Structure and Behavior in Hydrophilic Matrix Sustained Release Dosage Forms: 4. Studies of Water Mobility and Diffusion Coefficients in the Gel Layer of HPMC Tablets Using NMR Imaging

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Purpose. The purpose of this study was to characterise the water mobility in the gel layer of hydrating HPMC tablets. Water mobility in the gel layer of different HPMCs was studied.

Methods. NMR imaging, a non-invasive technique, has been used to measure the spatial distribution of self-diffusion coefficient (SDC) and T_2 relaxation times across the gel layer.

Results. It has been shown that there is a water mobility gradient across the gel layer of HPMC tablets. Although SDC and T_2 relaxation times in the outer parts of the gel layer approached that of free water, in the inner parts they decreased progressively. Water mobility and SDC in the gel layer of different HPMCs appeared to vary with degree of substitution of the polymer and the lowest values were obtained across the gel layer of K4M tablets.

Conclusions. Water mobility varies across the gel layer of hydrating HPMC tablets and it is dependent on the degree of substitution of the polymer.

KEY WORDS: hydrophilic matrix; self-diffusion coefficient; water mobility; T_2 relaxation; NMR-imaging; NMR-microscopy; hydroxypropylmethylcellulose (HPMC).

INTRODUCTION

Hydrophilic matrix sustained release dosage forms contain a therapeutic agent dispersed in a compressed water-swellable polymer matrix. When exposed to aqueous liquids, the surface polymer hydrates to form a viscous mucilaginous 'gel' layer (1), a diffusional barrier that retards further water uptake and the release of water soluble compounds. Despite the key role of the surface gel in the performance of these dosage forms, there have been few studies of the properties of this layer *in-situ*. Studies using cryogenic scanning electron microscopy (cryo-SEM) and other techniques have shown that a polymer concentration gradient exists across the gel layer (2) and that polymer in the outer regions of the gel is more homogeneously and extensively hydrated than the inner regions closer to the gel/core interface (3). The extent of polymer swelling and the hydration of the microstructure formed within the gel layer vary in accordance with the polymer interaction with the hydrating media (2, 4) and gas bubbles form an integral part of the gel structure (5).

Korsmeyer *et al.* has shown how pulsed-gradient spin-echo NMR can be used to measure the self-diffusion coefficient (SDC) of water in swelling drug delivery systems (6). More recently (7, 8), we introduced microscopic NMR imaging (NMR microscopy) as a method for studying non-invasively the formation of the gel layer in hydrating hydroxypropylmethylcellulose (HPMC) tablets. NMR microscopy has the advantage of providing a visual representation of the spatial variation of SDC and spin-spin relaxation time (T_2) across a cross-sectional plane through the sample, allowing areas of spatial heterogeneity to be detected within the limits of resolution. It has been used previously to measure the diffusion properties of water in other hydrated systems such as biological tissues (9) and partially swollen poly(methylmethacrylate) rods (10).

This present paper extends our previous work to a study of the state of water within the gel layer using NMR microscopy to measure the spatial distribution of SDC and T_2 relaxation times across the gel; parameters which both depend strongly on water mobility. Given its primary function as a diffusion barrier, the distribution and mobility of water within the gel layer is an important factor which would be expected to influence polymer hydration, drug dissolution and release. However to date, the majority of models proposed for the transport of water and corresponding drug release from hydrophilic matrices, ignore the macromolecular relaxation of the polymer on hydration and assume a constant water diffusion coefficient (11).

MATERIALS AND METHODS

Matrix Preparation and Hydration

Hydroxypropylmethylcellulose (HPMC) USP types 2208, 2906, and 2910 (Methocel™ K4M, F4M and E4M cellulose ethers) were a gift from Dow Europe GmbH, Stade, Germany and were used as supplied. 5mm flat-faced tablets (50–55mg) were prepared at a compression force of 1.2–1.4kN using a Manesty F3 tablet machine from 63–90 μm particle size fractions of each HPMC. Single tablets were mounted and hydrated for up to 3 hours in distilled water at 37°C in a glass NMR sample cell as described previously (7).

NMR Imaging

Samples were imaged in the NMR microscope as described before (7) using a standard half Fourier spin warp sequence incorporating a non-selective 180° RF pulse (8). The in-plane resolution was 100 μm, the slice thickness 650 μm and each image was acquired in approximately two minutes. T_2 weighted images were generated by extending the echo time, whilst diffusion weighting was produced by inserting gradient lobes on either side of the 180° refocusing pulse.

Measurements of the Self-Diffusion Coefficient of Water

The intensity in magnetic resonance images can be made dependent on the local self-diffusion coefficient by the appro-

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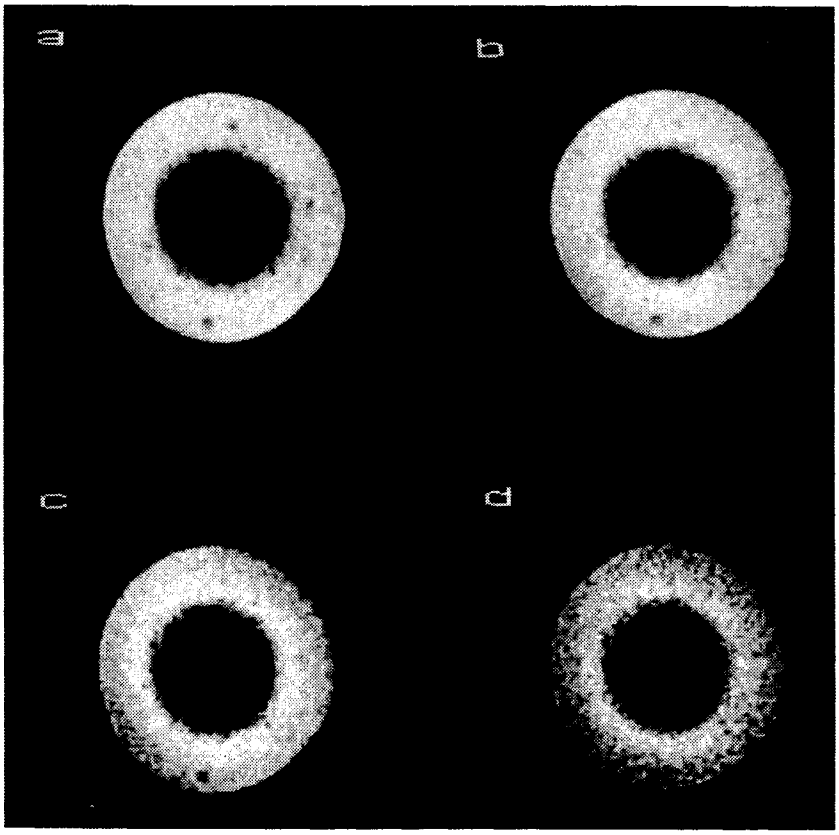

Fig. 1. Diffusion weighted images of a K4M tablet after 3 hours hydration in water at gradient field strengths; a) $0m^{-2}$, b) $1155m^{-2}$, c) $1632m^{-2}$, and d) $2000m^{-2}$.

priate application of magnetic field gradients. In a magnetic field gradient such that the magnetic field B = (Bo + G)*k*, the spins precess at an angular frequency, $\omega = \gamma(Bo + G)$, which depends on their spatial position. Bo is the static magnetic field strength, G is the applied magnetic field gradient, g is the magnetogyric ratio and where the unit vector *k* defines the field direction. As time proceeds spins acquire a phase which corresponds to the angle through which they have precessed. The strength of the NMR signal received in an experiment is proportional to the vector sum of the transverse component of the magnetisation generated by the nuclear spins. A large signal is only received, therefore, when the spins are in phase, so that their contributions to the transverse magnetisation reinforce one another.

In the sequence used in this study, the initial 90° RF pulse rotates the magnetisation into the transverse plane. At first all the spins are in phase, but when the magnetic field gradient is applied, spins in different spatial positions precess at different rates. The magnetisation thus dephases and the signal decays. The 180° RF pulse reverses the accumulated phase of the magnetisation, so that the second gradient pulse brings the spins back into phase, producing a large signal once more. This is only strictly true however if the spins are stationary. In a liquid sample, the spins will be in random thermal motion and thus will not stay in the same place during the experiment. As a result they experience a variety of different precession rates and are therefore not fully rephased at the end of the second gradient pulse. The resulting attenuation of the NMR signal, S, depends on the self-diffusion coefficient D and is given by:

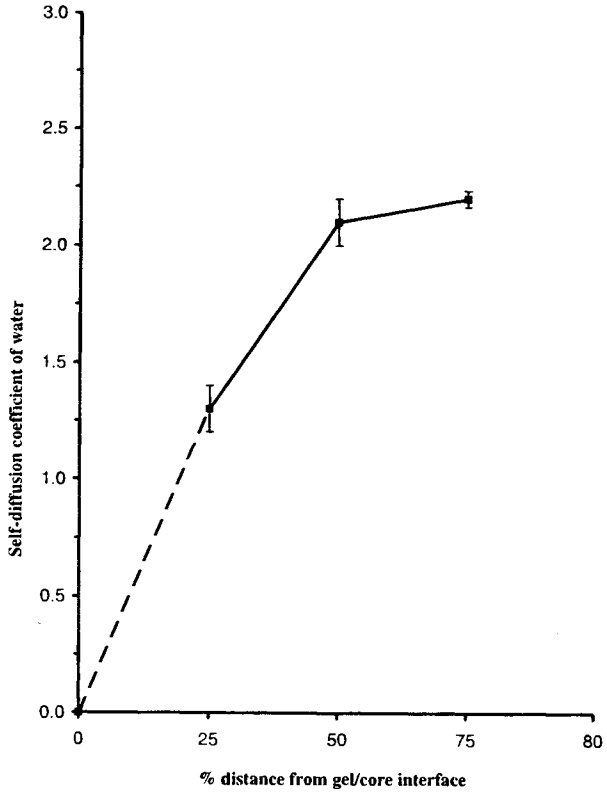

Fig. 2. SDC values across the gel layer of a K4M tablet after 3 hours hydration in water in the radial direction [Mean(n = 3) ± SD].

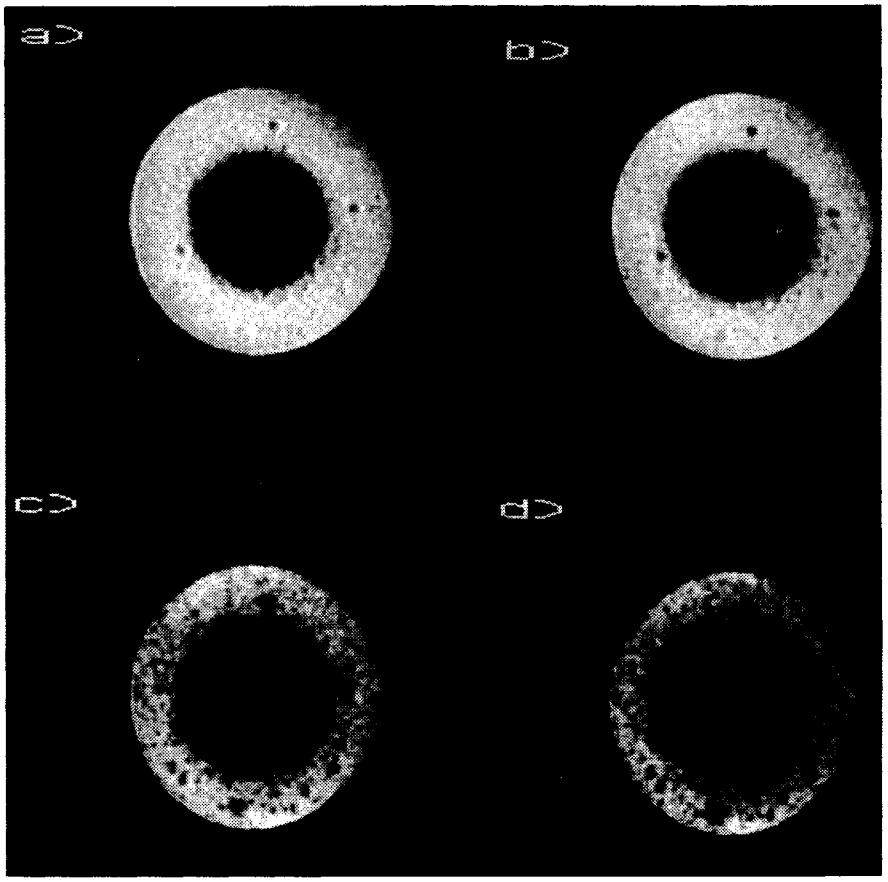

Fig. 3. T_2 weighted images of a K4M tablet after 3 hours hydration in water at TE values; a) 4.5ms, b) 10.5ms, c) 24.5ms, and d) 36ms.

$$S = S_0 \exp[-2/3(\gamma G)^2 D\tau^3] \quad (1)$$

Where τ is the length of each gradient pulse and S_0 is the signal strength when $\tau = 0$. A graph of the natural logarithm of the signal intensity versus $2/3(\gamma G)^2\tau^3$ is therefore a straight line with a slope equal to $-D$.

In our experiments the diffusion weighting consisted of 7 ms duration gradient pulses applied in the slice select direction, before and after the 180° refocusing pulse and in conjunction with the normal imaging gradients. Images with four different diffusion weightings were generated by varying the strength of the gradient pulses. Graphs showing the variation of the natural logarithm of the intensity in different regions of the image versus $2/3(\gamma G)^2\tau^3$ were then plotted and fitted, using a linear regression line to obtain the value of D.

Measurements of Spin-Spin Relaxations (T_2)

T_2 weighted images were obtained by varying the echo time (TE) from a minimum value of 4.5 ms to a maximum value of 76.5 ms. The signal intensity across the gel layer was then measured. In a simple spin echo experiment the signal intensity is given by:

$$S = S_0 \exp(-TE/T_2) \quad (2)$$

A plot of natural log of signal intensity (S) across the gel layer versus echo-time (TE) should be a straight line with a slope of $-1/T_2$.

RESULTS AND DISCUSSION

Figure 1 shows a series of diffusion weighted images of a K4M tablet after 3 hours hydration taken at different field gradients. A plot of natural logarithm of the signal intensity versus $2/3(\gamma G)^2\tau^3$ was linear in different regions of the hydrated gel layer. In figure 2 the graph represents mean SDC values across four sections of the gel layer taken at 90° angular intervals and shows how the SDC value progressively increases on moving away from the core in the inner regions of the gel, but reaches a limiting value in the more hydrated outer areas. This indicates that the water in the inner regions of the gel shows more restricted diffusion, corresponding with evidence from cryo-SEM studies (12) that the polymer is much less hydrated in the inner part of the gel. The limiting value of SDC in the outer layers approaches that of free water ($\approx 2.3 \times 10^{-9}$ m^2 S^{-1} at 25°C) suggesting the polymer in the outer gel may offer little diffusional resistance to small molecules in this region. The zero values of SDC in the core is due to the absence of free water and hence a lack of signal intensity in that region. The SDC values between dry core and the gel/core interface are expected to tend to small values and shown by dotted line in figure 2.

T_2 weighted images of the same tablet are shown in figure 3. At the longer echo times small circular areas of low intensity can be seen within the gel layer. These are probably due to gas bubbles which form an integral part of the structure of the gel layer (5). These appear bigger than their true size since diffusion

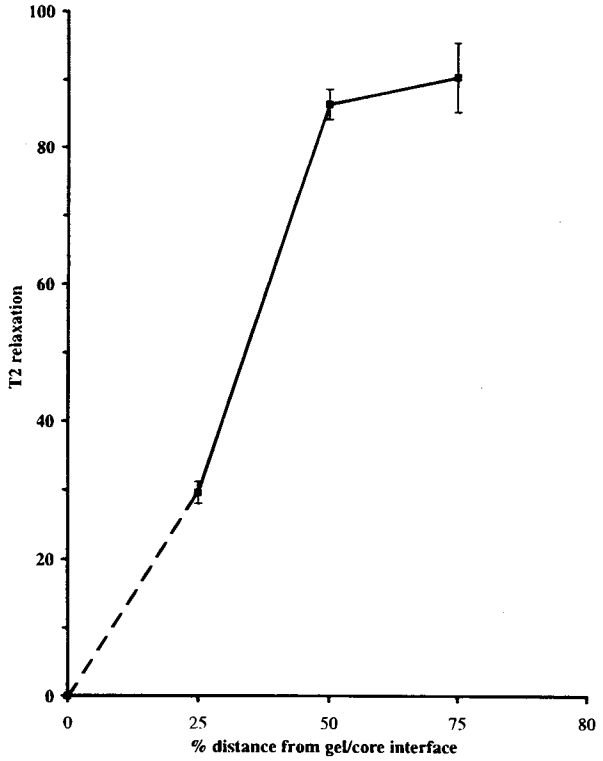

Fig. 4. T_2 relaxation times across the gel layer of a K4M tablet after 3 hours hydration in the radial direction [Mean(n = 3) ± SD].

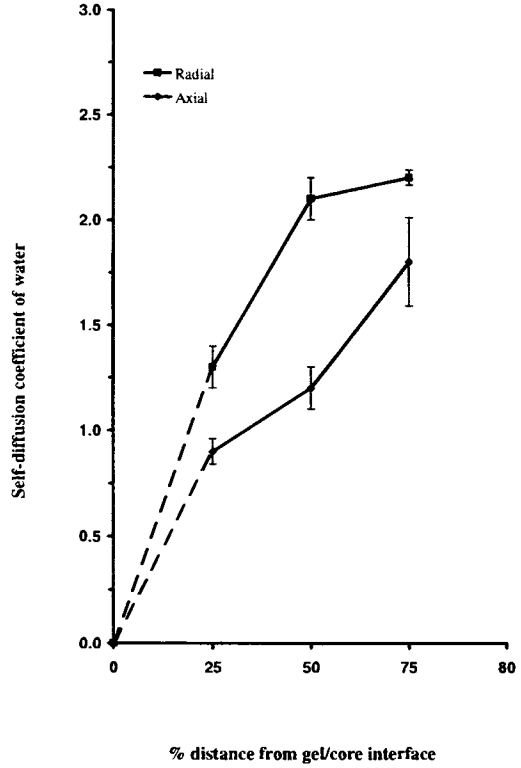

Fig. 6. Radial and axial SDC values versus % gel thickness in the gel layer of a K4M tablet after 3 hours hydration [Mean(n = 3) ± SD].

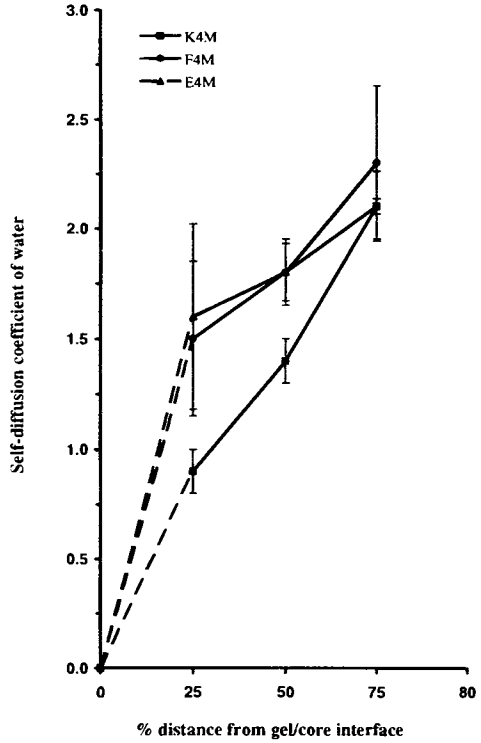

Fig. 5. SDC values versus % gel thickness in the gel layer, in the radial direction, of different HPMC types after 1 hour hydration [Mean(n = 3) ± SD].

of water molecules in the large magnetic field gradients which surround the bubbles gives rise to signal attenuation and thus magnified regions of low intensity. A plot of the natural logarithm of the signal intensity against echo time (TE) was linear for different regions within the gel layer. The slope of this graph is equal to $-1/T_2$. Figure 4 shows how a radial-averaged T_2 (calculated as in figure 2) varies across the gel layer following similar pattern to SDC values. T_2 is a measure of the rotational and translation freedom of the water molecules and this profile indicates that on average, a greater proportion of the water is more tightly bound in the inner regions of gel. The zero values of T_2 in the core is due to the absence of free water and hence a lack of signal intensity in that region. The T_2 values between dry core and the gel/core interface are expected to tend to small values and shown by dotted line in figure 4.

Effect of Degree of Substitution on Water Mobility in the Gel Layer

Figure 5 shows how the SDC of water varies between matrices prepared from HPMC having different substitution levels, after 1 hour hydration. As with the previous results at 3 hour, the SDC values in the outermost parts of the gel tended to those of free water for all grades. However, in the middle and inner regions of the gel, where the SDC profiles for E4M and F4M HPMCs were closely similar, values for K4M were significantly lower.

Differences in substitution levels have frequently been reported to give rise to different drug release characteristics, and earlier work has ascribed this to differing rates of polymer hydration (13). By this reasoning, K4M was explained as providing the slowest rates of release, ostensibly because it was

the most rapidly hydrating. However, it has subsequently been shown that the extent and rate of growth in gel layer thickness is closely similar between different HPMC types (7). The present study suggests that the K4M gel, although the same thickness as other types, offers a greater diffusional resistance to water within the inner gel region.

Water Mobility within the Gel Layers Formed at Different Surfaces of the Tablet

On hydration, HPMC matrices expand in the axial direction much more than in the radial direction (14,15). In a previous paper we showed that this difference could be explained entirely in terms of expansion in the core, and that the gel layer developed a similar thickness in both directions (7). Figure 6 compares the SDC profiles in both directions across the gel layer of a K4M tablet after 3 hours hydration. The T_2 relaxation profiles were similar to those patterns observed in the SDC profiles. The results imply that water in the radial direction is less bound within the gel than that in the axial direction. This suggest that the gel formed at the sides and top of the tablet may be different in nature and further work to ascertain the reason for these differences is presently underway.

When interpreting this with respect to an anticipated affect on matrix performance, two points should be bourne in mind. Firstly, these results represent average values over relatively large regions of gel within which techniques with higher resolution such as cryo-SEM show there may be considerable inhomogeneity of polymer hydration. This is particularly true of the innermost regions of the gel (5). Secondly, the behaviour represents pure polymer compacts and does not reflect additional effects of other components in a hydrophilic matrix formulation which may influence polymer hydration.

CONCLUSIONS

The variation of self-diffusion coefficient and T_2 relaxation times revealed that there is a water mobility gradient across the gel layer of HPMC matrices. This supports previous studies (3,12) which show different degrees of polymer hydration at different depths within the gel. In the outer parts of the gel, the SDC values approach that of free water. In the inner gel, they progressively decrease as the core/gel interface is approached. When HPMCs with different substitution levels were examined, SDC and T_2 values were lower across the gel for a K4M matrix than E4M or F4M, although all produced gel layers of the same thickness (7). In addition, water mobility gradients were different in the axial and radial directions. These results suggest that the gel layer formed by K4M HPMC may be different to other HPMCs, and that gel layer properties may differ between the flat and radial surfaces of an HPMC tablet.

This work clearly shows that NMR microscopy could be used to measure non-invasively the changing properties of water within other dosage forms as they perform.

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