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Magnetic resonance imaging study of the transport phenomena of solvent into the gel layer of hypromellose matrices containing tetracycline hydrochloride

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Abstract

Magnetic resonance imaging was used to study the diffusion of a water solution of hydrochloric acid into hypromellose (hydroxypropylmethylcellulose) matrices. Spatially resolved information was obtained about the self-diffusion coefficient and spin–spin relaxation time of solvent protons in the gel layer of hypromellose matrices loaded with different amounts of tetracycline hydrochloride. The data showed the influence of the drug concentration on the diffusion and spin–spin relaxation. Higher drug concentrations in the hypromellose matrix led to greater swelling of the matrix and faster diffusion of the water molecules inside the gel layer of the polymer. The observed differences between the radial and axial diffusion were interpreted in terms of the stresses imposed in the axial direction during the compression of the samples. The spin–spin and diffusion profiles indicated that the diffusion of a water solution of hydrochloric acid into hypromellose, pure and loaded with different amounts of tetracycline hydrochloride, was characterized as a Case II mechanism.

Introduction

Hypromellose (hydroxypropylmethylcellulose) is the most commonly used polymer in the production of controlled release, hydrophilic matrices. Thus, this polymer has been studied widely using different methods: electron microscopy and NMR spectroscopy (Melia et al 1992, 1994); an optical imaging technique (Gao et al 1996); a calorimetric technique (Colombo et al 1999); ultrasound method (Konrad et al 1998); gravimetrical technique (Michailova et al 2001); and by magnetic resonance imaging (MRI) (Snaar et al 2001; Tritt-Goc & Pislewski 2002; Kowalczuk et al. 2003). Those studies demonstrated that hypromellose swells while in contact with an aqueous liquid, dissolution medium or gastrointestinal fluid, and makes a continuous gel layer. The formation of the gel layer is the key parameter that controls the drug release from the matrix. The selected polymer must hydrate quickly enough to form a gel layer before the contents of the matrix tablet can dissolve. The matrix erosion (dissolution of the polymer) is also a rate-controlling factor in drug dissolution. However, for hypromellose and soluble drugs, the drugs may diffuse out of the gel before the dissolution of the polymer (Katzhendler et al 2000). The swelling behaviour of the hypromellose is controlled by the rate of its hydration in the aqueous liquid, which depends on the diffusion of the solvent molecules into hypromellose.

Since the rate of the hypromellose swelling determines the kinetics of the drug release from this matrix we undertook measurements to study the diffusion of the water solvent into the polymer. In our experiments, the diffusion (also swelling of the matrix) was not restricted to one direction as in most experiments performed up to now, but was allowed in the radial and axial directions. The aim of the study was to determine the influence of the drug concentration on the diffusion and swelling, and therefore on drug release properties. We used tetracycline hydrochloride as a model drug, which is used widely in medicine as a broad-spectrum antibiotic. The state of the water within the gel layer of hydrated hypromellose matrices (pure and containing

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tetracycline HCl) was measured by MRI. This method (Callaghan 1991; Blumich 2000) is sensitive to the mobile protons on solvent molecules and as such is particularly useful for studying the interaction of the solvent with the polymer. To characterize the solvent ingress and its effects on the structural and dynamical properties of the polymer, we acquired spatially resolved information such as self-diffusion coefficient (D) and spin–spin relaxation times (T_2).

Materials and Methods

Hypromellose and tetracycline hydrochloride were purchased from Aldrich Co., Germany, as powders and used as supplied. Hypromellose with an average M_n ca 86 000 has 29% methoxy and 7% propylene oxide content. Tetracycline hydrochloride (95% purity, pharmaceutical as described in the European Pharmacopoeia) with a molecular formula of $C_{22}H_{24}N_2O_8$ has a molecular weight of 480.91 and is very soluble in water.

The samples used in the microimaging experiments had a cylindrical shape (8-mm diameter, 5-mm thick). Pure and drug-containing hypromellose matrices (20%, 25% and 35%, w/w, tetracycline hydrochloride) were prepared by compressing a homogeneous mixture of the drug and polymer powders under a pressure of 90 MPa. Each of the samples was affixed to the base of a glass NMR tube by a silicone rubber compound adhesive. With the appropriate pulse sequence, 2-mm thick slices from the middle of the sample were selected for the image. The image slice was always well away from the area in contact with the glue. A water solution of hydrochloric acid, pH = 2 at 37 °C, was used as a dissolution medium to simulate the acidic (stomach) conditions in the gastrointestinal tract. The swelling experiment was initiated after adding an excess amount of the dissolution medium to an initially dry tube containing the sample and kept in a water bath at 37 °C. At various time intervals the solvent was removed from the tube, and the sample placed in the magnet of the NMR spectrometer for imaging.

The idea of using NMR to obtain spatial information on the spin density or an image of the studied sample was demonstrated for the first time by Lauterbur (1973). He proposed to superimpose a time dependent linear gradient field onto the static magnetic field to relate the strength of the magnetic field to the spatial position. Since the nuclear magnetic resonance frequency is proportional to the magnetic field, there is also a linear relationship between the resonance frequency and the spatial position. This makes it possible to produce two or three-dimensional NMR images. The intensity of the individual points of the image (so-called pixel in 2D or voxel in 3D images) is directly proportional to the spin density of the resonance nuclei at this point (Morris 1984; Foster 1987; Callaghan 1991; Blumich 2000). The method is called magnetic resonance imaging (MRI).

The MRI experiments were performed on a Bruker AVANCE 300 MHz spectrometer equipped with imaging facilities. The static B_o field of 7.05 Tesla corresponds to a ^1H resonance frequency of 300.23 MHz. A Bruker imaging probehead Micro 2.5 was used with a 15-mm birdcage coil. This probehead allows the application of pulse gradients of up to 10 T cm^{-1}. The progress of water diffusion into the polymer was studied by multi-echo pulse sequence. In this sequence the excitation radio frequency pulse is soft and thereby selective. The slice selection field gradient is linear and applied simultaneously with the radio frequency pulse. The bandwidth of the pulse and the strength of the slice selection gradient determine the slice thickness. The phase and frequency encoding gradients provide spatial information. We used a so-called spin-warp pulse sequence, so that the value (not the duration) of the phase encoding gradient was changed during the experiment. Multi-echo imaging is based on the CPMG echo sequence, which generates a series of echoes instead of a single echo. Due to this, one can acquire a series of T_2 weighted images. The data for the equivalent pixel in each of the images are fitted to a single exponential decay, according to the equation:

$$M(t) = M_0 \exp\{t/T_2\} \quad (1)$$

where M(t) is the measured transverse magnetization, M_0 is the equilibrium value of magnetization (proportional to proton density), T_2 is the spin–spin relaxation time, and t the distance between the pulses in the multi-echo pulse sequence (the echo time, which is varied during the experiment). Therefore, the fitting of equation 1 to the experimental data provides the spatial distribution of the fitting parameters T_2 and M_0 (proton density) or so-called T_2 and M_0 maps in the studied sample.

The intensity of the image signal is given by the following equation (Callaghan 1991; Blumich 2000):

$$S = M_0(\gamma)[1 - \exp\{-T_R/T_1(\gamma)\}] \exp\{T_E/T_2(\gamma)\} \quad (2)$$

where T_1 describes the spin-lattice relaxation time, T_E describes the echo time and T_R the repetition time. As seen in equation 2, the image intensity depends on T_2, T_1 and M_0. However, when the T_R is sufficiently long (3–5-times T_1) the T_1 contrast can be eliminated from the images (Callaghan 1991; Blumich 2000). This condition was fulfilled in our experiments. Therefore, only T_2 and M_0 influenced the acquired proton images, which follow the progress of the diffusion front into hypromellose matrix as a function of time.

In equation 1, T_2 is called the spin–spin relaxation time. However, the quantitative true T_2 values cannot be calculated in conventional microimaging experiments from a series of images with increasing echo time, because T_2 is strongly affected by the self-diffusion effect (Brandl & Haase 1994). The cumulative diffusion losses that lead to an underestimation of the T_2 relaxation time can be eliminated using a modified spin-echo pulse sequence, which was theoretically justified and confirmed in an appropriate experiment (Hsu et al 1995). However, in the experiments described in this paper, a conventional spin-echo pulse sequence was used. Therefore, the measured T_2

values are the "effective T_2" rather than the spin–spin relaxation time.

In our experiments the T_2 images were acquired with $T_R = 3000$ ms (T_1 for proton solvent into the gel layer of hypromellose was approximately 1 s) and the echo time T_E was varied from 9.3 to 334 ms to measure the spin–spin relaxation time.

The Stejskal–Tanner imaging sequence (Stejskal & Tanner 1965) was used to exploit the diffusion of the water solution of hydrochloric acid into hypromellose matrices. It uses two strong gradient pulses that allow controlled diffusion weighting, according to the following equation:

$$S = S_0 \exp[-bD] \tag{3}$$

where S and S_0 are the echo intensities with and without the field gradient, respectively; D is the self-diffusion coefficient and b is the co-called b factor given by the following relation:

$$b = \gamma^2 G^2 \delta^2 (\Delta - \delta/3) \tag{4}$$

γ is the gyromagnetic ratio; δ is the gradient pulse lengths; G is the magnetic field gradient strength; and Δ is the time from the start of the first gradient pulse until the start of the second so-called big delta.

The diffusion measurements were performed with all parameters kept constant while G was being incremented. The constant parameters were: $\delta = 2$ ms, $\Delta = 10$ ms, $T_R = 1000$ ms and T_E was incremented from 16.3 to 260 ms. The self-diffusion coefficient was determined from the non-linear regression of the peak intensity (S/S_0) against b. All measurements of diffusivity were conducted at 37 °C.

The images of the self-diffusion coefficient, spin–spin relaxation time and spin-density were acquired with a pixel resolution of approximately $117\,\mu m \times 117\,\mu m \times 2$ mm, where 2 mm was the thickness of the image slice of hypromellose. The signal intensity within the images was displayed using greyscale where black corresponds to a zero signal.

Results and Discussion

MRI is a method that obtains a visual presentation of the gel layer formation as a function of the immersion time of the studied polymer into the solvent. What is more, we can acquire spatially resolved values of self-diffusion coefficient (D), spin–spin relaxation time (T_2) or spin density (ρ) of protons solvent in the gel layer of the polymer. The formation of the gel layer in the hypromellose matrices, as a function of time, was the subject of our previous study (Tritt-Goc & Pislewski 2002).

In this work, spatially resolved transverse nuclear magnetic relaxation time and self-diffusion measurements have been used to gain information about the influence of the drug loading on the solvent dynamics behaviour in the hypromellose matrix and gel layer formation. In general, in the imaging of solvent transport in polymers, the nuclear magnetic relaxation properties of the polymer are such that no signal is received from it. However, in highly swollen polymers due to the increase of the polymer chain mobility, the relaxation time of the polymer becomes short enough and can contribute to the signal image. In our study, the experimental conditions (echo time and immersion time) were chosen in such a way as to eliminate the influence of hypromellose protons to the images. Therefore, the signal intensities throughout the measured images were mostly related to the solvent proton concentration.

Figure 1 presents a representative diffusion, T_2 and ρ images (so-called diffusion, T_2 and ρ maps) and their corresponding profiles of solvent protons into the gel layer of a hypromellose matrix loaded with 35% (w/w) tetracycline hydrochloride – the highest drug loading used in the experiment. The images were taken after 1.5-h swelling of hypromellose in a water solution of hydrochloric acid, pH = 2 at 37 °C. The gel layer, represented by the white and grey colour and the swelling front (between dry-wet polymer) is clearly visible in Figure 1. At the top of this figure the radial images and corresponding profiles are presented. Due to the fact that the diffusion gradient was applied in radial or axial directions, the diffusion coefficient was measured in radial and axial direction, respectively. The profiles clearly indicated that values of the self-diffusion coefficient D were higher for radial than for axial diffusion. Small differences between the left and right part of the D profiles can be caused by air bubbles, trapped during hydration and/or not homogeneous distribution of the drug into the hypromellose matrix.

In the spatially resolved spin–spin image (bottom-left in Figure 1) of the gel layer, the effective T_2 decreased from 100 ms to almost zero. On the T_2 profile of this image, the decrease of the relaxation time when going from the outer part of the swollen region to the dry core of hypromellose polymer was even more clearly visible. Such behaviour of relaxation time in the swollen part of the polymer is a clear indication of Case II diffusion (Ercken et al 1996). Fickian and Case II diffusions are two mechanisms viewed as the two limiting types of the transport process of the solvent into the polymer. In the Fickian mechanism the diffusion distance is proportional to the square root of the hydration time, whereas in Case II diffusion the distance is a linear function of time. In the proton-density image (bottom-right in Figure 1) and in this profile, the solvent concentration was almost constant throughout the swollen region. The sharp boundary between the glassy core and the swollen polymer was well pronounced. This was further justification that in the system composed of water solution of HCl with pH = 2 and hypromellose loaded with tetracycline hydrochloride, the diffusion mechanism known as Case II occurred. Since the drug release is correlated with the solvent diffusion, we can conclude that the release of tetracycline hydrochloride from hypromellose matrix occurred by way of the Case II mechanism as well (Masaro & Zhu 1999).

The images and profiles such as those presented in Figure 1 were measured for hypromellose matrices with 0%, 20% and 25% tetracycline hydrochloride and for different immersion times. As an example, the radially

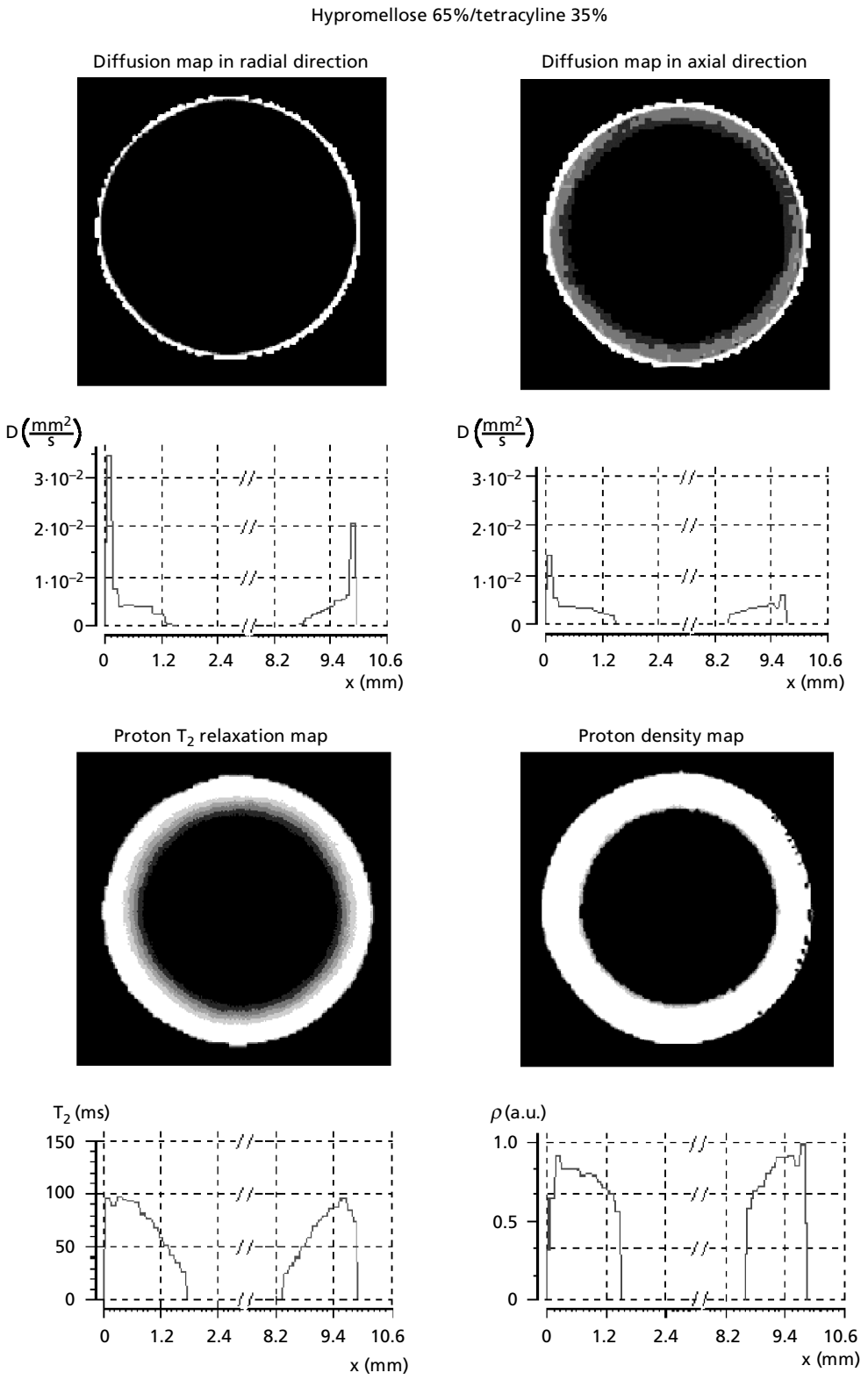

Figure 1 Radial images for the diffusion of a water solution of hydrochloric acid (pH = 2, 37 °C) into hypromellose loaded with 35% tetracycline hydrochloride are presented at the top of the figure. A proton T_2 relaxation map (left) and proton density map (right) are shown at the bottom. Additionally, corresponding profiles of diffusion coefficient, proton spin–spin relaxation time, and proton density in the gel layer of hypromellose under each of the images are presented. The images were acquired after 1.5-h immersion of the sample into solvent with a repetition time (T_R) of 3000 ms and an echo time (T_E) of 10 ms. The acquisition parameters were a field-of-view of 1.5 mm × 1.5 mm digitized into 128 × 128 pixels with a slice thickness of 2 mm (i.e. each voxel = 117 μm × 117 μm × 2 mm).

averaged T_2 profiles of protons of a water solution of hydrochloric acid (pH = 2 and temperature 37 °C) in the gel layer of pure hypromellose obtained for hydration times of 30, 90, 120 or 150 min are shown in Figure 2. The increase of the T_2 value and of the thickness of the gel layer in the function of the hydration time can be seen clearly. Similar behaviour of the T_2 dependence was observed for hypromellose matrices loaded with 20%, 25% or 35% tetracycline hydrochloride. For presentation in this paper we chose the T_2 and D profiles after the longest measured hydration time – 1.5 h. The diffusion of the solvent into hypromellose was allowed in all directions, therefore the sample started dissolving much faster. The measurements were stopped when the sample started to change its shape (after 1.5 h).

Figures 3 and 4 show the profiles of the self-diffusion coefficient and of the spin–spin relaxation times of solvent protons in pure hypromellose matrices and matrices loaded with 20%, 25% or 35% tetracycline hydrochloride, respectively.

The values of T_2 and D presented as the points in Figures 2, 3, and 4, respectively, were the values of these parameters derived from the voxels of the gel layer (117 μm × 117 μm × 2 mm). These voxels were situated along the diameter of the cylindrical samples from which 2-mm thick slices were imaged. In addition we called the profiles "radially averaged" because each point of a particular profile was the average value of four corresponding points read along the two perpendicular diameters of the samples.

The solvent molecules (water) in the gel layer of hypromellose can be described in the simplest way as existing in the free and bound state. The fact that only one exponential decay (or one relaxation component) was observed in our experiment indicated that water in the gel of the hypromellose was in rapid exchange between the free and bound state, relative to the NMR scale. The free water had a longer T_2 value than the bound water, and the resulting average in the fast-exchange limit was a combination of corresponding fraction of bound and free water. However, when the hydration time increased the polymer chain gained more freedom, and therefore the T_2 of bound water increased. As a result an increase of the total T_2 as a function of hydration time was observed, as indicated in Figure 2. The decrease of spin–spin relaxation time in the gel layer of the polymer from the outer part of the layer to the dry core of the polymer was due to the decrease of the polymer mobility.

Figure 3 presents the effect of drug concentration in hypromellose matrices on the spin–spin relaxation time T_2 of solvent protons in the gel layer of the polymers. It can be seen that in the hypromellose matrices characterized by a higher amount of tetracycline hydrochloride, longer values of the T_2 were measured in the gel layer. We can treat the studied matrices as the porous materials fill with drug. During the immersion of the polymer into the solvent two competitive processes take place: swelling of the polymer and the diffusion of the drug through the gel layer. Diffusion of the drug outside the gel layer of the polymer increased solvent holding capacity of the polymer. Hypromellose matrix with a higher loading of drug had a more porous structure and consequently (after drug release) the gel layer of such a matrix held more free water. Such water confined in larger cavities is characterised by higher mobility and consequently higher T_2 value when compared with the water in a less loaded hypromellose matrix.

We can conclude that the increase in the T_2 relaxation time observed in the hypromellose matrix loaded with different amounts of tetracycline hydrochloride not only reflected the change of the water binding, but also the change in the porous structure due to drug diffusion.

Figure 4 presents an average self-diffusion coefficient (D) of protons of a water solution of hydrochloric acid (pH = 2 and temperature = 37 °C) in the gel layer of hypromellose matrices loaded with different amounts of tetracycline hydrochloride: 0%, 20%, 25%, or 35%, after 1.5-h hydration time. The change of D when going along

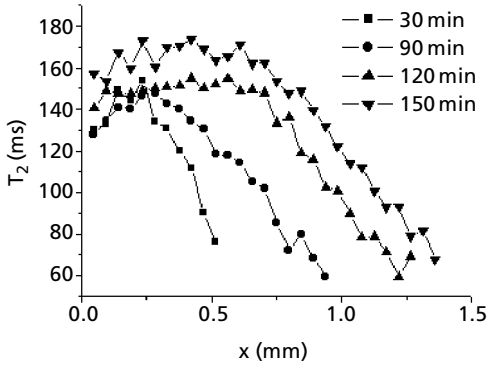

Figure 2 Radially averaged spin–spin (T_2) profiles of protons of water solution of hydrochloric acid (pH = 2, 37 °C) in the gel layer of hypromellose obtained for different hydration times.

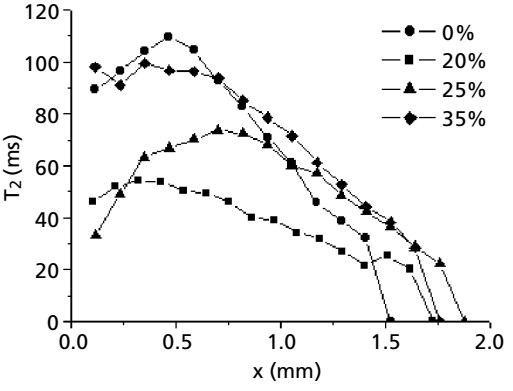

Figure 3 Radially averaged spin–spin (T_2) profiles of protons of a water solution of hydrochloric acid (pH = 2, 37 °C) in the gel layer of the hypromellose matrices loaded with different amounts of tetracycline hydrochloride. The relaxation times were measured after 1.5 h hydration time.

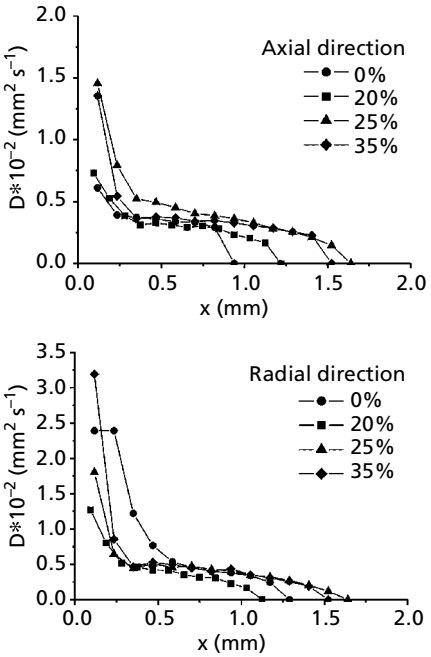

Figure 4 An average self-diffusion coefficient (D) of protons of a water solution of hydrochloric acid (pH = 2, 37 °C) in the gel layer of hypromellose matrices loaded with different amounts of tetracycline hydrochloride. The self-diffusion coefficients were measured after 1.5 h hydration time.

the x-axis in Figure 4 indicated the decrease of this value in the gel layer of the polymer from the outer part of the layer to the dry core of the polymer. Analysing the diffusion results we can see that there was a dependence of the drug concentration on the self-diffusion coefficient. The general tendency in the radial and the axial direction was the same: the higher the drug concentration, the higher the D values for solvent protons were measured. However, this tendency was true for the outer part of the gel layer where the polymer chains were more hydrated and characterized by a higher degree of motion. In the outer part of the layer the particles of the drug were already dissolved and therefore the polymer was characterized by higher free volume. Higher drug concentration in the matrix gave higher free volume of the polymer after the dissolution of the drug and consequently faster diffusion of the solvent into the polymer. When going inside the gel layer (in the direction of the dry core of the polymer) more and more pores were still filled with drug particles and the drug concentration dependence on the diffusion was less pronounced. When comparing the radial and axial diffusion we can conclude that the diffusion in the radial direction (in the outer part of the gel layer) was almost twice as fast as the one in the axial direction (see Figure 4). These differences may be attributed to the fact that in the axial direction, the solvent molecules had to overcome the stresses imposed in this direction during the compression of the samples.

Conclusion

It can be concluded that matrices composed of hypromellose and different amounts of the soluble drug tetracycline hydrochloride were characterized by similar tendencies of swelling and solvent diffusion into matrices. However, there was a visible influence of the drug concentration on the value of the self-diffusion coefficient and spin–spin relaxation time of the solvent (water) protons into the gel layer of the studied matrices. The diffusion and relaxation measurements revealed that a higher concentration of drug in the hypromellose matrix led to higher swelling of the matrix and faster diffusion of the water molecules inside the gel layer of the polymer. The observed differences between the radial and axial diffusion were interpreted in terms of the stresses imposed in the axial direction during the compression of the samples. The spin–spin and diffusion profiles indicated that diffusion of water solution of hydrochloric acid into hypromellose, pure and loaded with different amounts of tetracycline hydrochloride, was characterized as a Case II mechanism.

The results showed that MRI could be used with great success to study the diffusion of a solvent into hypromellose matrices and to obtain spatially resolved information about parameters such as self-diffusion coefficient and spin–spin relaxation time. The studied solvent diffusivity was of great interest because the solvent water penetration rates determined the kinetics of the gel layer formation of a controlled-release drug and, therefore, significantly affected drug dissolution and diffusion in the gel.

References

Blumich, B. (2000) *NMR Imaging of materials*. Oxford Clarendon Press

Brandl, M., Haase, A. (1994) Molecular diffusion in NMR microscopy. *J. Magn. Reson. B.* **103**: 162–167

Callaghan, P. T. (1991) *Principles of nuclear magnetic resonance microscopy*. Oxford Clarendon Press

Colombo, P., Bettini, R., Peppas, N. A. (1999) Observation of swelling process and diffusion front position during swelling in hydroxypropyl methyl cellulose (HPMC) matrices containing a soluble drug. *J. Control. Release* **61**: 83–91

Ercken, M., Adriaensens, P., Reggers, G., Carleer, R., Vanderzande, D., Gelan, J. (1996) Use of magnetic resonance imaging to study transport of methanol in poly(methyl methacrylate) at variable temperature. *Macromolecules* **29**: 5671–5677

Foster, M. A. (1987) *Practicle NMR imaging*. Oxford University Press

Gao, P., Skoug, J. W., Nixon, R. P., Ju, T. R., Stemm, N. L., Sung, K. C. (1996) Swelling of hydroxypropyl methyl cellulose matrix tablets. *J. Pharm. Sci.* **85**: 732–740

Hsu, E. W., Schoeniger, J. S., Bowtell, R., Aiken, R. N., Horsman, A., Blacband, S. J. (1995) A modified imaging sequence for accurate T_2 measurements using NMR microscopy. *J. Magn. Reson. B.* **109**: 66–69

Katzhendler, I., Mader, K., Friedman, M. (2000) Structure and hydration properties of hydroxypropyl methylcellulose matrices containing naproxen and naproxen sodium. *Int. J. Pharm.* **200**: 161–179

Konrad, S., Christ, A., Zessin, G., Cobet, U. (1998) The use of ultrasound and penetrometer to characterize the advancement

of swelling and eroding fronts in HPMC matrices. *Int. J. Pharm.* **163**: 123–131

Kowalczuk, J., Tritt-Goc, J., Pislewski, N. (2003) The swelling properties of hydroxypropyl methylcellulose. *Solid State NMR* In press

Lauterbur, P. C. (1973) Image formation by induced local interaction: examples employing nuclear magnetic resonance (MRI). *Nature* **242**: 190–191

Masaro, L., Zhu, X. X. (1999) Physical models of diffusion for polymer solutions, gels and solids. *Prog. Polimers Science* **24**: 731–775

Melia, C. D., Rajabi-Siahboomi, A. R, Daves, M. C. (1992) The development of structural features in the surface gel layer of hydrating HPMC hydrophilic matrices. *Contr. Rel. Bioact. Mater.* **19**: 28–29

Melia, C. D, Hodson, A. C., Daves, M. C, Mitchell, J. R. (1994) Polymer concentration profiles across the surface gel layer of xanthan, alginate and HPMC matrix system. *Contr. Rel. Bioact. Mater.* **21**: 724–725

Michailova, V., Titeva, St., Kotsilkova, R., Krusteva, E., Minkov, E. (2001) Influence of hydrogel structure on processes of water penetration and drug release from mixed hydroxypropylmethyl cellulose/thermally pregelatinized waxy maize starch hydrophilic matrices. *Int. J. Pharm.* **202**: 7–17

Morris, P. G. (1984) *Nuclear magnetic resonance imaging in medicine and biology*. Oxford Clarendon Press

Snaar, J. E. M., Hardy, I. J., Bowtell, R., Melia, C. D., Cook, W. (2001) MRI study of molecular mobility in hydroxypropyl methyl cellulose (HPMC) matrix tablets with and without propylene glycol–a rapid method for obtaining T_1 and T_2 images. *Magn. Reson. Imaging* **19**: 569–589

Stejskal, E. O., Tanner, J. E. (1965) Spin diffusion measurements: spin echoes in the presence of time-dependent field gradients. *J. Chem. Phys.* **42**: 288–292

Tritt-Goc, J., Pislewski, N. (2002) Magnetic resonance imaging study of the swollen kinetics of hydroxypropylmethylcellulose (HPMC) in water. *J. Control. Release* **80**: 1–3, 79–89