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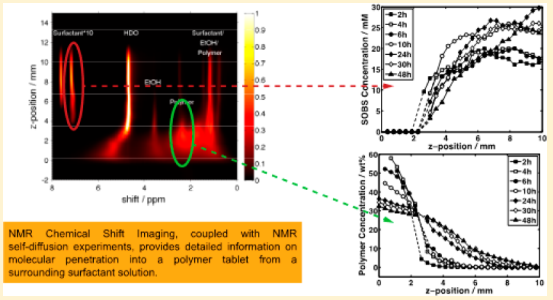
Effects of Added Surfactant on Swelling and Molecular Transport in Drug-Loaded Tablets Based on Hydrophobically Modified Poly(acrylic acid)

Patrik Knöös,*[,†] Marie Wahlgren,[‡] Daniel Topgaard,[†] Stefan Ulvenlund,[§] and Lennart Piculell*[,†]

[†]Division of Physical Chemistry, and [‡]Division of Food Technology, Lund University, Box 124, SE-221 00 Lund, Sweden

[§]CR Competence AB, c/o Chemical Centre, Box 124, SE-221 00, Lund, Sweden

ABSTRACT: A combination of NMR chemical shift imaging and self-diffusion experiments is shown to give a detailed molecular picture of the events that occur when tablets of hydrophobically modified poly(acrylic acid) loaded with a drug (griseofulvin) swell in water in the presence or absence of surfactant (sodium octylbenzenesulfonate). The hydrophobic substituents on the polymer bind and trap the surfactant molecules in mixed micelles, leading to a slow effective surfactant transport that occurs via a small fraction of individually dissolved surfactant molecules in the water domain. Because of the efficient binding of surfactant, the penetrating water is found to diffuse past the penetrating surfactant into the polymer matrix, pushing the surfactant front outward as the matrix swells. The added surfactant has little effect on the transport of drug because both undissolved solid drug and surfactant-solubilized drug function as reservoirs that essentially follow the polymer as it swells. However, the added surfactant nevertheless has a strong indirect effect on the release of griseofulvin, through the effect of the surfactant on the solubility and erosion of the polymer matrix. The surfactant effectively solubilizes the hydrophobically modified polymer, making it fully miscible with water, leading to a more pronounced swelling and a slower erosion of the polymer matrix.



NMR Chemical Shift Imaging, coupled with NMR self-diffusion experiments, provides detailed information on molecular penetration into a polymer tablet from a surrounding surfactant solution.

1. INTRODUCTION

Because of the large increase of the number of hydrophobic drugs within the pharmaceutical industry, a need for new formulation strategies has emerged.[1,2] Pemulen TR2, a commercially available cross-linked hydrophobically modified poly(acrylic acid) (HMPAA), has previously provided promising results in terms of controlled release of poorly soluble compounds from tablet formulations where an almost perfect zero-order release rate was achieved.[3,4] The studied HMPAA is cross-linked with allylpentaerytritol via ester bonds and hydrophobically modified with grafted C10−C30 alkyl chains (4 mM per wt % polymer).[5,6] We have previously investigated the release and dissolution behavior from tablets of HMPAA, and an initial hypothesis was that the "hydrophobes" (the hydrophobic substituents) interacted with the hydrophobic substance and sustained the release.[4] Strong effects were also found from surfactant added to the dissolution medium and/or to the HMPAA tablet.[3] However, the mechanisms for release have not been understood in detail.

The formation of a semidilute polymer solution on the surface of the dry tablet core is considered to be important for the performance of polymer matrix tablets for controlled release.[7−9] Traditionally this layer is referred to as the "gel layer", but since this terminology is not in accordance with the current understanding of gels,[10] we prefer to refer to the layer as the (solvent) swollen layer. The swollen layer surrounds the tablet and withstands the erosive force of the convective flow in the surrounding solution.[8] Consequently, an increased thickness of the swollen layer is expected to result in a slower dissolution and a longer way for the drug to diffuse, hence a slower drug release.[9,11,12] The time-dependent formation and thickness of the swollen layer depend on the mechanical strength and properties of the semidilute polymer solution, as well as the applied convection.[11−14] Hence, any factor that affects the properties of the semidilute solution could also potentially affect the dissolution and release behavior of the tablet.

The hydrophobes of a hydrophobically modified polymer (HM-polymer) typically self-aggregate in an aqueous environment, which generally leads to an enhanced viscosity but at sufficiently high degrees of hydrophobic substitution also to a poor water solubility, even if the polymer chain itself is hydrophilic.[15,16] Our studies of HMPAA transpired that this polymer indeed belongs to the latter class of polymers: When mixed with pure water, the acid form of the polymer was found to form two liquid phases, one concentrated and one very dilute. This had significant consequences for the observed tablet disintegration and drug release.[3,5] In pure water, where the studied HMPAA is virtually insoluble (that is, the solubility of the polymer in the dilute phase is extremely low), the swollen layer surrounding the tablet could only swell until it reached the composition corresponding to that of the

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concentrated polymer phase. By contrast, a partially charged "half-neutralized" HMPAA, where half of the carboxylic acid groups had been titrated with NaOH, was fully miscible with water.[5] The restricted swelling of the swollen layer for the acid form of HMPAA resulted in tablet particles being sheared off and released into the surrounding medium. This, in turn, led to a faster drug release than what was observed from tablets of the fully soluble half-neutralized HMPAA.

The properties of aqueous HM-polymer solutions can be greatly altered upon addition of surfactant because of interactions between the hydrophobic substituents and the hydrophobic tail of the surfactant.[15] The viscosity of the solutions can be altered, and moreover, added surfactant can also solubilize such HM polymers that are not by themselves soluble in water.[15,16] This suggests that the release and dissolution behavior of tablets based on a HM-polymer could be affected by the presence of an amphiphilic compound, for instance, the bile salts present in the intestine. In previous investigations, we established that the release of a hydrophobic model substance (ibuprofen) from a HMPAA tablet was greatly altered if a sufficient concentration of surfactant was added either to the surrounding medium or to the tablet.[3] In the presence of surfactant, the release rate of the model drug decreased and the tablets showed a much larger swelling. The effects could be correlated to the solubilizing effects of the surfactant. In unpublished results, we have studied the release in simulated intestinal fluid where we further showed that the formulation is affected by the amphiphilic compounds in the intestinal fluid. Differences in the dissolution and release behavior stemming from interactions with amphiphilic compounds often have implications for the in vivo performance of formulations containing poorly soluble substances.[17−20] More specifically, interactions with amphiphilic compounds potentially aggravate problems related to variable bioavailability. It is therefore noteworthy that our previous studies suggest that addition of surfactant to the tablet represents a way to make the release less sensitive to the presence of amphiphilic components in the dissolution medium.[3]

In order to obtain a detailed molecular picture of the events occurring when drug-loaded tablets of HMPAA swell and disintegrate in water, we have developed a new experimental setup using NMR chemical shift imaging (CSI).[21,22] The setup has been described previously,[5] and CSI gives time-resolved and position-dependent concentration profiles for several chemical species simultaneously. In our previous study,[5] we discussed the advantages and limitations of our employed CSI method, and we also compared it to NMR approaches used previously to obtain concentration profiles in swelling polymer matrix tablets.[23−32] Briefly, an important advantage with the CSI method is that information on the concentrations of, in principle, all different components in the swelling tablet can be obtained in a single experiment, provided that each component of interest gives rise to a separate peak in a ^{1}H spectrum. We applied the technique to study the dissolution behaviors of a soluble and an insoluble polymer matrix, where we modified the solubility of the HMPAA polymer by titrating the carboxylic acid groups with NaOH. The study revealed distinct effects of polymer solubility in the concentration profiles obtained. We also showed that the profiles give mechanistic insights into the dissolution and transport processes in the polymer-based tablets.

The present article addresses the effects of added surfactant on the dissolution and release of a hydrophobic model substance, griseofulvin (GF), from HMPAA tablets. The focus is on the solubilizing properties of the surfactant and the molecular transport taking place in the swollen tablets. GF was chosen as the model drug substance because of its hydrophobicity and low water solubility (40 μM at 25 °C).[33] In addition, it is uncharged. Surfactant is added to the surrounding media and/or to the tablets to study both situations and to compare with previous results.[3] In order to understand the molecular association phenomena and transport mechanisms inside the tablet, additional NMR self-diffusion experiments were performed on the same model system.

2. MATERIALS AND METHODS

2.1. Chemicals. Pemulen TR2 NF (lot no. 0100834373) was kindly provided by Lubrizol Advanced Materials (Brussels, Belgium). According to the supplier, the polymer consists of poly(acrylic acid), cross-linked with allylpentaerytritol, and contains 52−62% of −COOH groups. The polymer is hydrophobically modified with grafted C10−C30 alkyl chains. From ^{1}H NMR intensities of the terminal methyl groups of the alkyl grafts we have deduced that a 1 wt % solution of Pemulen TR2 NF in water contains ∼4 mM of alkyl grafts (hydrophobes), which compares favorably to previous estimates.[6]

Prior to use, dialysis was used to purify the polymer (molecular weigh cutoff of 100 000 Da) (SpectraPor Biotech CE, Spectrum Labs, Rancho Dominquez, CA, USA). The polymer was mixed in 0.2 M HCl solution overnight and subsequently added to dialysis tubes, which were placed in deionized Milli Q water. Dialysis was performed for 7−8 days while the conductivity of the dialysis medium was monitored. Purified polymer solutions were then freeze-dried and stored in a desiccator until used.

The following chemicals were used as supplied: griseofulvin (GF) (lot no. 028K1105) from Sigma-Aldrich (Steinheim, Germany) and 4-*n*-octylbenzenesulfonic acid, sodium salt (SOBS), from TCI Europe N.V. (Zwijndrecht, Belgium). Samples for NMR measurements were dissolved in deuterated water (D_2O) (Armar Chemicals, Döttingen, Switzerland) doped with a small amount of a paramagnetic gadolinium contrast agent (0.7 mL/L), Magnevist 469 mg/mL (Schering, Berlin, Germany, lot no. 64511D, 0.5 mmol of gadolinium/mL).

2.2. NMR Self-Diffusion Measurements. *2.2.1. Sample Preparation.* A series of samples containing increasing amount of polymer were obtained by appropriate polymer additions to a stock solution containing 20 mM SOBS dissolved in D_2O. To each sample GF was added in excess (relative to its solubility in 20 mM SOBS solution). Samples containing less than 0.05 wt % of polymer were obtained by further diluting a stock solution of 0.05 wt % Pemulen and 20 mM SOBS. The samples were then thoroughly mixed and added to 5 mm (o.d.) disposable NMR tubes for measurements. Samples containing more than 2 wt % of polymer were mixed directly in the NMR tubes.

2.2.2. Measurements. Self-diffusion ^{1}H NMR measurements were performed on a Bruker Avance II 200 spectrometer operating at 200 MHz ^{1}H resonance frequency and equipped with a Bruker DIF-25 gradient probe capable of delivering gradients of strength 9.6 T/m in the *z*-direction. All experiments were performed at 25 °C employing a stimulated spin echo sequence.[34] Two different experiments had to be performed on each sample because of the order-of-magnitude difference of diffusion coefficients for SOBS and GF. The gradient strength was applied between 30% and 100% of the

maximum value in 32 steps with a duration time (δ) of 0.72 ms for the gradient pulse. For each experiment the diffusion time (~20 ms) and the number of scans (between 32 and 128) were optimized. The diffusion of SOBS was evaluated from the peak located at 7.1 ppm. For GF, the peaks between 3 and 4.5 ppm were used collectively.

2.3. Tablet Production. To ensure proper mixing between the drug and the polymer in the powder for tablet production, GF and HMPAA were mixed in ethanol, then dried and milled. First, GF was added and dissolved in ethanol at concentrations of 1 or 0.5 mg/g. For the preparation of SOBS-loaded tablets, SOBS was added at this stage to the GF and ethanol mixture at a concentration of 5 mg/g. The purified polymer was then added to the solution, which was stirred until a homogeneous viscous polymer solution was achieved. The solution was left to dry in a fume hood overnight and then put in a vacuum oven at ambient temperature for 3 days. The dried polymer−drug mixture was milled into a powder with a coffee grinder (OBH Nordica) and kept in a desiccator until used or analyzed. For use in the NMR CSI experiment, the powder was compressed into cylindrical tablets using a modified IR pellet press (Parr Instruments, Moline, IL, US). The tablets had a diameter of 4 mm, a thickness of ~1.5 mm and a weight of ~20 mg. The amount of GF in the dry powder was 2 wt % for SOBS-free and 1 wt % for SOBS-loaded tablets. The SOBS-loaded tablets contained 10 wt % SOBS. Thermogravimetric analysis of the powder showed 3−4 wt % of residual ethanol.

Tablets for dissolution studies using the USP methodology were prepared with a single-punch tableting machine (DIAF type TM20, Denmark) to a weight of 270 ± 13 mg and diameter of 11 mm. The tablets for USP experiments contained 1 wt % of GF.

2.4. Dissolution Experiment. Dissolution experiments were carried out at 37 °C in a USP dissolution apparatus (Prolabo Intelligent dissolution tester, Novakemilab, Enskede, Sweden) with rotating disks (100 rpm). The disks were made of stainless steel and had a diameter of 50 mm and a thickness of 3 mm. The center of each disk had an indentation, 1 mm deep and 12 mm in diameter, to simplify mounting of the tablets. USP vessels were filled with 800 mL of water, deionized in a Milli Q apparatus, with desired amounts of SOBS added. Tablets were weighed prior to experiments and glued to the disks with Scotch contact adhesive (3M, Glostrup, Denmark).

The amount of released GF was analyzed by HPLC (Dionex 3000RS) on aliquots of 1 mL extracted from the dissolution medium. An isocratic solution with 30% acetonitrile and 70% water with 0.1% acetic acid was used with a flow of 0.4 mL/min on a reversed phase Acclaim RLSC C18, 2.2 μm, 120 Å, 2.1 mm × 50 mm column. The fraction of released GF (% released) was then calculated according to

$$\%\ \text{released} = \frac{\{C_{GF}[V_0 - V_a(n_a - 1)]\} + \sum_{n=0}^{n_a-1}(V_a C_{GF,n})}{m_t} \quad (1)$$

where the initial volume is denoted V_0, V_a is the volume (=1 mL) of an extracted aliquot, and the number of aliquots is given by n_a. c_{GF} is the experimentally determined (by HPLC) concentration of GF in the extracted aliquot. The mass of GF in the initial dry tablet is given by m_t. All dissolution experiments were performed twice, with a reproducibility of typically ±20% released at each time point for ≤3 mM SOBS in the medium and ±3% released for ≥7 mM SOBS. We ascribe the difference in reproducibility to the rather poor mechanical properties of the tablets; presumably interactions with surfactant (see below) in the swollen layer improved the situation at the higher surfactant concentrations.

2.5. Chemical Shift Imaging. *2.5.1. Experimental Setup.* All experiments were performed at 25 °C with the experimental setup shown in Figure 1. A detailed description of the setup and the experimental procedures has been given previously.[5] An evacuation procedure was performed before each experiment in order to minimize the formation of air bubbles in the dissolving tablets. The tablets were allowed to swell in the setup with continuous stirring before and between successive NMR measurements. At the time of each NMR measurement, a 1 mL sample was taken from the volumetric flask for analysis by HPLC (see above). The NMR tube with the tablet was then disconnected and placed in the spectrometer. After completion of each NMR measurement the sample was reconnected to the setup and the dissolution process continued. This was repeated at specified time intervals over a 48 h time period.

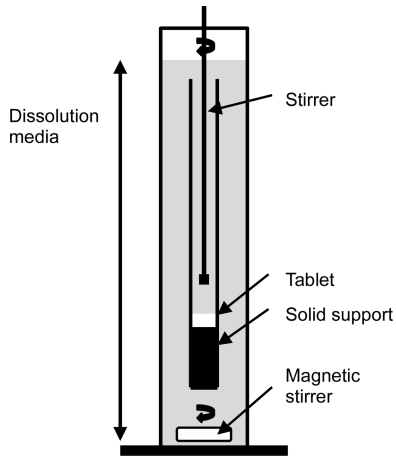

Figure 1. Schematic drawing of the experimental NMR setup. The tablet is placed on a solid support at the bottom of a 5 mm (o.d.) NMR tube, and the dissolution medium is injected on top. A small stirrer is used to ensure convection and shear on the tablet surface. The NMR tube is then put in a stirred volumetric flask containing 100 mL of dissolution medium. The relatively large volume ensures "sink" conditions; i.e., the concentration of griseofulvin at complete dissolution in the solvent is ≤30% of the solubility.

2.5.2. NMR CSI Measurements. NMR CSI measurements were performed using the same spectrometer and probe as for the self-diffusion measurements described above. A detailed description of the theory behind the technique and pulse sequence can be found in the following references.[21,22] Using the same nomenclature as in the said references, the following settings were applied: spectral width = 4 kHz (20 ppm), echo time (t_E) = 0.5 ms, repetition time (t_R) = 5 s, gradient pulse length (δ) = 0.1 ms, and gradient amplitude (G) incremented from −0.55 to 0.55 T/m in 64 steps, which gave a vertical spatial resolution of 317.8 μm. The acquired signal was then subjected to Fourier transformation and phase correction, which generated a z-resolved image recorded in around 20 min, using four scans per gradient increment.

3. RESULTS

3.1. Chemical Shift Image. Figure 2 shows a spatially resolved chemical shift image from a measurement of a

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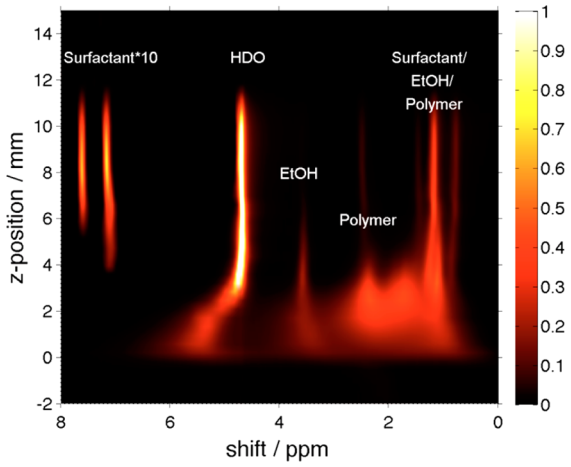

Figure 2. Chemical shift image (CSI) of a dissolving tablet with surfactant added to the dissolution medium, recorded after 6 h. The image is composed of 64 ^{1}H spectra, corresponding to slices at different heights along the vertical axis of the NMR tube. The intensities of the NMR signals are represented by colors as indicated in the right-hand scale. Peaks from the surfactant, appearing between 7 and 8 ppm, have been multiplied by a factor of 10 for clarity. The position 0 mm corresponds to the top surface of the solid support, while positions above 11 mm are located outside the rf coil used for NMR signal detection. The interface between the swollen tablet and the dissolution medium is at the position 4 mm.

dissolving tablet after 6 h (see caption for further explanations). In the image one can distinguish (from right to left) a cluster of peaks from protons of EtOH and polymer, followed by separate peaks from the polymer, EtOH, and HDO. Surfactant added to the medium contributes two well-separated peaks to the left and additional peaks to the right in the image. Because of the low solubility of the drug and the detection limit of the applied NMR experiment, no protons from the drug could be detected.

The data collected in the CSI experiments were analyzed using the method previously described in detail.[5] In short, by combination of information from the pronounced chemical shift change of the HDO peak (see Figure 2) with the peak areas from the polymer, a relation was obtained that was used to obtain molecular concentration profiles of the polymer across the entire sample. In some cases, surfactant peaks overlapped with the polymer peaks, making the determination of polymer peak areas more cumbersome compared to the surfactant-free systems. However, peaks from the surfactant, as well as protons from HDO and ethanol, could still be resolved. The areas of these peaks were used, together with the knowledge of the spectra for the individual components, to calculate the contributions from these compounds to the total peak area of overlapping peaks. The area corresponding to protons from the polymer could then be obtained by subtraction.

For the surfactant, the concentration profile was obtained from the measured image (Figure 2), using the peak area as a measure of concentration. The peak area was correlated to concentration, for samples dissolving in surfactant media, by using the area recorded from the polymer-free bulk region with a known surfactant concentration. When the swollen layer had expanded outside the observation volume, a reference measurement above the swollen layer was obtained by simply moving the NMR tube in the probe. However, for surfactant-loaded tablets dissolving in pure D_2O, no such internal reference was available. Attempts were made to calculate the SOBS concentration based on comparisons of the peak areas for SOBS and the polymer. However, studies on reference samples of known compositions showed that this method was quantitatively unreliable for samples of appropriate compositions, owing to the large difference in magnitude between the polymer peak area and the SOBS peak area. Therefore, the SOBS concentration could not be determined for SOBS-loaded samples swelling in pure water. For consistency, the contribution of SOBS to the total mass was neglected for all samples when calculating the polymer concentration from the polymer peak areas and HDO chemical shifts.

3.2. NMR/CSI Results for Swelling Polymer Tablets.

3.2.1. Polymer Swelling Profiles with and without Surfactant.

The polymer release from tablets in the NMR CSI setup was very slow, and over a period of 48 h all studied tablets had mostly swollen by taking up deuterated water. By use of the procedure described above, concentration profiles for the polymer could be calculated. The profiles for surfactant-free and surfactant-loaded tablets swelling in D_2O or in 20 mM SOBS solution are shown in Figure 3. Experimental results for the reference SOBS-free system, taken from ref 5, are included as Figure 3a for comparison. Our previous study showed that mixtures of HMPAA with D_2O display a miscibility gap at low concentrations of the polymer. Below ~25 wt %, the mixtures separated into one concentrated and one dilute solution phase, the latter containing a very low concentration of polymer. This miscibility gap was also manifest in the concentration profiles of the surfactant-free system (Figure 3a) as a clear break point developing at z = 3.2 mm (at $t \geq 24$ h), followed by a relatively steep decrease of the polymer concentration. Outside of the break point, a cloudy two-phase system was visually observed in the polymer swelling experiments.

With SOBS in the dissolution medium (Figure 3b) the break around 2.8 mm at long times became much less pronounced, since the profile at higher z values was much less steep. The cloudiness seen in the latter region seen for the tablet dissolving in pure water had also disappeared. This indicated that the polymer was soluble in 20 mM SOBS solution, as confirmed in separate measurements (see also section 3.4 below). At the final measurement time (t = 48 h) the swollen tablets extended further than the length of our observation volume. We note, however, that for surfactant-free tablets the differences in the two types of swelling media were only apparent at high z values; the profiles were virtually identical at all times at $z < 2.8$ mm.

Compared to the SOBS-free tablets, SOBS-loaded tablets typically showed a higher friability, which could lead to erosive detachment of macroscopic particles from the tablets during swelling. Nevertheless, the SOBS-loaded tablets were found to provide results with satisfactory reproducibility in the NMR CSI experiments. SOBS-loaded tablet in D_2O showed a deviation of ±2 wt %, calculated as the average standard deviation between the two polymer concentration profiles obtained at 6 h, and the two at 24 h, in two different experiments. No significant differences were observed between the swelling profiles in pure D_2O and in SOBS solution for SOBS-loaded tablets (cf. Figure 3c and Figure 3d). For surfactant-loaded tablets there was no sign of any break in the concentration profiles at long times and the tablets swelled extensively. After 48 h the polymer swelling profile extended outside the observation volume.

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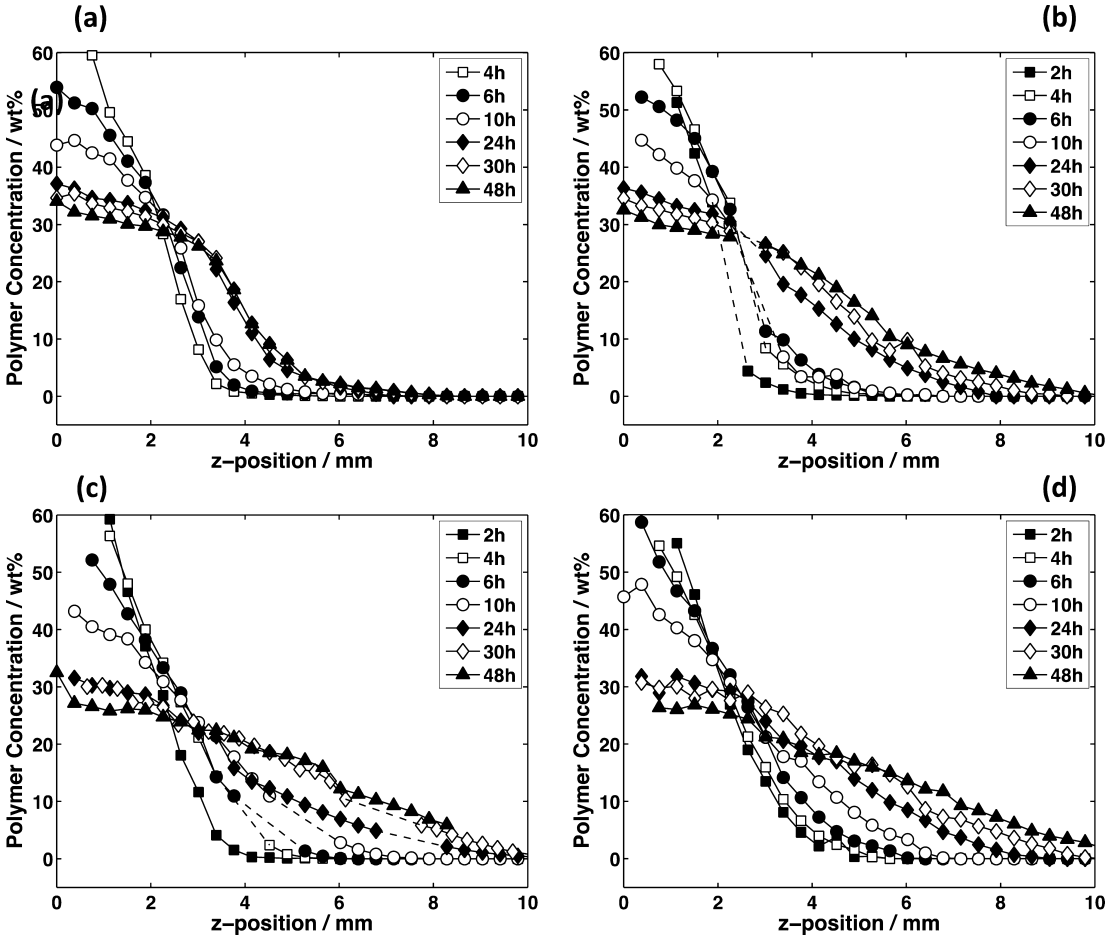

Figure 3. Concentration profiles at different times for surfactant-free polymer tablets swelling in D_2O (a, from ref 5) and in 20 mM SOBS (b) and for surfactant-loaded tablets swelling in D_2O (c) and in 20 mM SOBS (d). Each panel shows time-dependent profiles for one tablet. The top surface of the solid support is defined as $z = 0$. Regions where SOBS can be detected in the ^1H spectra but where the SOBS intensity is too low to be quantified are left blank. Here, dashed lines are drawn between the surrounding data points.

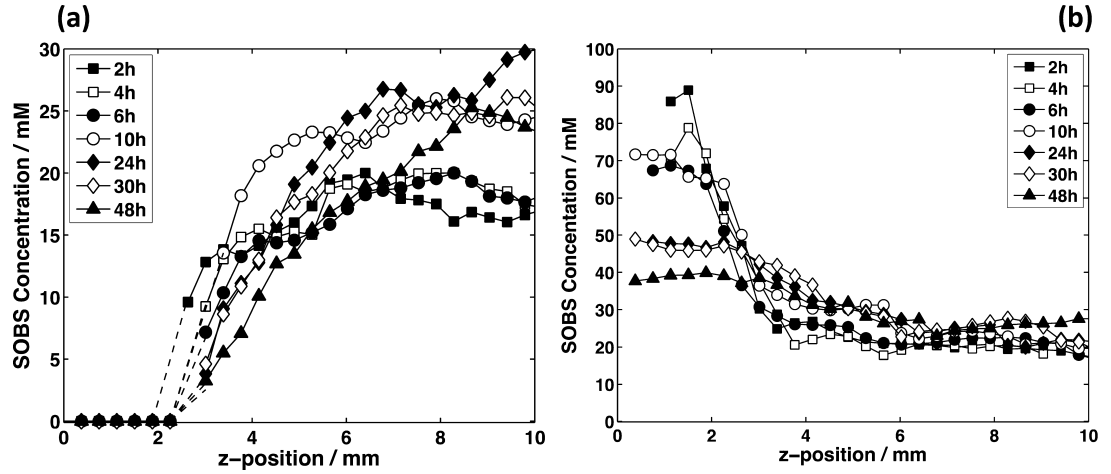

Figure 4. (a) Concentration profiles at different times for SOBS penetrating into surfactant-free tablets from a 20 mM SOBS solution. The solid support is set to a position of 0 mm. Data points from spectra where SOBS can be detected in the ^1H spectra but the SOBS intensity is too low to be quantified are left blank, and the concentration profile is indicated with a dashed line. (b) Concentration profiles of SOBS at different times in an experiment with surfactant-loaded tablets swelling in 20 mM SOBS. The solid support is set to a position of 0 mm.

3.2.2. Surfactant Concentration Profiles. Figure 4a shows surfactant concentration profiles at different swelling times for the same experiment as in Figure 3b above, where an initially SOBS-free tablet is swelling in 20 mM SOBS solution. The profiles reveal a quite complex time dependence of the surfactant penetration. Quite strikingly, SOBS never seemed, for the entire duration of our experiment, to reach the region $z < 2$ mm. This is consistent with the similarity in swelling

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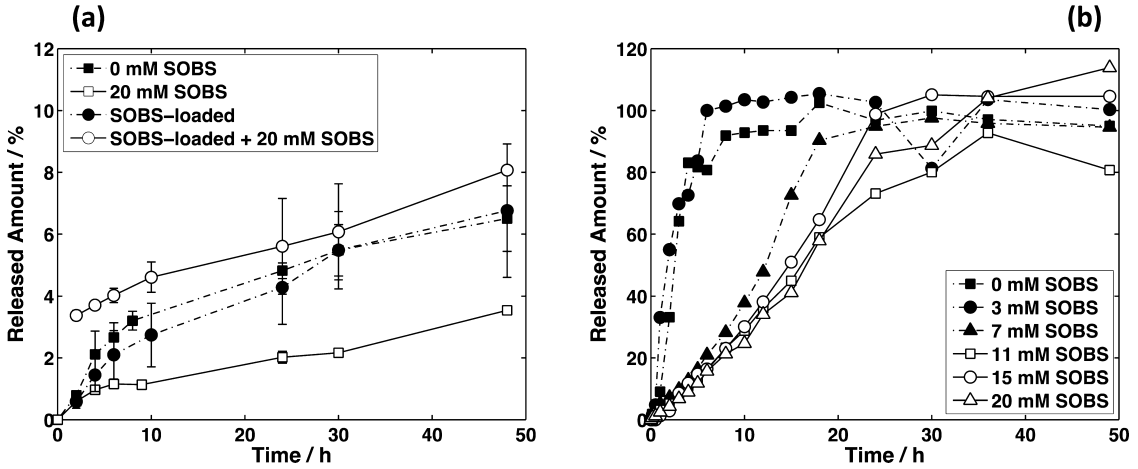

Figure 5. (a) Release of GF in the NMR experimental setup for SOBS-free (squares) and SOBS-loaded (circles) tablets in pure D_2O (filled symbols) or 20 mM SOBS in D_2O (open symbols). Error bars represent the standard deviation ($n \geq 2$). (b) Release of GF from SOBS-free tablets in USP baths containing deionized water with indicated concentrations of added SOBS.

behavior of the latter region with and without surfactant in the medium (Figure 3a and Figure 3b). As expected, the surfactant concentration profile became progressively less steep over time (Figure 4a). However, a remarkable feature of the results in Figure 4a is that, with time, the SOBS concentration profile is consistently moving *away* from the concentrated core of the tablet.

The surfactant concentration for a SOBS-loaded tablet dissolving in 20 mM SOBS is shown in Figure 4b. The first point to note is that during most of the experiment, the measured SOBS concentration in the interior of the swelling tablets exceeds the solubility of SOBS in D_2O, which we separately determined to ~40 mM. This observation indicates that SOBS is "solubilized" by forming mixed aggregates with the HMPAA hydrophobes. Second, the measured concentration of SOBS (in wt %) is always lower than $^1/_9$ (the mass ratio in the dry tablet) of the measured HMPAA concentration. This is tentatively explained by a slow dissolution/solubilization of SOBS, especially at low water contents.

3.3. Release of a Hydrophobic Model Substance from Swelling Tablets. As already pointed out, concentration profiles for GF could not be determined in the NMR CSI experiment. To complete the picture of the molecular transport in swelling HMPAA tablets, we instead studied the release of GF into the surrounding reservoir. This was done for all tablets studied with the NMR setup.

The release of GF in the NMR setup was very slow, and less than 10% was released during 48 h (Figure 5a). This conclusion was corroborated by analysis of the remaining tablet residues, which confirmed that the majority of the drug was still in the swollen tablets when the experiments were terminated. The result for the SOBS-free tablet swelling in pure D_2O, reproduced from our previous study,[5] is included in Figure 5a. In the previous study, the more rapid release (the "burst") during the first few hours was attributed to an initial release of semiswollen particles from the tablet. A similar effect is most likely the cause of the burst also from the SOBS-loaded tablets, owing to the relatively high porosity and friability of these tablets. The slowest release was found for the initially SOBS-free tablet in 20 mM SOBS. For the latter system, no initial burst of GF was apparent and within the experimental uncertainty, the release profile was linear.

The release was also studied using a standard USP equipment for larger (surfactant-free) tablets to allow a comparison with results previously reported in reference[3] and to correlate the results obtained with the NMR CSI setup with those obtained using standardized pharmaceutical testing procedures. The release profiles from the dissolution experiments in the USP bath (Figure 5b) show a slow and approximately linear release throughout the dissolution process, as previously observed for a similar formulation.[3] On increase of the surfactant concentration in the release medium, the release rate decreased, with the most rapid change in release rate occurring just below the CMC of SOBS. The tablets were observed visually during disintegration in the medium, and their appearance was found to depend on the surfactant concentration. From 7 mM SOBS and above, a transparent swollen layer surrounded the disintegrating tablets. The swollen layer generally increased in thickness with increasing SOBS concentration. At low concentrations of surfactant (≤3 mM) a clear but very thin swollen layer developed and the tablets had a visibly rough surface. For these tablets, semiswollen particles, clearly visible by the naked eye, eroded from the surface.

3.4. Self-Diffusion Experiments. In order to obtain a more detailed picture of the molecular transport in systems containing SOBS, GF, and HMPAA, we performed NMR self-diffusion experiments on a series of solutions of 20 mM SOBS in D_2O that contained an excess (with respect to the solubility) of GF and increasing amounts of HMPAA. With increasing polymer concentration these samples became extremely viscous and difficult to mix homogeneously; therefore, the HMPAA concentration was limited to <10 wt %. Nevertheless, from the polymer and surfactant concentration profiles shown in Figures 3 and 4 we can conclude that the samples chosen for NMR self-diffusion measurements were representative for the composition range found, at long times, across a large part of the swollen layer of a surfactant-free tablet swelling in SOBS solution. None of the prepared samples showed any indication of phase separation. The resulting diffusion coefficients for SOBS and GF are shown in Figure 6. We note already at the outset that most of the GF that dissolved in these samples was actually solubilized in SOBS micelles; hence, a satisfactory NMR sensitivity could be obtained. In independent experiments we found that 20 mM SOBS in D_2O can solubilize ~1 mM GF, whereas the solubility of GF in D_2O is ~40 μM, all at

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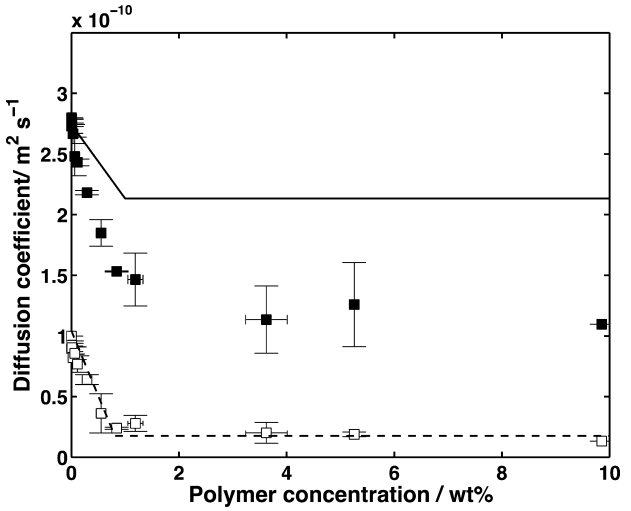

Figure 6. Measured self-diffusion rate of SOBS (filled squares) and GF (open squares) with increasing polymer concentration. Each point represents an average value, and *xy* error bars indicate the standard deviations. Lines are calculated (see text) from eqs 3a and 3b with the parameter values $p_{SOBS,mol} = 0.45$, $p_{GF,mol} = 0.04$, $D_{GF,mol} = D_{SOBS,mol} = 5 \times 10^{-10}$ m^2 s^{-1}, and $D_{mic} = 0.9 \times 10^{-10}$ m^2 s^{-1}.

25 °C.[33] The excess undissolved GF does not contribute to the measured NMR diffusometry signal on account of its short transverse relaxation time, typically on the order of 10 μs for solid substances.

In Figure 6 the sample without added HMPAA shows the most rapid self-diffusion for both the surfactant and GF. With increasing concentration of added HMPAA, the self-diffusion of both components initially decreased quite rapidly. Both curves then displayed clear breaks of the slopes around 0.8 wt % of HPMAA, after which the decrease in the self-diffusion became less steep. We observe that the diffusion coefficients had decreased quite substantially already at the break point, which corresponds to a quite low HMPAA concentration compared to the situation in the swelling tablets. Above ~3 wt % of HMPAA there was a relatively large scatter in the measured diffusion coefficients, most likely due to the mentioned difficulty to obtain totally homogeneous samples for these highly viscous systems. The high viscosity is a direct consequence of the polymer−surfactant interaction, as previously described in detail.[3,35]

4. DISCUSSION

4.1. Interpretation of the Self-Diffusion Experiments.

The data from the self-diffusion experiments can be used to obtain a more detailed interpretation of the results from the tablet swelling experiments. The data give direct information on the effective transport of SOBS and GF in polymer matrices of varying composition. Furthermore, they contain indirect information about the molecular states in these matrices, which we will now attempt to unravel. Therefore, we prefer to discuss these results prior to discussing the tablet experiments.

The studied samples contain the following diffusing molecules or aggregates.

1. Molecularly dissolved GF at a concentration $c_{GF,mol}$. This concentration is constant and given by the solubility of GF, since the systems always contains excess of solid GF.
2. Molecularly dissolved surfactant ions at a variable (see below) concentration $c_{SOBS,mol}$.
3. GF-loaded "free" SOBS micelles (not associated with the HMPAA polymers) at a varying concentration c_{mic}. The free micelles must always contain a maximum fraction of solubilized GF, since they are in equilibrium with molecularly dissolved GF at the solubility limit.

In addition to these diffusing species, the samples contain "polymer-bound" mixed micelles of SOBS, HMPAA-hydrophobes, and solubilized GF, which are associated with the huge HMPAA molecules. The polymer-bound micelles can be regarded as stationary on the time scale of the NMR diffusometry experiment (1−1000 ms for a normal PFG NMR experiments, with typical measured displacements in the range 1−100 μm).[36] However, the presence of the polymer-bound micelles affects the average diffusion coefficients, since both SOBS and GF exchange rapidly between all the above identified states on the NMR time scale. On the other hand, the exchange with solid GF should be slow so that the presence of a reservoir of solid GF does not affect the observed diffusion coefficients. For each of the two studied diffusing species we can then write the following expression for the observed diffusion coefficient.[37]

$$D_{i,obs} = p_{i,mol} D_{i,mol} + p_{i,mic} D_{mic} \quad (2)$$

Here, $D_{i,mol}$ is the diffusion coefficient for the molecularly dissolved species i (GF or SOBS) and D_{mic} is the diffusion coefficient for a GF-loaded free micelle. The fractions of molecules in the respective states are given by $p_{i,mol}$ and $p_{i,mic}$.

When the amount of polymer is increased, more and more surfactant will be bound in mixed micelles with the polymer hydrophobes until, finally, all free micelles have been "consumed". Moreover, as long as there are free micelles in the system, the polymer−surfactant complex will be "saturated" in the sense that the polymer hydrophobes have taken up a maximum amount of surfactant. In the simplest case this stationary saturated complex has a constant composition (independent of the total polymer concentration) and the free micelles disappear linearly with the polymer concentration. From the above considerations we obtain the following expressions for the variation of $D_{i,obs}$ with the concentration of added polymer.

$$D_{i,obs} = p_{i,mol} D_{i,mol} + (1 - p_{i,mol})(1 - c_{pol}/c_{sat}) D_{mic} \quad \text{for} \quad c_{pol} \le c_{sat} \quad (3a)$$

$$D_{i,obs} = p_{i,mol} D_{i,mol} \quad \text{for} \quad c_{pol} \ge c_{sat} \quad (3b)$$

Here c_{pol} is the polymer concentration and c_{sat} is the polymer concentration at which the free micelles have just disappeared. At and above c_{sat} all micelles are associated with the hydrophobes. The rapidly disappearing contribution from free micelles to the measured diffusion coefficients, as predicted by eq 3a, thus explains the observed break points in Figure 6 and allows us to identify c_{sat} = 0.8 wt % in 20 mM SOBS, an important parameter for our analysis below. From the latter value, the CMC of SOBS, and the measured content of hydrophobes in HMPAA, we find that a saturated polymer−surfactant complex contains three to four surfactant molecules per polymer hydrophobe.

We will now make an attempt at a quantitative interpretation of the data in Figure 6 primarily in the interval $c_{pol} < c_{sat}$, based on eq 3a and the following assumptions.

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(1) As long as free micelles are present in the systems ($c_{pol} < c_{sat}$), $c_{SOBS,mol}$ is constant and approximately equal to the CMC, making also $p_{SOBS,mol}$ constant in this interval. To account for the fact that the solubilized GF must lower the CMC slightly, we will use the estimate $c_{SOBS,mol}$ = 9 mM, giving $p_{SOBS,mol}$ = 0.45.
(2) The capacity of the system to solubilize GF is only due to the surfactant; the effect of the polymer is negligible. A stated above, we found in independent experiments that 20 mM SOBS in D_2O can solubilize ∼1 mM of GF and that the solubility of GF in D_2O is ∼40 μM. This implies that $p_{GF,mol}$ is constant and equal to 0.04.

To proceed, we will assume that $D_{GF,mol} = D_{SOBS,mol}$ (owing to their similar size). By use of the quantitatively realistic values $D_{SOBS,mol} = 5 \times 10^{-10}$ m^2 s^{-1} and $D_{mic} = 0.9 \times 10^{-10}$ m^2 s^{-1} (cf. self-diffusion data for comparable ionic surfactants[33,37,38]), eq 3a predicts the solid and dashed lines shown in Figure 6 for $D_{SOBS,obs}$ and $D_{GF,obs}$, respectively, at $c_{pol} \leq c_{sat}$. The continued, horizontal lines drawn at $c_{pol} \geq c_{sat}$ correspond to a (hypothetical) case where $p_{i,mol}D_{i,mol}$ is constant in this region.

The simple model prediction, with essentially no free parameters, reproduces all results for GF almost quantitatively and also fits the results for SOBS at zero polymer concentration. At finite values of c_{pol}, however, the simple model overestimates the diffusion of SOBS in the gels. From eq 3, we can see that the reason for the discrepancy must be that the term $p_{SOBS,mol}D_{SOBS,mol}$ cannot be constant but must decrease in the interval $c_{pol} \leq c_{sat}$. One could argue that there should be a finite decrease in $p_{SOBS,mol}$, since the assumption of a constant value of $c_{SOBS,mol}$ as long as free micelles are present is based on the approximate phase-separation model of micelle formation. However, we expect this effect to be small. On the other hand, our initial assumption of a constant value of $D_{SOBS,mol}$ is not quantitatively correct because of the well-known so-called obstruction effect; the path for diffusing molecules will be increasingly more tortuous around the increasingly more numerous, quasi-stationary polymer chains.[39] The obstruction effect generally depends on the size of the diffusing molecule and on the concentration and the pore size distribution of the obstructing polymer network.[40,41] Experimental results show considerable system-dependent variations, but strong reductions (20−30%) have been observed even for low molecular weight solutes, such as urea and glucose, already at volume fractions as low as 1% polymer.[39] In 1 wt % solutions and gels of ethyl(hydroxyethyl) cellulose, the diffusion of the dodecylsulfate surfactant ion was found to be reduced by 25% compared to the diffusion in pure water.[38] The system under study in the present work has a complicated structure, where the possibly unevenly distributed polymer-bound charged surfactant micelles also give rise to a long-range repulsion of the diffusing free surfactant ions. Hence, a quantitatively reliable prediction of the obstruction effect does not seem possible.

We note in passing that the observed decreases in both $D_{SOBS,obs}$ and $D_{GF,obs}$ with increasing c_{pol} also above c_{sat} should be partly due to an increasing obstruction effect. For SOBS, a decrease in $p_{SOBS,mol}$ may also be expected, since above c_{sat} the polymer hydrophobes become increasingly more dominant, and the fraction of SOBS decreases, in the mixed polymer-bound micelles.

In conclusion of this section, from the qualitative (for SOBS) and semiquantitative (for GF) agreement, shown in Figure 6, between the model predictions and the two separate experimental data sets we may conclude that the simple model resulting in eq 3 has captured the essential factors that influence the self-diffusion of SOBS and GF in the systems. As will be important for the following, we have obtained a quantitatively reliable value of c_{sat} in 20 mM SOBS. We have also confirmed that the independently measured values for the solubility of GF in D_2O (∼40 μM), as well as the capacity of 20 mM SOBS to solubilize GF (1 mM), are consistent with the observed self-diffusion of GF.

4.2. Molecular Transport and Swelling of HMPAA Tablets. *4.2.1. Swelling of HMPAA Tablets with and without Surfactant.* Figure 3 shows that addition of surfactant to the dissolution medium and/or the dry polymer tablet has significant consequences for the time-dependent penetration of water into the initially dry polymer matrix and the subsequent swelling. First of all we note that the addition of surfactant, to the medium and/or to the tablets, affected the solubility of the polymer and gave rise to more extended swelling profiles with time. The effect of surfactant on the behavior of the tablets was qualitatively similar to the effect, previously observed, of partially charging the HMPAA molecules by neutralization with NaOH.[3,5]

4.2.2. Transport and Swelling in SOBS-Free Tablets. The penetration of the components of the SOBS solution into the tablet is a multicomponent coupled diffusion process that depends on the local chemical composition and aggregate structure (as discussed above) and the activities of three components: water, SOBS, and polymer. As above, we can regard the polymer self-diffusion coefficient as effectively zero, since the large HMPAA molecules are internally cross-linked, effectively precluding reptation.

The transport of SOBS into the surfactant-free tablet is very slow (see Figure 4a) and over the duration of our experiments SOBS never reached the concentrated interior, despite the presence of a steep gradient in the SOBS activity (∼$c_{SOBS,mol}$) inside the swollen layer. The diffusion experiments provide us with a clue to this behavior. First of all, the results in Figure 6 show that already at a polymer concentration of 0.8 wt % (c_{sat}), all micelles present in 20 mM SOBS are bound in mixed aggregates with the polymer hydrophobes. Such a low polymer concentration is reached already in the very dilute exterior of the swollen layer; hence, surfactant diffusion toward the interior of the swollen tablets will mainly occur through a decreasing fraction of individual surfactant molecules. Using the observed surfactant diffusion coefficient of 10^{-10} m^2 s^{-1} (see Figure 6 at $c_{pol} > c_{sat}$), we calculate a root-mean-square displacement of SOBS of 9 mm in 24 h. However, this already slow transport applies for a total surfactant concentration of 20 mM and a polymer concentration of <10 wt %. Most certainly, the diffusion rate and the fraction of molecularly dissolved surfactant molecules will decrease even further at higher polymer concentrations and lower surfactant concentrations, that is, toward the tablet interior. In other words, the front of the penetrating surfactant becomes effectively trapped by association to the hydrophobes of the increasingly concentrated polymer toward the tablet interior. This conclusion is corroborated by preliminary NMR CSI experiments (not shown) using tablets of nonmodified PAA. In the latter system the front of penetrating surfactant had indeed penetrated the whole tablet before the termination of the experiment (after 48 h).

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Since the self-diffusion of the polymer molecules is effectively zero in the swollen tablet, we may regard the rate of water penetration into the polymer matrix as dependent only on the water self-diffusion coefficient, which is high in the polymer matrix, and the gradient in water activity (or equivalently osmotic pressure), which is shallow, leading to a slow penetration. However, even if the water penetration is slow, it is more rapid than the SOBS penetration. This is evidenced by the observation that the penetrating SOBS front is actually pushed outward from the swelling tablets with time (Figure 4a). Evidently, the water molecules "outrun" the surfactant molecules, which, as described above, are effectively caught and trapped by the polymer hydrophobes. From this observation it follows that the gradient in osmotic pressure that drives the water penetration cannot be generated by the penetrating surfactant but must essentially be due to the osmotic pressure gradient further inside the surfactant-free polymer matrix. The latter conclusion is supported by our observation that the overall rate of transport into the surfactant-free interior is identical in baths with (Figure 3b) or without (Figure 3a) SOBS.

4.2.3. Transport and Swelling in SOBS-Loaded Tablets. In pure water, the SOBS-loaded HMPAA tablet swelled faster than the SOBS-free tablet (Figure 3a and Figure 3c). Moreover, the swelling of the SOBS-loaded tablet was rather insensitive to the presence or absence of 20 mM SOBS in the surrounding medium (Figure 3c and Figure 3d). By comparison of the swelling of SOBS-free and SOBS-loaded tablets in 20 mM SOBS (Figure 3b and Figure 3d), the main difference seems to be in the rate of penetration of water into the concentrated interior of the tablets. This difference can be readily understood from Figure 4b and the discussion above. Since the surfactant never reaches the interior of the SOBS-free tablet, the interior cannot swell beyond the maximum water content for the concentrated phase of HMPAA in D_2O (~75 wt %; see ref 5). For the SOBS-loaded tablet no such limitation exists, and smoothly varying polymer concentration profiles are therefore obtained at all times, both in water and in 20 mM SOBS.

4.3. Release and Transport of a Model Drug Substance. In a previous article we studied the release of GF from insoluble HMPAA tablets (results reproduced in Figure 5a) and soluble "half-neutralized" HMPAA tablets, in which the polymer had been titrated to half the equivalence point with NaOH.[5] In that paper, we concluded (for both tablets) that particles of excess solid GF accompanied the polymer throughout the swelling process; i.e., the GF/polymer ratio remained constant in the swelling tablet. We found that even at the boundary of the swollen layer, the total GF content was above the solubility limit, a process previously referred to as translocation.[42−44] We found, furthermore, that the GF release from the swelling half-neutralized HMPAA tablets agreed with the estimated release rate from an unstirred reservoir of GF at a concentration equal to the solubility. For the standard "non-neutralized" HMPAA (see Figure 5a), there was an initial "burst" in the release, followed by a linear release with a slightly larger slope than for half-neutralized HMPAA. Both the burst and the larger slopes could be explained by the erosion of small, swollen, tablet particles from the matrix, as has previously been seen by Williams et al.[45]

What, then, is the effect of the added SOBS on the GF release in our NMR experiments? Remarkably small, according to Figure 5a. The release from the SOBS-free tablet swelling in SOBS solution is linear and slow and, within error, the same as previously seen for the half-neutralized tablets.[5] Evidently, the main effect of SOBS in the outside solution is to make the polymer soluble, similar to partially charging up the polymer, as in the half-neutralized case. From our analysis of the molecular transport in the SOBS-containing polymer matrices the reason for this behavior seems fairly straightforward. Since essentially all SOBS micelles are associated with the polymer and move with the polymer, there are no free micelles that can transport solubilized GF with a significant diffusion rate. The polymer-bound SOBS aggregates hence function simply a second depot of griseofulvin, in addition to the solid griseofulvin. Since both these depots are translocated with the polymer as it swells, the effect of transferring some griseofulvin from the solid state to the solubilized state has no effect on transport. For the SOBS-loaded tablets, initial bursts are seen in both media, which we ascribe to the poor mechanical quality of such tablets. After that, the GF release is again slow, suggesting that the release is mainly given by diffusion of molecularly dissolved GF.

By comparison of the release of GF in the NMR CSI setup with the release in the USP method (Figure 5a and Figure 5b), clear differences can be seen. We see that the release and disintegration of the tablets becomes much faster in the USP bath, where all tablets are completely disintegrated already after 48 h. These differences are readily attributable to differences in convection and stirring. In the NMR setup a relatively small surface area of the swelling tablet was exposed to the surrounding solution, and the small stirrer placed inside the tube most likely exerted only minor shear forces on this surface. The NMR setup was designed to produce concentration gradients only in one direction, i.e., *z*-direction, which could then be measured in the CSI experiment. Furthermore, the stirrer was added to introduce a well-defined boundary condition in the setup; i.e., at the stirrer (which was maintained at a constant distance from the top surface of the swollen layer) we expect to have sink conditions. Efficient exchange of dissolution medium between the NMR tube and the reservoir was further ensured by a stirrer in the reservoir (Figure 1). These conditions are important to remember when attempting to apply information from the NMR setup for predictions regarding the performance of a tablet in vivo or under common test conditions. In the NMR setup, the low convection and shear will to some extent emphasize effects from diffusional transport whereas the erosional transport will be comparatively minor. Nevertheless, the NMR and the USP setups both show the same qualitative effects of the presence or absence of surfactant on the investigated tablets. In particular, both techniques show that the release of hydrophobic model drug was slowed upon addition of surfactant.

5. CONCLUSIONS

The swelling and molecular transport in polymer tablet formulations designed for controlled release in water are highly complex processes. We have here demonstrated that the NMR CSI method provides detailed information on the time-dependent concentration profiles of the diffusing components in such systems, which can lead to an improved in-depth molecular understanding of the studied processes. This is useful for pharmaceutical development and, more generally, for the study of processes where a polymer swells and dissolves in a surrounding solution.

We have specifically investigated the effects of added surfactant on the behavior of drug-loaded HMPAA tablets. Interactions between surfactants and HM-polymers have been

studied previously, but to the best of our knowledge the effects of surfactant addition on the molecular transport into solid matrices of HM-polymers have not been investigated at this level of detail. As has been shown previously, addition of surfactant to the surrounding medium, or to the tablets themselves, slowed the release of a hydrophobic drug, griseofulvin, incorporated into the tablet. From the NMR CSI measurement we could here confirm that the main reason for this effect was that the water-insoluble HM-polymer became solubilized by the added surfactant and thus could swell indefinitely and erode less efficiently. These differences in the rate of tablet erosion became more pronounced under the more conventional experimental conditions prevailing in a USP bath.

We have here studied in detail the combined water and surfactant penetration into a solid HM-polymer matrix from a surrounding aqueous solution. It was found that during an extended time period the surfactant penetrated only the outer parts of the tablets, since it became efficiently bound in mixed micelles to the hydrophobes of the polymer. Water, on the other hand, effectively diffused past the front of the polymer-bound surfactant, driven by the chemical potential gradient created by the concentrated polymer further inside the tablet. Conversely, surfactant initially included in the tablet was released only very slowly, owing to the efficient binding of the surfactant to the HM-polymer, when the surfactant-loaded tablet was allowed to swell and dissolve in a reservoir of water. Additional NMR self-diffusion experiments gave quantitative information on molecular transport in the mixtures and on the capacity of the HM-polymer to bind surfactant. These data confirmed the proposed molecular explanations to the observed slow surfactant transport in the HM-polymer matrix: The transport in and out from the tablets was inefficient, since it occurred only via a small fraction of individually dissolved surfactant molecules.

Finally, it was shown that the transport of hydrophobic griseofulvin in a HM-polymer tablet in the presence of surfactant was very slow, since the griseofulvin was effectively incorporated in polymer-bound mixed micelles. The latter hydrophobic aggregates functioned primarily as another depot, in addition to excess undissolved solid griseofulvin, that essentially "translocated" with the polymer as water penetrated into the polymer matrix. Thus, with or without surfactant, the release of griseofulvin from the polymer matrix only occurred via a very small, molecularly dissolved fraction.

AUTHOR INFORMATION

Corresponding Authors

*P.K.: e-mail, patrik.knoos@gmail.com; phone, +46 46 222 81 63; fax, +46 46 222 44 13.

*L.P.: e-mail, lennart.piculell@fkem1.lu.se; phone, +46 46 222 95 18; fax, +46 46 222 44 13.

Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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