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Using NMR Chemical Shift Imaging To Monitor Swelling and Molecular Transport in Drug-Loaded Tablets of Hydrophobically Modified Poly(acrylic acid): Methodology and Effects of Polymer (In)solubility

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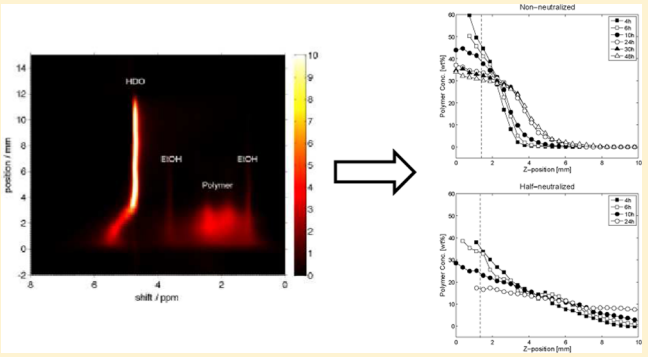
ABSTRACT: A new technique has been developed using NMR chemical shift imaging (CSI) to monitor water penetration and molecular transport in initially dry polymer tablets that also contain small low-molecular weight compounds to be released from the tablets. Concentration profiles of components contained in the swelling tablets could be extracted via the intensities and chemical shift changes of peaks corresponding to protons of the components. The studied tablets contained hydrophobically modified poly(acrylic acid) (HMPAA) as the polymer component and griseofulvin and ethanol as hydrophobic and hydrophilic, respectively, low-molecular weight model compounds. The water solubility of HMPAA could be altered by titration with NaOH. In the pure acid form, HMPAA tablets only underwent a finite swelling until the maximum water content of the polymer-rich phase, as confirmed by independent phase studies, had been reached. By contrast, after partial neutralization with NaOH, the polyacid became fully miscible with water. The solubility of the polymer affected the water penetration, the polymer release, and the releases of both ethanol and griseofulvin. The detailed NMR CSI concentration profiles obtained highlighted the clear differences in the disintegration/dissolution/release behavior for the two types of tablet and provided insights into their molecular origin. The study illustrates the potential of the NMR CSI technique to give information of importance for the development of pharmaceutical tablets and, more broadly, for the general understanding of any operation that involves the immersion and ultimate disintegration of a dry polymer matrix in a solvent.



1. INTRODUCTION

The present study is concerned with the process where an initially dry polymer matrix swells and ultimately disintegrates in a surrounding aqueous solution. To understand this process is of obvious and considerable interest for controlled release applications, where the matrix also contains some additional compound(s) to be released. More generally, it is important for any unit operation that involves the swelling and/or dissolution of a sample of initially dry polymer in a solvent.

In drug delivery, one of the most common strategies to achieve a controlled release function is to use a swelling polymer tablet. Consequently, there are numerous published studies on this subject.[1−6] The swelling and disintegration of a polymer tablet, and the concomitant release of its contents of low-molecular weight compounds, is a highly complex process that involves several steps.[1,3,4] The process of solvent penetration and the subsequent transition of the initially glassy polymer leading to a layer of solvent-swollen polymer at the surface of the dry tablet is often considered essential for the performance of the tablets.[4] Traditionally this highly viscous layer, which withstands convective flow in the surrounding solution, is referred to as the "gel layer".[1] However, since the latter terminology is not in accordance with the current molecular understanding of gels (in reality, the layer is a more or less concentrated polymer solution),[7] we prefer to refer to the layer simply as the (solvent) swollen layer. The ultimate release of polymer into the surrounding solution occurs from the surface of the swollen layer by erosion caused by convective flow in the surrounding solution.[1,4,8] Under properly chosen conditions, the polymer release can be very slow, so that it takes several hours or even days for the tablet to totally disintegrate. During this time, the swollen layer acts as a transport barrier for the diffusing drug. An increased thickness of the swollen layer results in a slower disintegration of the tablet, a longer way for the drug to diffuse, and hence, a slower drug release.[9,10]

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Hydrophobic drugs are of increasing importance for the pharmaceutical industry today, and there is a need to develop formulations that allow for a controlled release of such compounds.[11] Tablets of Pemulen TR2, a commercially available cross-linked hydrophobically modified poly(acrylic acid), here referred to as HMPAA, have shown a promising ability to control the release of poorly soluble hydrophobic compounds.[12−15] A hypothesis underlying initial experiments with HMPAA tablets was that interactions between the hydrophobic compound and the "hydrophobes" (C10−C30 alkyl-chains grafted onto the PAA backbone) on HMPAA play a major role for the drug release from the tablets.[12] However, other effects may also contribute.[13−15] In particular, at sufficiently high degrees of substitution HMPAA will no longer be totally miscible with water, even though the parent PAA polymer is hydrophilic.[16,17] Like other amorphous polymers in worse-than-theta solvents,[18] a water-insoluble hydrophobically modified polymer typically swells to a finite, but large, water content when immersed in a reservoir of water. The equilibrium concentration of the polymer dissolved in the dilute water phase may be exceedingly low. As we will show below, Pemulen TR2 in the acid form is a water-insoluble but water-swelling form of HMPAA, which, however, becomes soluble if a sufficient fraction of the carboxylic acid groups are deprotonated by alkali titration. In a very recent study, we investigated the release of ibuprofen from pharmaceutically realistic Pemulen TR2 tablet formulations that contained, in addition to polymer and drug, large proportions of lactose and small proportions of talc and magnesium stearate.[15] A striking observation was that the rate of tablet disintegration and ibuprofen release could be altered drastically by changing the solvent conditions. Of specific interest here is that the release processes were much more rapid in water than in phosphate buffer at pH 7.2, suggesting major consequences of even a slight deprotonation of the HMPAA carboxylate groups.

Given the above observations, the main objective of the present study is to obtain a detailed molecular picture of what happens when a tablet of HMPAA, containing also low-molecular weight additives, swells and releases its molecular content in water. We have chosen to study idealized tablets where the excipient polymer totally dominates the composition, but where low amounts of two uncharged low-molecular model compounds are also included: a poorly water-soluble model drug, griseofulvin, and an infinitely water-soluble compound, ethanol. Moreover, we compare the behavior of tablets based on the water-insoluble acid form and a partially neutralized water-soluble form of HMPAA, respectively. In view of the fact that not all our studied tablets actually dissolve molecularly in dilute solution, we have in this work chosen the more general term "disintegration", with the understanding that this may also include dissolution into a dilute solution in the conventionally considered situations where the polymer is fully miscible with the solvent.

For the studies described above, we have chosen to use NMR Chemical Shift Imaging (CSI)[19,20] as our method to obtain spatially resolved information on the chemical composition of a swelling and disintegrating polymer tablet. Important advantages with the CSI method are that information on concentrations of, in principle, all different components in the swelling tablet can be obtained in a single experiment, and that there is no need for the sample to be optically transparent. CSI is a known technique in the NMR community,[20−23] but it has not been widely applied to the study of transport processes. However, Salvati et al.[20] demonstrated the potential of the technique for such purposes when they used CSI to monitor molecular transport in colloidal gels and were able to obtain a submillimeter spatial resolution with a low time-resolution of 30 min, while still maintaining a high spectral resolution.

A number of other NMR or MRI (magnetic resonance imaging) techniques have previously been employed to study swelling tablets for controlled release formulations, as summarized in recent reviews.[24−27] Studies have been performed both in the absence[28−34] or presence[35−38] of convection in the release medium ("static" or "nonstatic" conditions, respectively). A problem with NMR/MRI methods is that the signal intensity from regions with a high polymer content is affected by the T_1 and T_2 relaxation times.[35] Consequently, only qualitative information on processes such as swelling are often obtained,[36,37,39] as opposed to quantitative information on position-dependent concentrations of polymer or other components in the swelling tablets. However, methods do exist where a quantitative description can be achieved; see refs 30, 35, 38, and 40−42. Many of the latter studies are summarized in the review by Mikac et al.[43]

Systems containing more components than the polymer and the solvent have been far less studied by NMR methods,[25] and previous such studies have often used also other nuclei in addition to the proton, for example, fluorine (^{19}F).[41,44−46] Dahlberg et al. have developed a method combining three different NMR experiments where they could detect the polymer, the model drug, and the penetrating solvent.[44−46] They could also detect the released amount of the model drug. A practical limitation when using additional nuclei such as ^{19}F is that this severely restricts the choice of model substances and introduces a lower signal-to-noise ratio, which influences the experimental time.

This work and a future publication will examine solvent swelling and molecular transport in drug-loaded HMPAA tablets using the NMR CSI method. In the future work we will focus on an additional feature of HM polymers, namely, their interactions with amphiphilic compounds, such as surfactants.

2. MATERIALS AND METHODS

2.1. Chemicals. Pemulen TR2 NF (lot no. 0100834373) was kindly provided by Lubrizol Chemicals. According to the supplier, the polymer consists of poly (acrylic acid), cross-linked with allylpentaerytritol, and contains 52−62 wt % of −COOH groups. The polymer is hydrophobically modified with grafted C10−C30 alkyl-chains, and by comparing the recorded ^{1}H NMR intensities (for the soluble half-neutralized HMPAA) of the terminal methyl groups to those of the PAA backbone, we deduced a degree of substitution of approximately 3 hydrophobes per 100 repeating units in the HMPAA chain. From titration experiments we obtained the effective mass per carboxylic acid group of the cross-linked HMPAA and could finally calculate that a 1 wt % solution of Pemulen TR2 NF in water contains ca. 4 mM of alkyl grafts (hydrophobes). This is in good agreement with previous analyses of similar materials by Paulsson and Edsman (2002).[14]

Prior to use, dialysis was performed to purify the polymer. The polymer was mixed in 0.2 M HCl solution overnight and subsequently added to dialysis tubes (MWCO = 100 000 Da), which were placed in deionized Milli-Q water. Dialysis was performed for 7−8 days while monitoring the conductivity of the medium. Purified polymer solutions were then freeze-dried and stored in desiccators until used. The purified polymer in the acid form will henceforth be referred to as the non-neutralized polymer. Neutralized polymer (half or fully neutralized) was achieved via addition of a stoichiometric amount (according to previously performed titrations) of 1 M NaOH solution

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to a 1 wt % solution of purified polymer. After thorough mixing the neutralized polymer was freeze-dried.

Griseofulvin (lot no. 028K1105) from Sigma Aldrich was used as supplied. Deuterated water (D_2O) (Armar Chemicals, Döttingen, Switzerland), doped with a small amount of a paramagnetic gadolinium relaxation agent (0.7 mL/L), Magnevist 469 mg/mL (Schering, Berlin, Germany, lot no. 64511D, 0.5 mmol gadolinium/mL), was used as the solvent for the NMR experiments. Magnevist was added to increase the T_1 relaxation rate. The very low concentration of Gd^{3+} (0.35 μM) in the solvent should not influence the studied processes.

2.2. Preparation of Reference Samples. Reference samples were prepared containing polymer (non-neutralized or half-neutralized) and D_2O to study the visual appearance of the samples and the chemical shift of residual protons in D_2O. All components were added directly to 5 mm NMR tubes, which were subsequently flame-sealed. The samples were then thoroughly mixed by repeated centrifugation where the samples were turned end-overend several times. A high-resolution ^1H NMR spectrum from each sample was then obtained using a Bruker Avance II 200 spectrometer operating at a ^1H resonance frequency of 200 MHz and equipped with a Bruker DIF-25 gradient probe. The settings (tuning, matching, shimming, spectral width, acquisition time, and number of scans) were optimized for each sample.

2.3. Tablet Production. To ensure proper mixing of the model drug and the polymer in the powder used for tablet production, griseofulvin and polymer were first mixed in ethanol, then dried and milled. Griseofulvin was dissolved in ethanol at 1 mg/g, and purified polymer was then added to yield a 5 wt % solution, which was stirred until a homogeneous viscous solution was obtained. The latter solution was left to dry in a fume hood overnight and was then placed in vacuum oven (at ambient temperature) for 3 days. The dried polymer/drug mixture was milled into a powder using a coffee grinder (OBH Nordica) and was then kept in a desiccator until used or analyzed. Tablets containing half-neutralized polymer were made by mixing the griseofulvin-containing powder of the non-neutralized polymer with freeze-dried powder of the fully neutralized polymer, using the coffee grinder. Using a modified IR press, the final powder was compressed into tablets for NMR swelling experiments with a tablet diameter of 4 mm, a thickness of ca. 1.5 mm, and a mass of ca. 20 mg.

The amount of griseofulvin in the dry tablets was 2 wt % for the non-neutralized polymer and 1 wt % for the half-neutralized polymer. Thermogravimetric analysis of the powder showed the presence of residual ethanol (3−4 wt %).

2.4. Chemical Shift Imaging. *2.4.1. Experimental Setup.* All tablets used in the experiments were brittle and porous and had to be freshly prepared before the experiments. There were, however, no indications that the quality of the tablets affected the reproducibility of the CSI experiments. The tablet was glued on a solid support, placed in a 5 mm o.d. NMR tube, and routinely left to dry overnight in a desiccator (repeat experiments indicated, however, that the overnight drying was not critical) before the NMR experiment. The solid support kept the tablet fixed horizontally in the NMR tube (see Figure 1). Solvent (D_2O doped with Gd^{3+}) was injected on top of the tablet and the NMR tube with the tablet was then placed in a volumetric flask containing 100 mL of solvent. This corresponds effectively to "sink conditions", since at complete dissolution the concentration of griseofulvin in the solvent was ≤30% of the solubility. A small stirrer was placed at a constant distance of 10 mm above the upper surface of the swollen layer in order to produce shear forces on the surface. All experiments were performed at 25 °C.

To minimize the risk of air bubbles forming in the dissolving tablet, an evacuation procedure was performed before each experiment. The procedure is based on the setup by Fyfe and Blazek (1998).[47] The NMR tube with the tablet was placed in a chamber and exposed to vacuum (P < 1 mmHg) for 5 min. The vacuum was then broken by addition of Gd^{3+}-doped D_2O, and a low pressure was maintained for an additional 5 min to ensure that all pores of the tablet were emptied. The start of the evacuation procedure was defined as the starting point

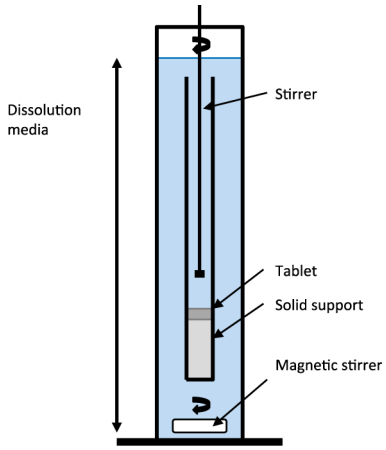

Figure 1. Experimental setup to monitor molecular transport in a swelling and disintegrating tablet. See text for explanations.

of the experiment, and the amount of D_2O added was noted and used when calculating the released amount of drug.

The tablets were left to swell and release polymer, drug, and ethanol in the setup with stirring in between the NMR measurements. In connection with each NMR measurement a 1 mL aliquot was taken from the volumetric flask and analyzed with high-performance liquid chromatography (HPLC) (Dionex 3000RS) using an isocratic solution of 30% acetonitrile and 70% acetic acid (0.1%), with a flow of 0.400 mL/min on a reversed phase Acclaim RLSC C18 2.2 μm, 120 Å, 2.1 × 50 mm column. The released amount (% released) after analysis of aliquot number n_a, giving the griseofulvin concentration c_g, was then calculated according to

$$\%\ \text{released} = \frac{(C_g(V_0 - V_a(n_a - 1))) + \sum_{n=0}^{n_a-1}(V_a C_{g,n})}{m_{g,t}} \quad (1)$$

where the initial volume is given by V_0 = 100 mL, V_a denotes the volume (= 1 mL) of the aliquots, and the number of aliquots is denoted n_a. The mass of griseofulvin in the initial dry tablet, $m_{g,t}$, was equal to 1 or 2 wt % of the dry tablet mass for tablets of half-neutralized and non-neutralized polymer, respectively. All CSI experiments were performed at least twice to validate reproducibility. The reproducibility was evaluated as the relative difference between repeat measurements (at times 6 h and 24 h). The reproducibility was generally ±10−20% of the reported concentrations and slightly better (±5%) in the concentrated region for the non-neutralized tablets.

Upon measurement the NMR tube with the tablet was disconnected and placed in the spectrometer. After each measurement the sample was reconnected to the setup and the dissolution process continued. This was repeated at specific time intervals over a 48 h time period. After the last measurement, a rough mass balance test was performed. The solution above the swollen tablet in the NMR tube was poured out, and the remainder of the jelly-like swollen tablet was then pushed out in 100 mL of Milli-Q water, where it was allowed to disintegrate completely. After complete disintegration, the solution was analyzed spectrophotometrically (Varian, Cary 300 Bio) at 295 nm for griseofulvin.

2.4.2. NMR Measurements. NMR experiments were performed on a Bruker Avance II 200 spectrometer operating at a ^1H resonance frequency of 200 MHz and equipped with a Bruker DIF-25 gradient probe, capable of delivering gradients of strength 9.6 T/m in the z-direction. A detailed description of the theory behind the technique and pulse sequence can be found in Salvati et al. and Brown et al.[19,20]

Using the nomenclature of ref 20, the CSI the pulse sequence was applied with the following parameters: 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. The stability of the technique and the spectrometer at these gradients has been validated previously, via

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measuring diffusion using low gradient amplitudes and small steps.[48] This gave a vertical spatial resolution of 317.8 μm. Using four scans per gradient increment, a z-resolved image could be recorded in around 20 min. Because of the very slow solvent penetration the concentrations of all components could be considered to be constant during a CSI experiment.

Figure 2 shows a chemical shift image, composed from 64 spatially resolved ^{1}H spectra, from a measurement of a swelling/eroding tablet after 6 h. In the image one can distinguish the following peaks (from left to right): An HDO peak from residual protons in D_2O, a well-separated peak from ethanol, and a cluster of peaks from protons of ethanol and polymer. Due to the low solubility of the drug, no protons from the drug could be detected with the limited number of scans used in the CSI experiment.

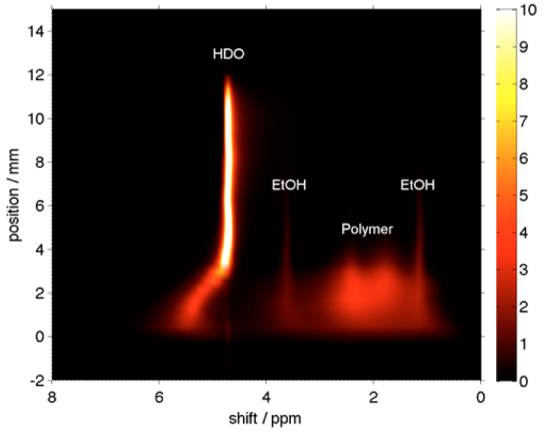

Figure 2. Chemical Shift Image (CSI) composed from 64 ^{1}H spectra at different vertical positions (slices) of a swelling and disintegrating tablet, taken after 6 h. The bottom part refers to the swelling tablet and the top part to the surrounding bulk solution. The region used for quantitative analysis along the vertical axis was limited by the solid support at the bottom of the tube and the homogeneity of the B_1 field at the top. Each color-coded band in the image corresponds to a proton peak from a tablet component, as noted in the image.

3. DATA EVALUATION

As shown by Salvati et al., the short echo time (t_E) reduces the effects from T_2 relaxation and J-coupling.[20] The effects of T_1 relaxation on the recorded signal intensity were reduced via the addition of the gadolinium relaxation agent, keeping $t_r > 5T_1$ as confirmed by experiments. Thus, from the areas obtained via integration of the proton peaks, the concentrations of all NMR-detectable components in the system could be calculated for each slice (corresponding to a well-defined vertical position) of the sample tube. In cases where some peaks overlapped a deconvolution was performed, using MATLAB with a sum of Lorentzian functions (see Figure 3A), to estimate the peak areas for all components. The areas, plotted against the vertical position, for peaks corresponding to protons from residual ethanol (see above), D_2O and the polymer are shown in Figure 3B.

The ethanol peak area shows an expected behavior in Figure 3B, decreasing outward toward the surrounding medium. For the polymer, however, the peak areas go through a maximum at a certain distance from the stabilizer. This illustrates that, even with short echo times, effects from T_2 relaxation on the measured peak area (see section above) may remain at high polymer concentrations.[25] The area from residual HDO protons in D_2O is increasing to the left, toward the solid support, in Figure 3B. Furthermore, there is a shift of the peak frequency as the concentration of polymer increases (Figure 2). Both of these features are due to labile carboxylic acid protons on the polymer. As water penetrates into the dry tablet, it hydrates the polymer, and an exchange occurs between the carboxylic acid protons and those of the water molecules. (There is also an exchange between the hydroxyl group of ethanol and D_2O; however, because of the low amount of ethanol (less than 5 wt %), the latter effect is estimated to be $\leq$0.05 ppm). We thus have two populations p_a and p_b, of exchanging protons a and b with intrinsic resonance frequencies ν_a and ν_b, respectively. If the exchange between the populations is faster than the frequency difference between the two peaks, "fast exchange" conditions prevail, resulting in a single peak with an area equal to the sum of the individual peak areas at a

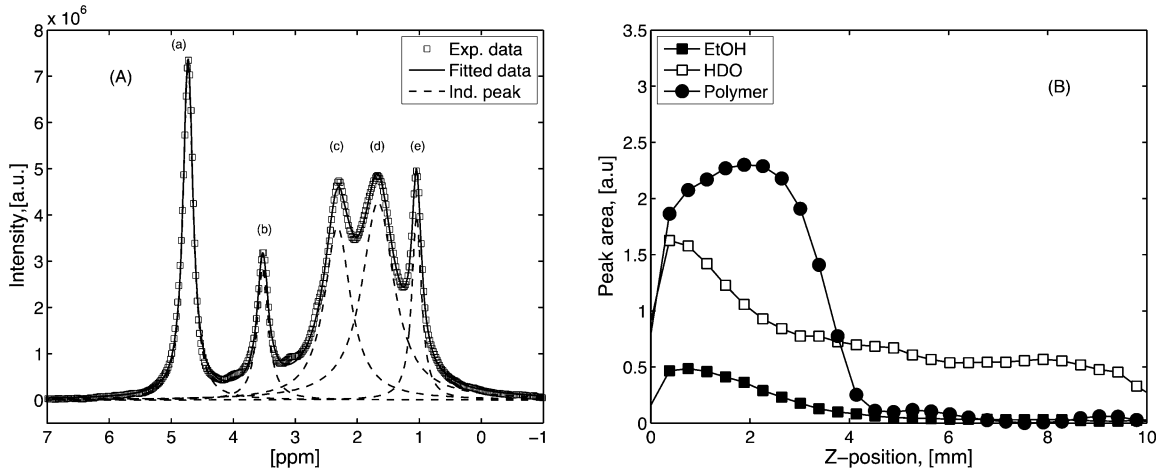

Figure 3. (A) ^{1}H spectrum from a CSI experiment at 6 h for a slice at z-pos = 3 mm with 13 wt % polymer. The peaks correspond to (from left to right) HDO (a), ethanol (b), polymer (c), polymer (d), and ethanol (e). The area of the ethanol (b) peak was used for determining the ethanol concentration. The peaks (a) and (c) were used to calculate ΔCS (see text). Squares show the experimental data and the full line the fitted sum of five Lorentzian functions, individually indicated by dashed lines. (B) A non-neutralized polymer tablet after 6 h showing the measured peak areas, obtained via integration, plotted as functions of the vertical position in the NMR tube. The zero position is chosen as the top surface of the solid support.

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frequency (ν_{av}) corresponding to a weighted average of their individual frequencies[49]

$$\upsilon_{av} = p_a \upsilon_a + p_b \upsilon_b \quad (2)$$

From the above, it becomes clear that the shift and the peak area of the observed average peak depend on the polymer/D_2O weight ratio. The observed shift can be used to determine the polymer concentration at high concentrations, avoiding issues with T_2 relaxation, as described in detail below.

The measured peak areas and the observed HDO shifts were used to calculate the polymer and ethanol concentrations for all slices in the NMR tube using the following procedure (see also Figure 4).

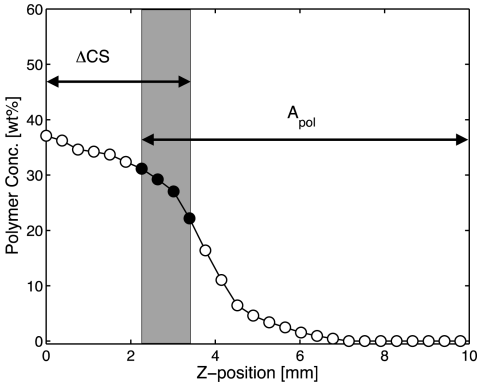

Figure 4. Illustration of the procedure used to calculate the polymer concentration profiles. At high concentrations, calibrated HDO shift data (ΔCS) were used. At low concentrations, the polymer peak areas (A_{pol}) were used. The shaded area in the middle shows the region where A_{pol} data were calibrated against ΔCS data to obtain a quantitative relation between A_{pol} and polymer concentration.

1. The HDO shift data (ΔCS) gave, via NMR experiments on reference samples of known compositions (see below), the polymer concentration in the concentrated region, where the shift effect was large.

2. An intermediate region of polymer concentration (ca. 25–30 wt % for non-neutralized and 15–30 wt % for half-neutralized) was identified where the HDO shift was large, while the polymer peak area was still quantitatively reliable. This region was used, together with the information from step 1, to obtain a relation between the polymer peak area and the polymer concentration. The latter relation was then used to calculate low polymer concentrations in slices where the HDO shift was insignificant but the polymer peak area was still measurable (see Figure 4 for clarification).

3. Using peak area relations obtained from reference samples with known contents of polymer, D_2O and ethanol, together with the polymer concentrations obtained from steps 1 and 2, the ethanol concentrations were calculated by comparing the ethanol and polymer peak areas in regions of intermediate polymer concentration (the shaded area in Figure 4), where the polymer peak area was reliable.

4. The ethanol concentrations obtained in step 3 were used to obtain a relation between ethanol peak area and the ethanol (volume) concentration (mol/L) that was then used for the entire CSI experiment, including regions of high polymer concentration. The latter extrapolation, together with the accumulated errors from two peak area determinations described in (3), led to a rather poor reproducibility, in the worst case a factor of 2, but typically less. The concentration of ethanol was, finally, converted from mol/L to wt % units using an experimentally determined (linear) variation of the density of polymer/D_2O mixtures with the weight fraction of polymer.

4. RESULTS

4.1. Behavior of Reference Mixtures of Polymer and D_2O. A visual examination of reference samples where the non-neutralized polymer was mixed with D_2O revealed a miscibility gap when the polymer concentration was decreased. Below 25 wt % polymer, the mixtures separated into one concentrated and one dilute phase, the latter containing (according to NMR)

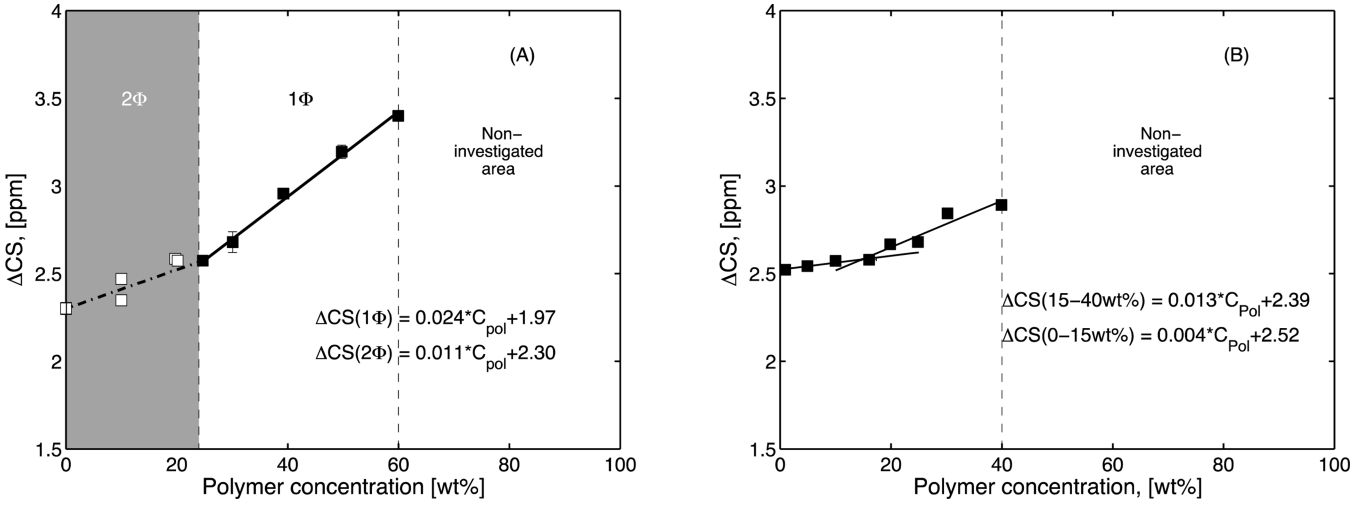

Figure 5. Chemical shift difference (ΔCS) between a polymer peak and the HDO peak (see Figure 3) plotted against the polymer concentration for non-neutralized (A) and half-neutralized (B) polymer. Filled squares represent one-phase samples (ΔCS error bars indicate standard deviations from replicate samples, in some cases smaller than the symbols) and open squares two-phase samples, where peaks from both the dilute and the concentrated phase were observed; see text. The gray area represents the miscibility gap. The solid lines indicate the linear fits to the data, and the dashed line drawn across the miscibility gap connects the measured ΔCS value from the most dilute sample with that from the least concentrated single-phase sample.

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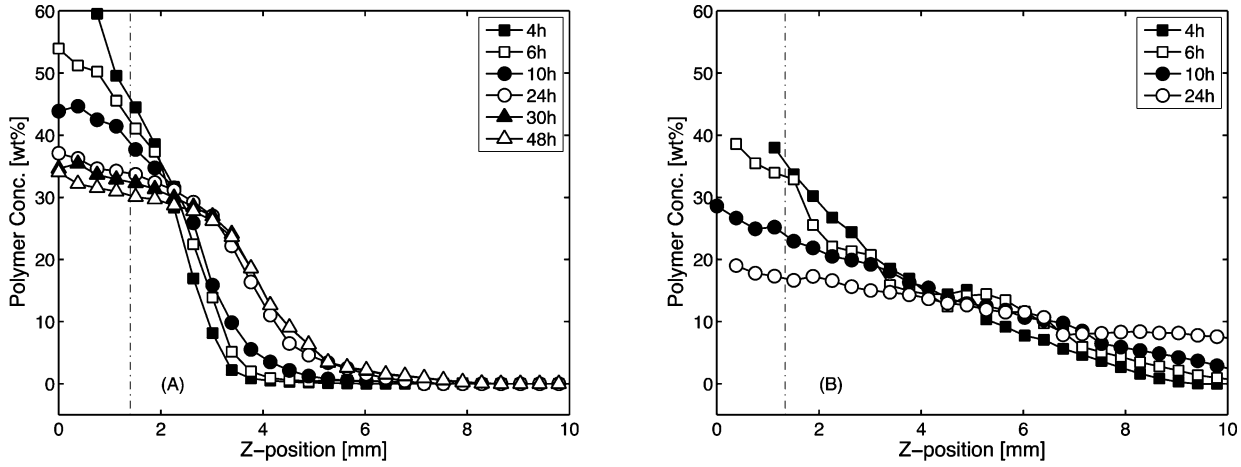

Figure 6. Polymer concentration profiles at different times for tablets swelling in D_2O: non-neutralized (A) and half-neutralized (B) polymer. The surface of the solid support is at the position 0 mm, and the dashed line indicates the position of the surface of the initial dry tablet. Each panel shows the (representative) development with time for a single tablet. The available calibration data (Figure 5) limit the quantifiable polymer concentrations to ≤60 wt % for non-neutralized and ≤40 wt % for half-neutralized tablets.

a finite but very low concentration of polymer. However, even in samples containing quite low amounts of polymer (less than 0.5 wt %) phase separation could be visually established. A fractionation is expected in biphasic samples, so that the dilute solution contains mainly low-molecular fractions. Due to a very high viscosity and very long equilibration times, homogeneous samples could not be obtained above ca. 60 wt % of polymer. By contrast, all half-neutralized samples were fully miscible with D_2O.

NMR shift data from reference samples of HMPAA mixed with D_2O are shown in Figure 5 for the non-neutralized (A) and the half-neutralized (B) polymer, plotted against the measured chemical shift difference (ΔCS) between the peak from residual HDO protons and a peak of nonexchanging polymer protons (see Figure 3). A clear variation of ΔCS with the polymer concentration is apparent. The chemical shift of the HDO peak is less affected by the polymer concentration in the half-neutralized samples, which is expected (cf. eq 2), because there are half as many carboxylic acid protons available for fast exchange in the half-neutralized sample.

NMR spectra from the phase-separated samples of the non-neutralized polymer generally featured two HDO peaks, thus confirming the phase separation. At high or low polymer concentrations in the phase separation region, the peak from the minority phase appeared only as a shoulder on the peak of the dominating phase; here, only the shift of the dominating phase could be extracted with satisfactory accuracy. However, for samples containing 10 wt % of polymer, the two peaks were of comparable size, and the ΔCS values for both phases are given in Figure 5A. By contrast, in the CSI experiments, only a single HDO peak was seen (see Figure 2), with a shift that varied smoothly with the position in the NMR tube. Presumably, the domain sizes of the concentrated phase were sufficiently small to allow rapid exchange of protons between the phases. In this concentration region, the linear interpolation (dashed line in Figure 5A) was used to obtain the global polymer concentration from ΔCS.

For the half-neutralized samples, the relation between ΔCS and the polymer concentration was nonlinear. Below ca. 15 wt % polymer the slope of the curve in Figure 5B is lower, and a satisfactory fit to the data could be made simply with two straight lines. At concentrations above 40 wt % polymer the samples became too viscous to handle, and no homogeneous samples could be achieved even with vigorous centrifugation.

4.2. Concentration Profiles from NMR Imaging.

4.2.1. Polymer. An initial very rapid penetration of D_2O into the tablet was evident from the CSI experiments, and already at 2 h D_2O had penetrated the whole tablet. We attribute this rapid penetration to the evacuation procedure preceding the measurements (see above). In some cases a small amount of water had actually gone past the dry tablet, forming a thin water layer between the tablet and the solid support. This gave rise to an initial dissolution also from the bottom of the tablet. All later transport processes monitored by the CSI experiments were slow and purely diffusion-driven.

Using the procedure described in "Data Evaluation", concentration profiles for the polymer could be calculated for tablets swelling in D_2O. Water concentration profiles are not shown since they, neglecting the small content of ethanol, simply mirror the polymer concentration profiles. Figure 6 compares the results for non-neutralized (A) and half-neutralized (B) polymers. Significant differences are apparent, but in both cases the release of the matrix polymer was far from complete after the 48 h duration of an experiment. The confined geometry of the NMR setup clearly results in a slow tablet disintegration compared to more standard conditions, as in a stirred USP bath.

For all tablets, the concentration of polymer at low z values decreased over time, as the polymer expanded further into the surrounding medium. However, after 24 h a break in the polymer concentration profile had developed for the non-neutralized polymer tablets (Figure 6A) at ca. 3 mm from the plug, observable as a relatively steep decrease of the polymer concentration beginning at ca. 25 wt % of polymer. It appears that a constant concentration of ca. 25 wt % is being approached throughout the inner regions of the swollen tablet at very long times. Significantly, this limiting concentration is within error the same as that of the maximally swollen concentrated phase, bordering the two-phase region, in Figure 5A. A visual examination of the dissolving tablet in the NMR tubes indeed revealed a two-phase region appearing as a cloudy region in the swollen layer. Generally, four regions could be established visually in the swollen tablet, as illustrated schematically in Figure 7. From bottom to top, these were

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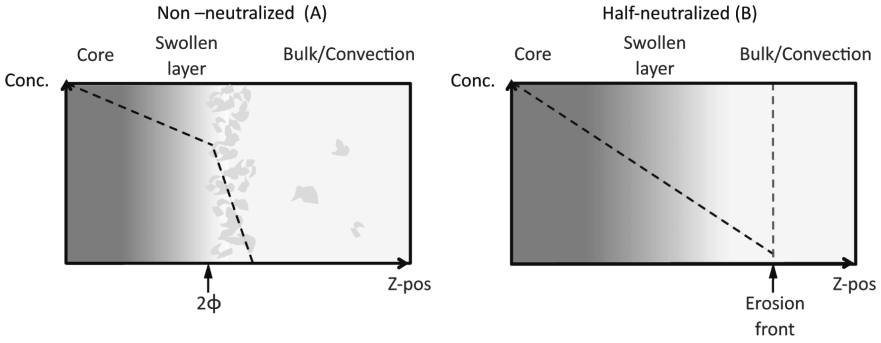

Figure 7. Schematic figure comparing the visual appearances of non-neutralized (A) and half-neutralized (B) polymer tablets; "2φ" indicates the beginning of the two-phase region. The dashed black lines show schematically the corresponding variations of the polymer concentration determined by NMR CSI.

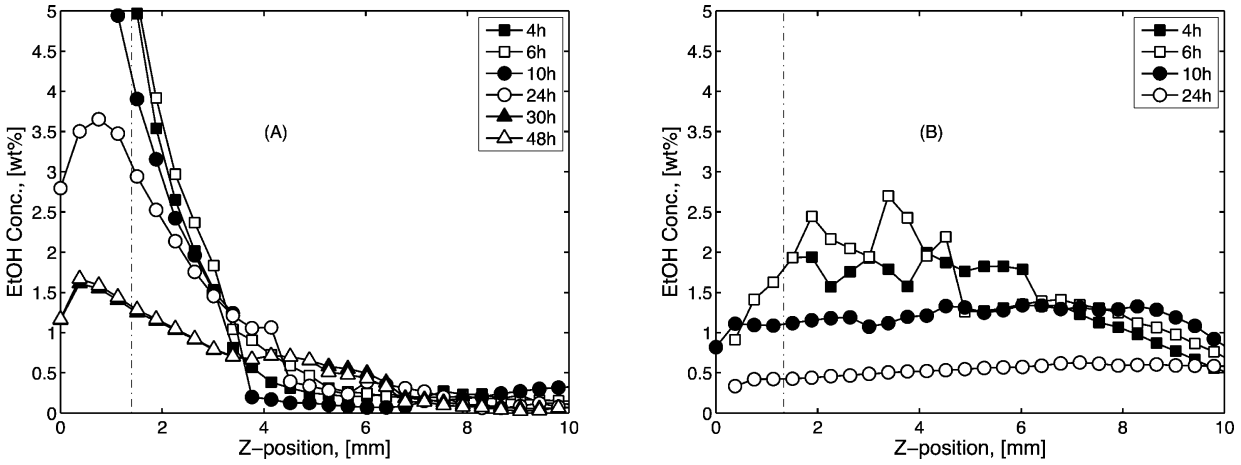

Figure 8. Concentration profiles of ethanol in tablets from non-neutralized (A) and half-neutralized (B) polymer swelling in D_2O. The surface of the solid support is at 0 mm, and the dashed line indicates the initial tablet surface.

(1) an inhomogeneous region containing, presumably, partially swollen particles originating from the initial dry compressed tablet, (2) a clear swollen region, (3) a cloudy region (indicating a two-phase), and (4) a low-viscous dispersion of swollen particles that flowed upon inversion of the tube. However, the boundaries between the various regions were not sharp. For instance, small amounts of undissolved material could be seen in the clear swollen region. The most concentrated region (1) of the tablets showed the same visual appearance throughout the experiment, and at 48 h there was still a large amount of partially swollen particles in the bottom part of the tablet.

Partially neutralizing the polymer strongly affected the swelling of the polymer. The concentration profiles of the half-neutralized polymer (Figure 6B) were extended and smoothly decreasing. An examination of the tablets visually during dissolution in the NMR tube confirmed, in agreement with the experiments on the reference samples (Figure 5) that no two-phase region formed. The visual appearance is schematically illustrated in Figure 7. The tablets seemed to swell more and faster, and already after 24 h the surface of the swollen layer (visually established to be at ~4 cm) extended far beyond the observable region determined by the length of the coil of the NMR probe. Consequently, the NMR measurements were terminated, although sampling for measurements of griseofulvin release (see below) continued until 48 h.

4.2.2. Ethanol—A Water-Soluble Model Substance. Despite the uncertainties in the absolute ethanol concentrations obtained from NMR (see section "Data evaluation"), Figure 8 demonstrates unequivocally that the transport of ethanol was clearly different for the non-neutralized and half-neutralized polymer tablets. For the non-neutralized polymer tablet the ethanol concentration was initially high in the inner region of the tablet but started to decrease rapidly after 24 h, at which time the water had penetrated the entire tablet (see Figure 6A). At longer times the ethanol concentration profiles had leveled off much more than the corresponding polymer concentration profiles. For the half-neutralized tablet the concentration profiles leveled off very rapidly, indicating a rapid and unhindered diffusion of ethanol. This is consistent with the rapid penetration of water throughout the half-neutralized polymer tablet (Figure 6B).

4.3. Release of a Hydrophobic Model Substance. As explained above, griseofulvin was not detected in the NMR CSI experiments. Instead, the release of griseofulvin into the surrounding solution was measured by HPLC. The release of griseofulvin in the experimental setup was very slow (Figure 9) but significantly faster for the non-neutralized than for the half-neutralized polymer tablets. Analyses of the remaining swollen tablets after termination of the NMR experiment confirmed that the majority of the drug still remained in the tablets. However, as some of the swollen tablet was lost in the crude extraction procedure, the latter determination of unreleased griseofulvin was not quantitative.

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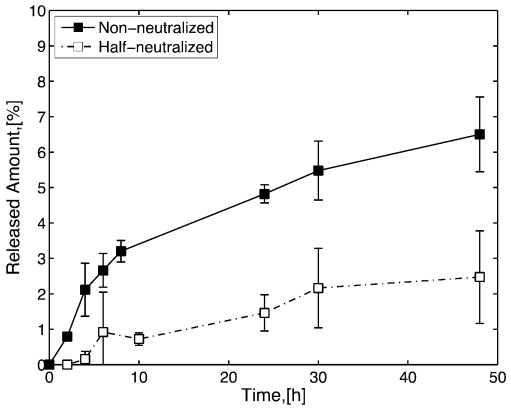

Figure 9. Release of griseofulvin in D_2O from swelling tablets of non-neutralized (filled symbols) and half-neutralized (empty symbols) polymer tablets. Error bars represent standard deviation ≥2.

5. DISCUSSION

5.1. Using NMR CSI To Study Swelling and Molecular Transport in Polymer Tablets. Using NMR CSI to study molecular transport in colloidal systems has many advantages: there is no need to use labeling, and the technique is noninvasive. Specifically, we have here shown that the novel method and experimental setup developed in the present study are able to give detailed information on solvent penetration and transport of low-molecular model compounds in polymer tablets in contact with a surrounding solvent. We have been able to simultaneously obtain quantitative concentration data on polymer and ethanol as D_2O penetrates the tablet. With this information, together with visual observations and complementary studies of model drug release and polymer phase behavior, we could highlight important differences between tablets that differ significantly in their miscibility with water. It should however be noted that the experimental results obtained cannot be directly compared to those obtained in standardized in vitro tests, for example, the USP bath and in vivo. Most probably, the low convection from the small stirrer in the NMR tube produces only minor erosion of the polymer matrix due to low shear. Furthermore, the swelling and release in the CSI experiment only proceed in the axial direction.

5.2. Water Penetration, Molecular Diffusion, and Release from Polymer Tablets. The two cases studied in this paper illustrate two different situations of polymer disintegration from tablets. On the one hand we have a polymer that is fully miscible with water and can swell indefinitely, and on the other hand we have a polymer that is not fully miscible with water and, hence, only undergoes a finite swelling until the maximum water content of the polymer-rich phase has been reached. This gives rise to quite different scenarios with respect to water penetration, polymer release, and release of the two low-molecular components, ethanol and griseofulvin, that were included in the dry tablets.

The half-neutralized polymer tablet shows the most classical behavior, where the swollen polymer layer simply swells until the shear forces from the convection are larger than the cohesive forces in the layer.[1,9,10,50] Additionally, the water penetration is comparatively rapid, which is most likely caused by the numerous counterions to the carboxylate charges, which provide a major contribution to the osmotic pressure gradient. As a result of the rapid water penetration, the tablet becomes entirely transformed (in a time period of less than 24 h) into a transparent, swollen semidilute polymer solution. In this matrix, the ethanol transport is rapid, and the ethanol concentration gradient within the tablet rapidly decreases.

By contrast, the release of griseofulvin is rather slow. However, this observation can be explained by the low solubility of griseofulvin. Let us assume that, when water penetrates the polymer matrix, an equilibrium develops between a solid griseofulvin phase and a saturated solution. (Our preliminary experiments showed that a small amount of griseofulvin is also solubilized in aggregates formed by hydrophobes, but this small fraction can be neglected here). Let us furthermore assume that the polymer self-diffusion is very slow, so that the mutual diffusion between water and polymer is totally determined by water diffusion in a chemical potential gradient. Then it follows that the mass ratio between polymer and griseofulvin in the swelling tablet should be practically unaffected by water penetration. By simply turning the NMR tube upside down, we could locate the erosion front in this system, and from the CSI experiments we could deduce that the polymer concentration at the erosion front was ca. 0.3 wt %. With a griseofulvin/polymer mass ratio of 0.01, this gives a total griseofulvin concentration of 85 μM, which is more than twice the solubility of griseofulvin, which is 35 μM.[51] Thus, it seems reasonable to assume that particles of solid griseofulvin follow the polymer all the way to the erosion front, so that the entire swollen tablet contains a saturated solution of griseofulvin. Such a scenario has indeed been confirmed by previous studies.[52−54] The rate of hydration of the polymer is faster than the dissolution of the drug and the polymer expansion moves the nondissolved drug particles outward toward the surrounding medium.

Modeling the release from a swollen tablet as a one-dimensional diffusion from a saturated reservoir where the concentration of dissolved griseofulvin equals the solubility, the transport of griseofulvin is given by

$$J = \Delta C \times \frac{D}{\sigma} \tag{3}$$

where J is the flux of griseofulvin from the reservoir through a stagnant layer of thickness σ, with a diffusion rate D, and ΔC is the difference in concentration across the stagnant layer. Assuming a linear release rate of the griseofulvin, the rate determined from the release profile in Figure 9 is 0.05% of the total griseofulvin content per hour. This gives a flux of griseofulvin of 6.5×10^{-9} mol s^{-1} m^{-2}. Using a diffusion coefficient of 1.1×10^{-9} m^2 s^{-1} for griseofulvin,[51] and assuming that ΔC equals the solubility of griseofulvin, we calculate a thickness of the stagnant layer of 6 mm, which is of the expected order of magnitude, considering the position of the stirrer. From this simple calculation we conclude that the observed slow release of griseofulvin may, in fact, be expected.

The non-neutralized polymer shows a different behavior where, owing to the miscibility gap, the swollen layer around the tablet can only swell until it reaches the maximum solvent content that is consistent with the polymer−solvent phase diagram (Figure 7A and Figure 5A). Previous studies on HPMC tablets have established similar behavior upon addition of solutes that lowered the polymer cloud points.[55−57] To the best of our knowledge, our paper is the first to show concentration profiles of the polymer inside swelling tablets of this type. Another consequence of the poor solubility of the polymer is that the osmotic pressure gradient in the system becomes rather weak; thus the water penetration becomes slow.

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This is presumably why the most concentrated region of the non-neutralized tablet remains heterogeneous throughout the experiment. We suggest that in this region there remain long-lived particles of polymer into which there is a slow water transport. Hence, even a soluble compound, such as ethanol, can remain trapped for a long time, giving rise to the pronounced concentration gradient of ethanol in the swollen tablet that begins to flatten out only at the longest investigated times (cf. Figure 8A).

The process at the boundary between the swollen tablet and the surrounding medium is also different from that for a soluble polymer. When the swollen layer is subjected to shear, pieces of the swollen concentrated polymer phase are sheared off and released into the medium as swollen particles. A disintegration of the tablets is seen; however, the polymer is never dissolving molecularly in the medium.[55,56] For our tablets we could establish, by inverting the samples, that a low-viscous dispersion of semiswollen particles had formed outside the swollen layer.

Paradoxically, the release of griseofulvin is more rapid from the tablet of the poorly soluble, non-neutralized polymer; see Figure 9. Studies with caffeine and HPMC tablets have shown a similar, rapid release that occurred when the polymer solubility and swelling of the tablets was decreased, which there was attributed to the absence of a swollen layer.[55] However, in our studies we have been able to obtain a detailed picture of this process, where with time a break in the measured polymer concentration profile develops that directly corresponds to the independently determined polymer/solvent phase behavior. For our tablets a limited swollen layer is formed; however the erosion of swollen particles from the tablets increases the release rate of the drug. The drug release from many small particles, with a large specific surface area, is more efficient than the release from the erosion front of a single macroscopic tablet. There was also an increased initial release rate from the non-neutralized polymer tablets, that is, a "burst" effect, which most likely is due to inhomogeneities in the tablets and the existence of the miscibility gap.[55,56]

6. CONCLUSIONS

Our study demonstrates than NMR CSI is a powerful method to study solvent penetration and molecular transport into and out of an initially dry polymer matrix that also contains additional components. By combining information from the peak areas and chemical shifts in the acquired CSI images, concentrations can be calculated for the various components as functions of position and time. The detailed time-dependent concentration profiles that are thus obtained provide a basis for conclusions regarding the nature of the various molecular transport processes observed and how they depend on the specific experimental conditions. Such insight is of general interest for the understanding of concentrated polymer systems and of obvious relevance for the design of controlled release formulations.

For the specific systems studied, the CSI measurements allowed us to clearly demonstrate the differences in polymer concentration profiles between tablets of a soluble and an insoluble polymer, respectively, and relate the profile of the insoluble polymer to an independently determined phase diagram. For a swelling but insoluble polymer, the tablet swells until it reaches the maximally swollen state at the phase boundary, seen as a clear break of the concentration profile. Solvent-swollen polymer particles then detach from the swollen layer and are released into the surrounding solvent at a rate that may be assumed to depend on the flow conditions in the surrounding. By contrast, a soluble polymer swells continuously, and the polymer that is sheared off by convection ultimately dissolves molecularly in the surrounding solution.

The polymer solubility and the disintegration have large effects on the release of both highly soluble and sparingly soluble substances. The soluble substance is quickly transported out from the swollen tablet of a soluble polymer, but in the insoluble polymer matrix the substance is trapped for an extended time in slowly swelling, partially hydrated polymer/tablet particles. The net result is a faster release of the soluble compound from the soluble polymer matrix. For the hydrophobic substance with a low solubility the case is the opposite: the release is faster from the insoluble polymer matrix. The erosion of small swollen polymer/tablet particles speeds up the release from an insoluble matrix, since the release from the small particles occurs rapidly. Therefore, the erosion of the tablet becomes the governing factor.

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Notes

The authors declare no competing financial interest.

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