectively (similar to the conditions in the intestine at fed state [60]). For SDS varying amounts were added, yielding concentrations between 0–10 mM (phosphate buffered solution) and 0–20 mM (Milli-Q water). The amount of SDS added to the tablets represents a concentration in the bath of maximum 0.4 mM, which is below the CMC for SDS. Tablets were weighed prior to the start of the experiments. From this the total amount of ibuprofen in a tablet was calculated.

For tablets dissolving in Tween80 and crude bile salts the absorption from the spectrophotometer could not be used due to the large absorbance from the solutions. Instead aliquots ( $V = 1$  mL) were manually withdrawn from each vessel at specified time intervals and analyzed with HPLC (HP Series 1050), using a flow of 0.4 mL/min on a reversed phase Acclaim RLSC C18 2.2  $\mu$ m, 120 Å, 2.1  $\times$  50 mm<sup>2</sup> column. The HPLC detected the ibuprofen as the UV absorption at  $\lambda = 222$  nm. For samples containing Tween80, an isocratic solution with 40% ACN and 60% water with 0.1% acetic acid was used. Samples containing bile salts were mixed with AcN prior to analysis (50/50 mixture) and analysed with an isocratic solution of 35% ACN and 65% water with 0.1% acetic acid.

$$\% \text{ Release} = \frac{(C_{\text{ibu}} \times (V_0 - V_s \times n_s) + \sum^{ns} (V_s \times C_s))}{m_{\text{ibu, tablet}}} \quad (1)$$

The released amount (%released) was calculated according to Eq. 2.5.1, where the concentration of ibuprofen according to the HPLC is given by  $C_{\text{ibu}}$  and the initial volume of the vessel is  $V_0 (= 800$  mL).  $V_s$  and  $C_s$  denote the volume ( $= 1$  mL) and the concentration in the samples respectively and the number of samples is denoted  $n_s$ . The amount of ibuprofen in the tablets is given by  $m_{\text{ibu, tablet}}$ . All experiments, if not stated otherwise, were performed at least two times in order to validate reproducibility.

### 2.4. Rheology

#### 2.4.1. Sample preparation

Rheology experiments were conducted on systems of 1 wt% CLHMPAA in either deionised water or in 0.1 M phosphate buffered solution at varying concentrations of added SDS. The procedure was the same for both types of dissolution media. A stock SDS solution was diluted to the desired concentration, and then CLHMPAA was added to give 1 wt% concentration of polymer. For samples prepared in buffered

solution, 2 M NaOH-solution was used to adjust the pH to 7, after addition of polymer. Care was taken to ensure that the same amount of NaOH was added to each sample, yielding equal ionic strength. The pH of each sample was confirmed prior to analysis. After addition of polymer all samples were agitated and put on a tilt table until analysed. The samples were also repeatedly mixed manually with a spatula and centrifuged directly afterwards. All samples were mixed for 1 week to ensure that equilibrium had been reached. Prior to analysis, the samples were centrifuged to eliminate air bubbles formed during the mixing. All samples were prepared in triplicate.

#### 2.4.2. Oscillatory rheology measurements

The measurements were carried out on a controlled stress rheometer (StressTech IMP5040, Reologica, Viscotech). Cone-plate symmetry with a diameter of 40 mm was used and the temperature was set to 37 °C. All experiments started with equilibration of the sample for 60 s, followed by a stress sweep at 1 Hz between 0.2 and 200 Pa in 50 logarithmic steps. Directly afterwards a frequency sweep between 0.005 and 10 Hz at a constant stress of 1 Pa was performed. The frequency-dependent complex viscosity ( $\eta^*$ ) was obtained from

$$\eta^* = \frac{G^*}{\omega} = \frac{[(G') + (G'')^2]^{1/2}}{\omega} \quad (2)$$

where  $G'$  is the storage modulus,  $G''$  is the loss modulus and  $\omega$  is the frequency of oscillation.

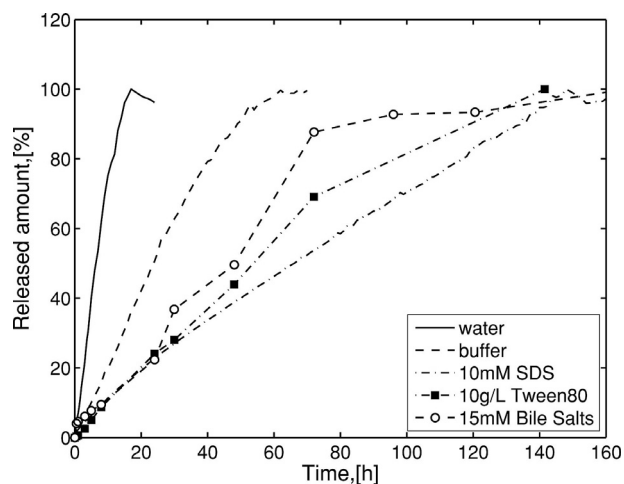
## 3. Results

### 3.1. Dissolution of HMPAA tablets in different media

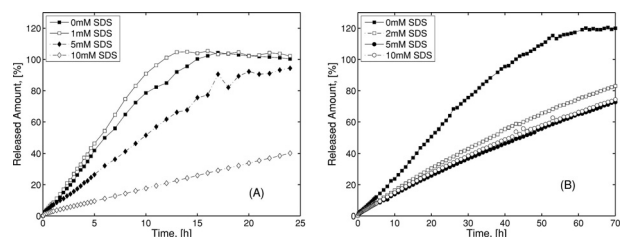
The release of ibuprofen from tablets made from CLHMPAA is generally characterized by a slow and linear release profile (Figs. 1 and 2) throughout the dissolution process and the release was faster in water than in buffered solution. Addition of surfactant to the dissolution medium slowed down the release further, however retaining the linear release. The different surfactants used reduce the release rate in a similar manner and to a similar extent, in Fig. 1, all surfactants are added in concentrations over the CMC. Examining the dissolving tablets visually shows that the tablets form larger gel layer upon addition of buffer and surfactants. However, upon addition of bile salts a clear gel layer is not formed, instead the tablets were cloudy nonetheless swollen. Moreover studies have been performed, where the release of lactose from the tablets has been quantified using a new analytical method, which will be published soon. These show that the lactose (a hydrophilic model substance) is quickly released from the tablet, and the release is less affected by the presence of surfactants.

Examining the release rate for different concentrations of SDS there is a discrepancy between the buffered solution and water below concentrations of 7 mM (Fig. 2). On the other hand, above 7 mM SDS, the rate was similar and very slow in both media and here the tablets were not fully dissolved after 67 h. In some cases the tablets appeared to release more than 100% when fully dissolved; this is most likely due to solvent evaporation during the extended dissolution time. The amount of polymer in the tablets is high in these experiments; a lowering of the polymer concentration will increase the release rate but also make the experiments sensitive to polymer concentration. Thus all the work done here is performed at a polymer concentration high enough to avoid this sensitivity.

In order to compare the release rates for different concentrations of SDS in the various dissolution media, the release rate at 20% released amount (R-20) was evaluated from each release profile by a linear fit to 10 data points centred around 20% released amount. The choice of 20% is somewhat arbitrary, but owing to a very slow release, a few experiments had reached less than 50% of released ibuprofen at termination, see Fig. 2. The R-20 data are collected in



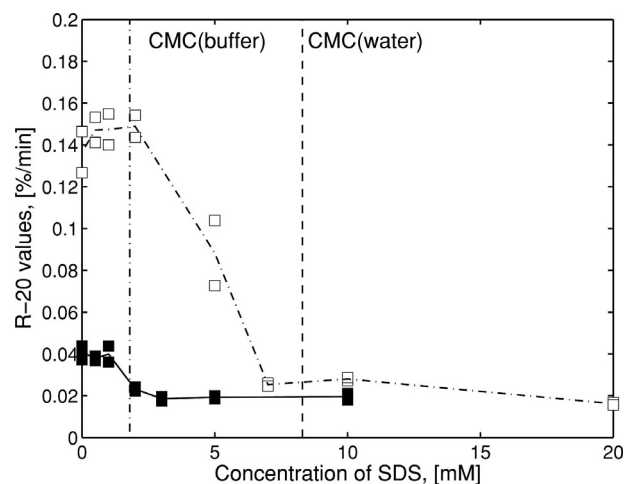
**Fig. 1.** Release of ibuprofen from CLHMPAA tablets into different solutions containing pure water and buffer (0.1 M, pH = 7.2) as well as buffer with added surfactants (SDS, Tween80 and bile salts) as noted in the figure. Each dataset represents one measurement and is shown as representative data. The released amount is normalized against the released amount for fully dissolved tablets, i.e. released amount at  $t_{\text{end}} = 100\%$ . Lines without data points represent measurements every 20th minute up to 6 h and after that measurement each hour.



**Fig. 2.** Release of ibuprofen from CLHMPAA tablets in water (A) and buffered solution (0.1 M, pH = 7.2, B) without and with added SDS at the indicated concentrations. The release is compared to the release of ibuprofen without addition of surfactant (0 mM SDS). Each dataset represents one measurement and is shown as representative data.

**Fig. 3,** which clearly illustrates the effects of the buffer and/or surfactant added to the dissolution media. In either medium, the release of ibuprofen was hardly affected by the presence of surfactant in a low-concentration plateau region, below a concentration of ca. 2–3 mM SDS. Above the latter concentration, the ibuprofen-release rate decreased rapidly with added SDS until a second high-concentration plateau was reached. The concentration of SDS at the onset of the high-concentration plateau coincides quite well with the critical micelle concentration, CMC, of SDS in both buffered solution and pure water. There was a strong effect of the buffer at zero and low concentrations of SDS, whereas the release rate at the high-concentration plateau was insensitive to the presence of the buffer.

The tablets were observed visually during dissolution in the medium with SDS and sample tablets were also taken out of the dissolution medium. All dissolving tablets were surrounded by transparent gel layers and in the middle of the tablet a white “core” could be seen; closer examination showed that this core was not solid but rather had a sponge-like texture. The gel layers of the tablets generally increased in thickness with increasing SDS concentration, but large differences in the dissolution behaviour in water and buffered solution were observed at low SDS concentrations. In water a clear but very thin gel layer developed and the tablet had a rough surface from which semi-swollen particles, visible to the naked eye, eroded during dissolution. The latter feature disappeared when the SDS concentration had reached the high-concentration plateau; here a thick, smooth gel layer developed. In buffered solution, a sizeable gel layer



**Fig. 3.** Slopes of ibuprofen release profiles at 20% released amount for tablets dissolving in buffered solutions (0.1 M, pH = 7.2, filled) and water (open) at varying concentrations of SDS added to the dissolution media. Each symbol represents one measurement and the lines are drawn through the average values. Vertical lines show the critical micelle concentrations of SDS in buffered solution and in pure water.

developed already without SDS, and no eroding particles were detected visually at any SDS concentration.

### 3.2. Physico-chemical behaviour of CLHMPAA in different media

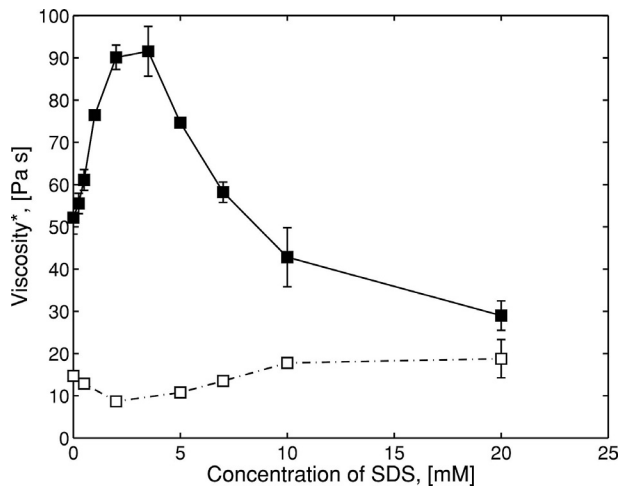
In order to better understand the dissolution and drug release behaviour in the various systems, we performed additional studies of the physico-chemical behaviour of CLHMPAA in the various media. One series of simple experiments addressed the solubility of CLHMPAA. From a physico-chemical point of view, Pemulen™ consists of huge cross-linked polymer molecules that may either dissolve in, or phase separate from, a given solvent. To test this we made up a series of dilute mixtures of CLHMPAA in the various dissolution media. The concentration (0.015 wt%) of these dilute mixtures was chosen to be equal to the concentration at complete dissolution in the dissolution experiments. The samples were then agitated and put on a tilt-table for a period of 1 week and were subsequently subjected to centrifugation (1 h at 5000 rpm).

CLHMPAA did not dissolve in pure water, but formed a cloudy dispersion of swollen gel particles that could be separated by centrifugation. On addition of 1–2 mM SDS, the cloudiness disappeared, but centrifugation still resulted in the separation of the polymer, this time as a clear, gelatinous bottom phase. At and above 5 mM SDS in water, finally, the polymer appeared totally dissolved and no polymer separated out on centrifugation. In buffered solutions clear samples were obtained both with and without SDS, but centrifugation resulted in the separation of a clear, polymer-rich bottom phase at SDS concentrations at or below 2 mM. Above 2 mM SDS in buffered solution, CLHMPAA was again found to be soluble.

We also measured the viscosity of CLHMPAA in the various media. The measurements were done at higher concentrations (1 wt%) of the polymer, to probe conditions that should be more relevant for the gel layers surrounding the tablets. Since the concentration of carboxylic acid groups from the polymer was comparable to the concentration of phosphate buffer in the buffered systems, the buffer alone did not succeed in maintaining a pH around 7. Therefore, the pH for these systems was adjusted to  $7 \pm 0.2$  by addition of 2 M NaOH, again to mimic the situation in a gel layer exposed to a large reservoir of buffer at pH 7.2. The resulting systems were in all cases highly viscous.

**Fig. 4** shows the complex viscosities at 0.2 Hz of 1 wt% CLHMPAA in water and buffered solution plotted against the concentration of added SDS. In both media, the viscosity varied significantly with





**Fig. 4.** Complex viscosity\* ( $\eta^*$ ) (at 0.2 Hz) for 1 wt% CLHMPAA in buffered solution ((0.1 M, pH = 7.2, pH = 7) (filled) and water (open) with increasing SDS concentration. Error bars indicate the standard deviation ( $n = 3$ ).

the SDS concentration, clearly revealing an interaction between SDS and CLHMPAA. Mixtures prepared in water solution consistently displayed a lower viscosity compared to the buffered systems, but the two sets of results approach each other at high surfactant concentrations.

### 3.3. Additional dissolution experiments

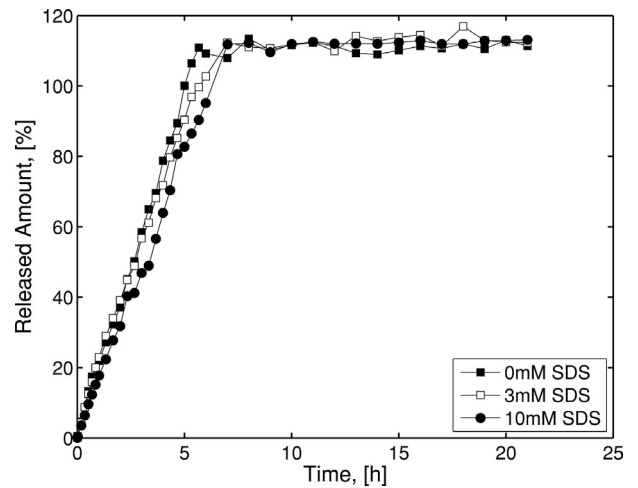
#### 3.3.1. Tablets of non-modified cross-linked PAA

For reference, we also studied the release of ibuprofen into buffered solution from dissolving tablets made from non-modified CLPAA, see Fig. 5. The latter behaved differently from those made from CLHMPAA. The CLPAA tablets developed a very thin gel layer and disintegrated faster, with small gel particles eroding continuously from the tablets. These tablets were fully dissolved after ca. 340 min. Visually there was no obvious effect of SDS added in the dissolution medium on the size and shape of the gel layer, nor on the erosion of gel particles. The non-modified tablets also gave a faster release of ibuprofen, compared to the CLHMPAA tablets, but the release was still linear. Although the effects of added SDS on the release are largely lost for tablets without hydrophobes, closer examination reveals a small decrease in the release rate on addition of surfactant to the release medium.

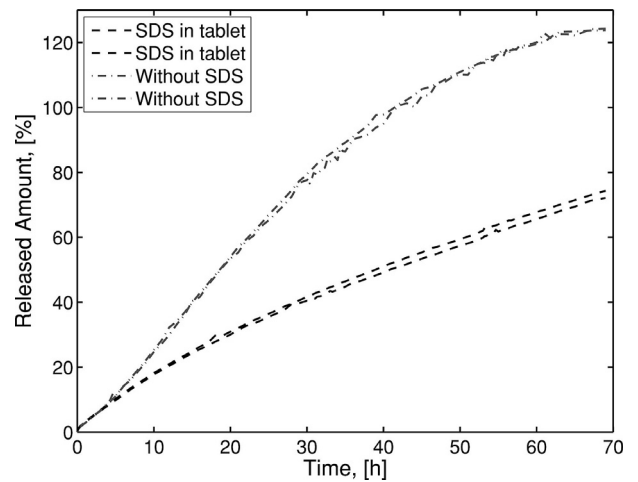
#### 3.3.2. CLHMPAA tablets containing added SDS

In a final set of experiments, we studied the dissolution and release from CLHMPAA tablets that also contained SDS. Small additions of SDS to the tablets did not result in large changes in tablet properties during production, except an increased sensitivity during solvent addition during granulation, and tablets with satisfying properties were achieved. However, if the amount of SDS in the tablet was increased above 7.5 wt%, a soapy granulation was obtained, which with our equipment resulted in poor tablets with a low hardness and poor friability. In all cases the total amount of SDS added to the tablets was lower than the lowest total amount of SDS that was added to the dissolution media in the previous set of experiments.

The effect of adding SDS to the tablet on the release of ibuprofen into buffered solution was similar to the effect of adding surfactant to the release medium. A slow linear release was observed that extended over days, see Fig. 6. Adding increasing amounts of SDS to the tablet decreased the release rate, until a point where the tablet and granulation properties became unsatisfying. SDS added to the tablet increased the thickness of the gel layer, again similar to the effect of adding SDS to the dissolution medium.



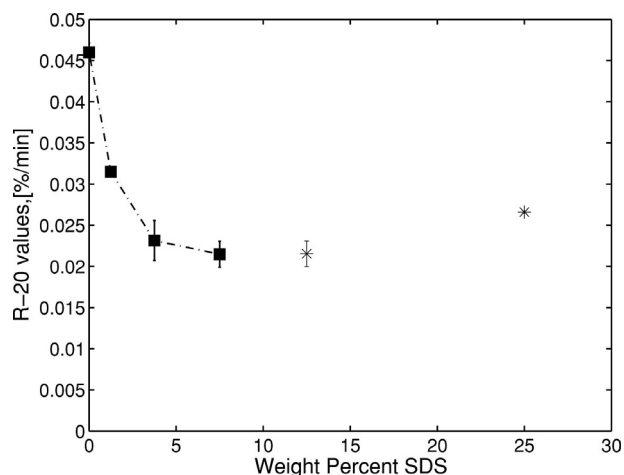
**Fig. 5.** The release of ibuprofen from CLPAA tablets in buffered solution (0.1 M, pH = 7.2) containing pure buffer (0 mM SDS), 3 mM and 10 mM SDS. Each dataset represents one measurement and is shown as representative data.



**Fig. 6.** The release of ibuprofen in buffered solution (0.1 M, pH = 7.2) from tablets of CLHMPAA containing 7.5 wt% SDS (SDS in tablet), compared with tablets with no SDS (without SDS). The lines represent repeat measurements on different tablets performed at the same time and illustrate the experimental reproducibility. Lines represent measurements every 20th minute up to 6 h and after that measurement each hour.

Further investigating the effects of surfactants on the release, SDS was added also to the medium during the dissolution of SDS-loaded tablets. Two different concentrations of SDS in the buffered solutions were used, one at the low-concentration plateau seen in Fig. 3 and one at the high-concentration plateau. As illustrated in Fig. 7, there were no apparent effects on the ibuprofen release from the SDS-loaded tablets of adding SDS to the dissolution medium: the already slow release was retained.

To further investigate surfactant effects the release from CLHMPMPAA tablets with SDS in media containing Tween or Bile salt was investigated. As can be seen the profile is quite similar as for the pure buffer or SDS media. The release could be somewhat slower but one should keep in mind that these experiments were performed with another batch of tablets and using a different analytical method. It has been observed that the UV analyses usually give a final amount released that is slightly above 100% but that the HPLC measurements normally only give 100% of release.



**Fig. 7.** R-20 values in buffered solution (0.1 M, pH = 7.2) for tablets of CLHMPAA that contained indicated amounts of added SDS. Points marked with an asterix represent tablets that did not fulfil the requirements regarding hardness and friability. Error bars represent the standard deviation of the measurements ( $n > 2$ ).

#### 4. Discussion

The aim of the present study was to elucidate the consequences of hydrophobic modification on the behaviour of PAA-based tablets in different media. Our major findings may be summarised as follows. (1) Hydrophobic modification generally gives rise to a slower ibuprofen release from a CLPAA-based tablet, and to a marked surfactant sensitivity of the release. (2) Added surfactant, either dissolved in the medium or incorporated in the tablet, makes the release even slower until a plateau is reached at high surfactant levels. (3) With surfactant incorporated in the tablet, the ibuprofen release becomes insensitive to surfactant added in the dissolution medium. We will now attempt to understand these features in the light of prior knowledge as well as the additional observations made in this study.

Established knowledge on aqueous mixtures of HM-polymers and surfactants may be summarized as follows [54]: the hydrophobes of HM-polymers typically self-associate in water, leading to a high viscosity of their semi-dilute aqueous solutions, but also to a decreased water solubility. Charged HM-polymers are more soluble than uncharged ones, other factors being equal. When surfactant is added to a HM-polymer in water, the surfactant molecules enter into the aggregates of the hydrophobes, forming mixed micelles of hydrophobes and surfactant molecules. At low fractions of incorporated surfactant molecules, their effect is mainly to strengthen the pre-existing hydrophobic association between the polymer molecules. With increasing levels of surfactant, however, the number of mixed micelles increases and, eventually, all hydrophobic cross-linking is lost as the polymer hydrophobes are solubilised in the abundant surfactant micelles.

In Fig. 3, the rheology of 1 wt% CLHMPAA in buffered solutions at pH 7 illustrates the typical response of a water-soluble HM-polymer to added surfactant [52–54]: at low levels, the viscosity increases (strengthening of the hydrophobic association) but eventually, the viscosity decreases again, owing to a dissolution of the hydrophobic polymer–polymer association. The water solubility of the HMPAA is here achieved by a large fraction of charged carboxylate groups at pH 7. In unbuffered water, on the other hand, the initial rheological response of the essentially uncharged CLHMPAA to added surfactant is typical of a system with water-swollen, but insoluble, hydrophobically modified polymer aggregates. Here, the initial strengthening of the hydrophobic association leads to a de-swelling of the polymer–surfactant aggregates and, hence, a decrease in viscosity. At high levels

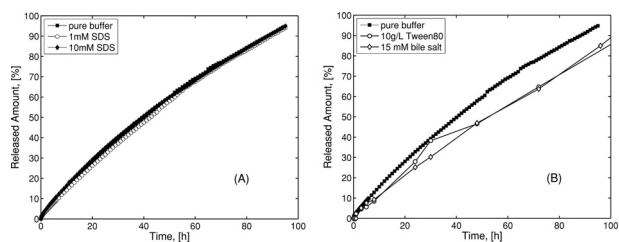
of surfactant, solubilisation of the hydrophobes in the surfactant micelles make the CLHMPAA/SDS aggregates soluble in water both with and without buffer.

We note that the mixtures investigated by rheology in Fig. 4 are not directly comparable to the dissolving tablets, since the latter systems are connected to a large reservoir of surfactant and buffer. Owing to the binding of surfactant to the HMPAA hydrophobes, the total concentration of surfactant in the outer part of a gel layer surrounding a tablet may be substantially higher than the concentration in the surrounding reservoir. On the other hand, our simple solubility tests, which were made in dilute systems, should be directly comparable to the tablet dissolution experiments. In the solubility tests, we found that both in water and in buffered solution, a complete dissolution of CLHMPAA required surfactant concentrations of the order of the surfactant CMC or higher. We also saw that the CLHMPAA-rich phase that separated out at zero or low levels of surfactant was much more swollen in buffer than in unbuffered water, a difference that we attribute to the difference in polymer charge.

The varying water solubility of HMPAA and its complexes with SDS, and the varying water uptake of those complexes that separate out of the solution, should have profound consequences for the disintegration of the tablets and the drug release. For dissolution media at high surfactant concentrations we have the common case of a soluble polymer that can swell indefinitely in the dissolution medium. The situation should then be similar to, e.g., poly (ethylene oxide) tablets dissolving in water, which have been studied in detail [47,51]. For the latter systems, it was concluded that the disintegration of the tablets was governed by the viscosifying efficiency of the polymer. For the very viscosifying HMPAA studied here (see Fig. 4), a thick gel layer develops and tablet disintegration and drug release become very slow. At high surfactant concentrations, the observed plateau release rate (see Fig. 3) then suggests that the viscosity of the system has become insensitive to further surfactant addition. This is indeed expected when the concentration of surfactant in the medium has reached CMC; then free micelles form, the surfactant monomer concentration remains approximately constant, and there is little additional surfactant binding to the complex.

At low surfactant concentrations, CLHMPAA is not soluble in the investigated media, and this means that the gel layer around the tablet can only swell until it reaches the composition of the polymer-rich phase that would separate out at equilibrium when polymer is added to the same medium. When such a gel layer is subjected to shear, pieces of the swollen but insoluble gel layer will be sheared off, as was indeed observed in the release experiments. The erosion of small gel particles not only speeds up the disintegration of the tablet itself, but also the release of the drug, since the drug release from many small gel particles, with a large specific surface area, is much more rapid than the release from a single macroscopic tablet. A comparison between surfactant-free water and buffered solution as dissolution media show that the maximum degree of swelling of the concentrated phase is also important for the tablet disintegration and the drug release. In the buffer the PAA chains are partly charged and the maximum swelling is larger, compared to the situation in unbuffered water. This results in a thicker gel layer in buffered solution, leading to a less efficient disintegration of the tablet by shear (less polymer is removed per unit time), and a slower drug release.

An alternative way to produce soluble HM-polymer/surfactant complexes is to incorporate a sufficiently high level of surfactant in the tablet, as in the release experiments in buffered solution summarized in Figs. 6–8. Although surfactant should be released from the tablet and thus from the complexes, this is a slow process since the concentration of uncomplexed surfactant in the tablet gel layer must be of the order of CMC (2 mM in buffered solution) or less. With sufficient levels of surfactant in the tablets, the release also becomes insensitive to the presence of surfactant in the bulk (Fig. 8).



**Fig. 8.** Release of ibuprofen in buffered solution (0.1 M, pH = 7.2) from tablets of CLHMPAA with SDS added to the tablet (7.5 wt%) and with surfactants added to buffer solution, SDS (A), Tween80 and bile salt (B) at the indicated concentrations. Each dataset represents one measurement and is shown as representative data.

We are now in the process of trying to further understand the release mechanisms behind the seen results. Our hypothesis is that solubilisation of the active substance into micelles will reduce transport in Pemulen as micelles aggregate on the hydrophobes of the polymer. One further explanation could be that the micelles and polymer aggregates change the rheology of the polymer and thus the dissolution of the polymer.

Tablets with CLPAA in buffered solution showed similar dissolution characteristics as CLHMPAA in pure water: the tablets did not seem to dissolve and small pieces of cloudy semi-swollen particles eroded from the tablets. The low solubility of CLPAA was indeed confirmed by mixing 1 wt% CLPAA in buffered solutions, which resulted in cloudy dispersions. Since CLPAA lacks hydrophobes that interact strongly with SDS, there was no strong effect of SDS added in the dissolution medium on the dissolution and drug release of the CLPAA tablets.

## 5. Concluding remarks

In this study we have elucidated important effects of polymer hydrophobic modification and of added surfactant, separately and combined, on the disintegration and release properties of polymer matrix tablets, and we have also proposed mechanistical explanations to the observed effects. From a more practical point of view, we conclude that CLHMPAA is a potential candidate to be used in tablet formulations for controlled release with poorly soluble drugs. Tablets containing ibuprofen and CLHMPAA have a slow and almost ideal linear release, which is kept until the tablet is completely disintegrated. The release times seen in these experiment are very long and further optimisations need to be done for the formulation to be used in vivo. However the tablets give indications as to how the release of the different tablets would be in in vivo and, more specifically, how it could be affected by the presence of surface active compounds, for example bile salts. We note that the tablets contain a high amount of polymer (30 wt%) and that preliminary experiments have shown that by decreasing the amount of polymer the extended release time can be decreased (unpublished data).

The release is strongly affected by the presence of surfactant and/or buffer, which affects both the solubility of CLHMPAA and the maximum swelling of the gel layer that surrounds the disintegrating tablets. Importantly, two mechanisms of tablet disintegration were observed under shear, that is, conventional dissolution of a soluble tablet matrix or erosion of swollen insoluble gel particles from the tablet.

Interestingly, the effects from surfactant in the surrounding medium can be circumvented by addition of surfactant to the tablet. With added surfactant, tablets that might not be susceptible to the differences in bile salt level between fasted or fed states have been produced. This should be further evaluated using simulated intestinal fluid, e.g. FaSSIF/FcSSIF, which could also include optimisation of the

extended dissolution time. This suggests that the potential of CLHMPAA and surfactant in tablet formulations is high and that further studies should be conducted. This includes optimising the content of Pemulen to give a desired time frame of release as well as obtaining approval for oral use of the polymer.

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