Magnetic Resonance Imaging (MRI) Study of Swelling and Water Mobility in Micronized Low-Substituted Hydroxypropylcellulose Matrix Tablets[1)]

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The swelling and water mobility in directly compressed tablets of micronized low-substituted hydroxypropylcellulose (LH41) were studied by magnetic resonance imaging (MRI), in comparison with those in tablets of hydroxypropylcellulose (HPC) and hydroxypropylmethylcellulose (HPMC). Images of a hydrating LH41 tablet showed that the contrast of the outer moiety of the tablet became slightly brighter in the coronal and transverse planes. A transverse image of the LH41 tablet showed that swelling, deformation and cracking occurred on the edge of the tablet. Images of hydrating HPC and HPMC tablets clearly showed an interface layer between the dry core and the swollen gel layer. Imaging data analyses showed that overall swelling of the tablets decreased as follows: HPMC > HPC ≫ LH41; the amount of absorbed water also decreased in this order. The three kinds of tablets expanded in the transverse section much more than in the coronal direction. The spin-spin relaxation time (T_2) of water in the LH41 tablet was much smaller than that of free water, indicating that the water is located in a highly restricted environment and suggesting that strong interaction occurs between the absorbed water and the polymer. The apparent self-diffusion coefficient (ADC) of water absorbed into the LH41 tablet was smaller than that of free water, indicating that the water diffusivity is restricted in the polymer matrix. In the other two tablets, nearly the same tendency was observed for T_2 and ADC. The T_2 analyses of the water components in almost the whole coronal section of the hydrating tablets revealed that one type of water existed in the LH41 tablet and that two types of water with different mobility existed in the HPC and HPMC tablets. These results indicate that the gel layer properties may be different among the three hydrophilic polymers.

Key words magnetic resonance imaging; hydroxypropylmethylcellulose; NMR relaxation; micronized low-substituted hydroxypropylcellulose; hydroxypropylcellulose; diffusion

Water-soluble and swellable cellulose derivatives have been widely used in the formulation of hydrophilic gel-forming matrices for controlled drug delivery systems.[2)] There have also been several articles discussing the use of derivatives like hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC) and carboxymethylcellulose (CMC), which form a gel and swell on contact with water.[2–4)] These polymers are used for controlled release where the swelling and water mobility in a gel phase play important roles in drug release.

We previously reported that water-insoluble and swellable celluloses of fine particle size have potential use as matrix carriers in controlled release tablets.[5–7)] Among them, micronized low-substituted hydroxypropylcellulose (LH41) with a particle size less than 5 μm can be used as a directly compressible carrier for a controlled release tablet. Kawashima *et al.*[8)] also reported that micronized LH41 works as a controlled release matrix.

The drug release rate from those swellable and gel-forming matrices strongly depends on the rate and extent of swelling of the matrix, subsequent drug diffusion through the outer gel layer[9,10)] and the change in matrix area exposed to the water.[11)] In the LH41 tablet, we presumed that the mechanisms of drug release may be the fast hydration of the tablet on contact with water, resulting in the formation of a diffusion-limiting pseudogel layer at the tablet surface. This layer, in turn, decreases drug release and water penetration into the tablet. However, there are few reports describing the hydrogel properties of LH41.

There are a number of reports dealing with swelling and water mobility in the hydrophilic polymer matrix using magnetic resonance imaging (MRI).[12–17)] The MRI technique can provide a method of studying non-invasively the dynamics of hydration and the changing internal structure in dosage forms undergoing hydration.

The purpose of the present study was to characterize swelling and water mobility in directly compressed tablets of LH41 by comparing with those in HPC and HPMC tablets using the MRI technique. The kinetics of dimensional change in the LH41 tablet during the hydration process was investigated, and the spin-spin relaxation time (T_2) and the apparent self-diffusion coefficient (ADC) of water in the tablet were also measured.

Experimental

Materials and Matrix Tablet Preparation Micronized low-substituted hydroxypropylcellulose (L-HPC) (type LH41, mean particle size, 5 μm, Shin Etsu Chemical Co., Ltd., Japan), HPC (type HPC-H, particle size, under 150 μm, Nippon Soda Co., Ltd., Japan) and HPMC (type Metholose 60SH-4000, Shin Etsu Chemical Co., Ltd., Japan) were generously donated by the respective manufacturers. Each sample (500 mg) was directly compressed into tablets at a compression force of 400 kgf by a universal testing machine (Autograph, type AG-5000B, Shimadzu Co., Ltd., Japan) at a compression speed of 10 mm/min. A flat-face punch 10 mm in diameter was used for tabletting.

Tablet Hydration and NMR Imaging A single tablet was hydrated in a glass bottle filled with ultrapure water replaced with nitrogen gas. The sample was then placed inside the core of the MRI for imaging. Images were taken at room temperature from the coronal and transverse planes through the center of the tablet oriented as shown in Fig. 1. The

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experiments were performed on a Bruker BIOSPEC CSI 47/40 NMR spectrometer equipped with a 4.7 T superconducting magnet system operating at 200 MHz for ^{1}H-NMR. Images were typically acquired using the spin echo pulse sequences, and the imaging parameters were as follows: recovery time (TR), 14000 ms; echo time (TE), 20 ms; two averages; 256 × 256 lines; slice thickness, 5 mm.

Measurements of Dimensional Changes in the Tablets during Hydration The dimensional changes in the coronal and transverse planes of the tablets were measured using an image analysis apparatus (Quantimet 600, Leica, Japan). The signal of each pixel in the T_2-weighted image acquired using the MRI was converted into the signal used for the analyses.

Measurements of Spin-Spin Relaxations (T_2) T_2-Weighted images were produced in the standard manner using multiple spin echo (MSE) methods.[18] The spin-spin relaxation time (T_2) of water in the hydrating tablets was calculated as follows. The signal intensity of each pixel of the T_2-weighted image was measured by extending the TE from a minimum value of 20 ms to a maximum value of 240 ms. In the spin-echo method, the signal intensity is given by:

$$S = S_0 \exp(-\mathrm{TE}/T_2)$$

A plot of the natural log of the signal intensity (S) of each pixel *versus* TE should be a straight line with a slope of $-1/T_2$.

Measurements of the ADC The ADC of water was measured based on the method established by Stejskal and Tanner.[19] In fact, the diffusion-weighted images were produced by inserting gradient pulses on either side of the 180° refocusing pulse. The gradient factor b was obtained as the strength of the gradient pulse applied in one direction and was changed from 0 to 80000 s/cm^2. The ADC of water in the hydrating tablets was calculated as follows. The signal intensity (S) of each pixel of the diffusion-weighted images was measured. The ADC is given by:

$$\mathrm{ADC} = \ln(S_0/S)/(b - b_0)$$

where S_0 is the signal intensity and b_0 is the gradient factor without inserting gradient pulse. A plot of $\ln(S_0/S)$ *versus* $(b - b_0)$ should be a straight line with a slope of $-$ADC.

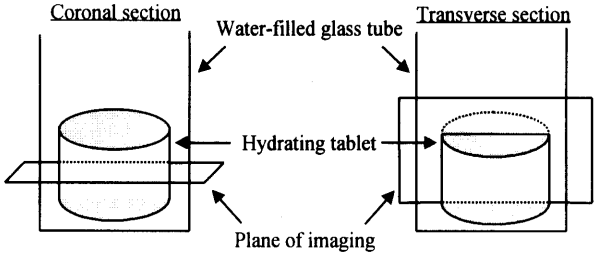

Fig. 1. The Planes of Imaging in the Coronal and Transverse Sections through the Sample

Results and Discussion

Water Uptake of Polymer Tablets Directly compressed tablets (500 mg with a diameter of 10 mm) under 400 kgf made from pure LH41, HPC and HPMC were exposed in excess distilled water at room temperature. The increase in weight of the tablets was determined at intervals of 5 up to 20 h. Figure 2 shows the water uptake, expressed as the weight fraction of water in the dry polymer. The amount of water uptake of the LH41 tablet was much smaller than those of HPC and HPMC tablets, suggesting that the swellability of LH41 is much less than that of HPC and HPMC.

Images of Various Tablets during Hydration Figures 3 and 4 show typical T_2-weighted images through the

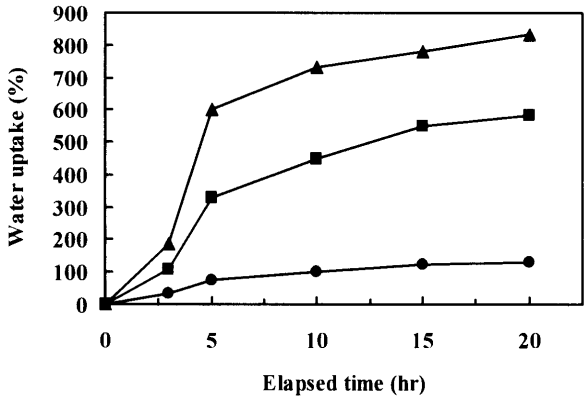

Fig. 2. Water Uptake Profiles of LH41, HPC and HPMC Tablets Compressed under 400 kgf during Hydration

●, LH41; ■, HPC; ▲, HPMC.

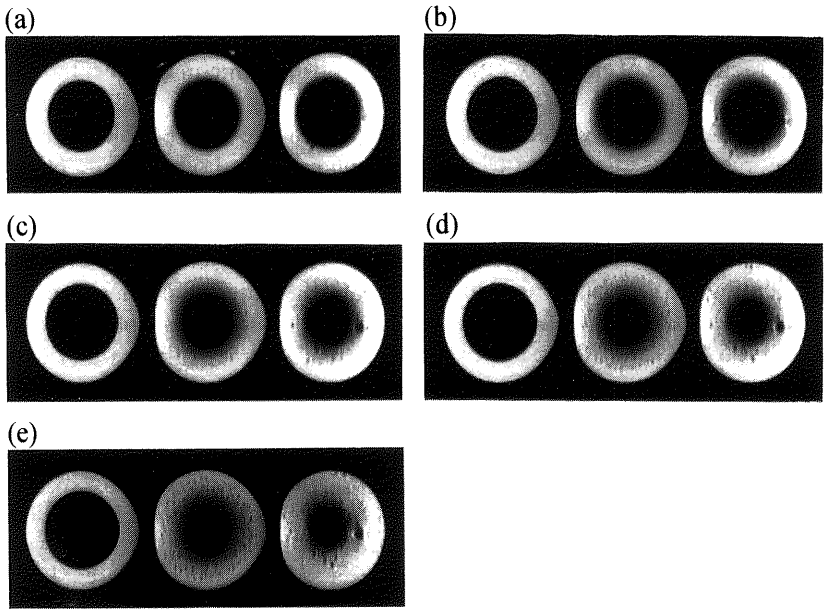

Fig. 3. Images of LH41, HPC and HPMC Tablets Undergoing Hydration after (a) 20 min, (b) 5 h, (c) 10 h, (d) 15 h and (e) 20 h in the Coronal Plane

Left, LH41; center, HPC; right, HPMC.

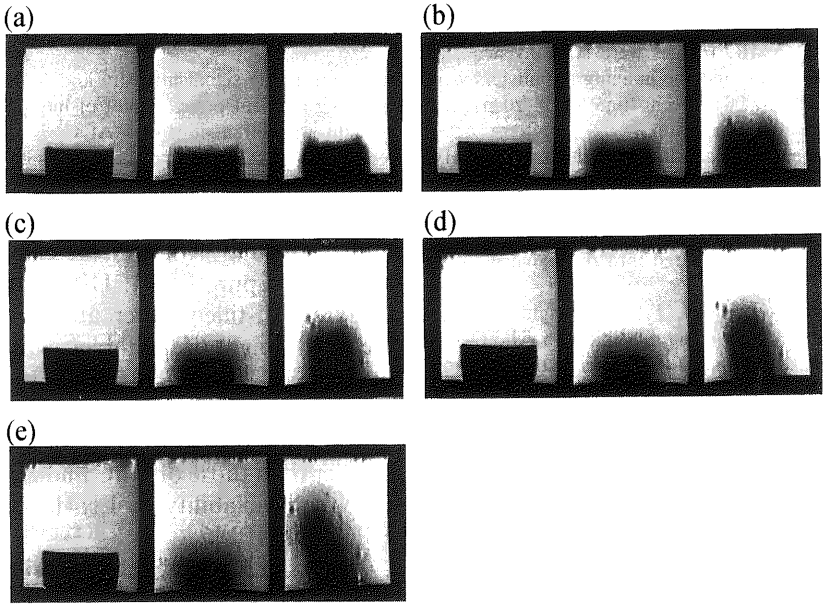

Fig. 4. Images of LH41, HPC and HPMC Tablets Undergoing Hydration after (a) 20 min, (b) 5 h, (c) 10 h, (d) 15 h and (e) 20 h in the Transverse Plane

Left, LH41; center, HPC; right, HPMC.

coronal and transverse planes of the three kinds of tablets which had been hydrated for 20 h. The most outer circle or cylinder in Fig. 3 indicates the glass bottle, the inner moiety which clearly looks white is water, the most inner black moiety shows the dry core and the moiety between the water and the dry core indicates the gel layer which increased during the hydration process. In the hydrating LH41 tablet, a phenomenon in which the contrast of the outer moiety of the tablet became slightly brighter was observed in the coronal and transverse planes. In the transverse plane, swelling, deformation and cracking of the edge of the tablet were observed. The presence of different swelling and gelation ability of LH41 particles due to the different particle sizes in the tablet probably causes internal stress, resulting in this deformation and cracking. This is also probably due to LH41 gel characteristics: the LH41 gel has characteristics of elasticity rather than viscosity. On the other hand, in the hydrating HPC and HPMC tablets, the growth of the gel layer can clearly be seen; the size of the dry core decreased as more of the tablets became hydrated. In addition, as shown in Fig. 5, an interface layer between the dry core and the gel layer was clearly recognized. During imaging, the brightness of this layer was very dim, indicating that the water mobility in this layer is probably restricted. Consequently, it was confirmed through images in the MRI that there are two moieties (pseudogel layer and dry core) in the hydrating LH41 tablet but three moieties (gel layer, interface layer and dry core) in the hydrating HPC and HPMC tablets. As is clear from the data shown in Fig. 2, the penetration amount of water in the tablet consisting of LH41 which is a water-insoluble polymer was remarkably small in comparison with those in the tablets consisting of HPC and HPMC which are water-soluble polymers. This suggests that the clear gel layer visible in HPC and HPMC tablets cannot be seen in the LH41 tablet because of the very low proton density in that hydrated tablet.

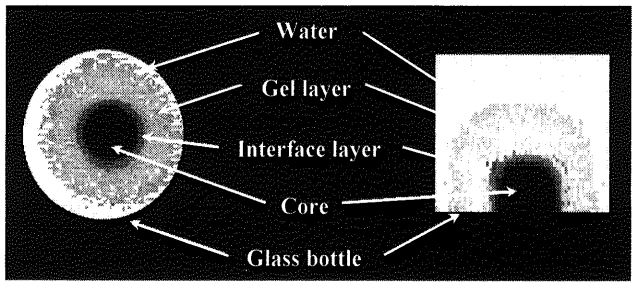

Fig. 5. Images of HPC Tablet Undergoing Hydration after 20 h in the Coronal and Transverse Planes

Dimension Changes during Hydration Process Each area of a dry core, an interface layer and a gel layer, measured using an image analysis apparatus, plotted *versus* the exposure time in the coronal and transverse planes, is shown in Fig. 6(a), and the rate and extent of core growth for the LH41 tablet are seen to be similar in the two planes. As shown in Fig. 6(b) and 6(c), the extent of gel layer growth in the coronal plane of the HPC and HPMC tablets was much larger than that in the transverse plane. The gel layer growth in the coronal plane occurred both in the outer and inner directions, while the gel layer growth in the transverse plane occurred mainly in the outer direction. As a result, the outer expansion of the gel layer was much larger in the transverse direction than in the coronal direction. The area of this layer increased as the size of the dry core decreased, whereas the area of the interface layer hardly changed.

Overall Swelling during Hydration Process The changes in overall swelling of various hydrating tablets recorded over a period of 20 h are shown in Fig. 7. Overall swelling decreased as follows: HPMC > HPC ≫ LH41; the amount of absorbed water also decreased in this order. All of the tablets expanded in the transverse direction much more than in the coronal direction. One possible

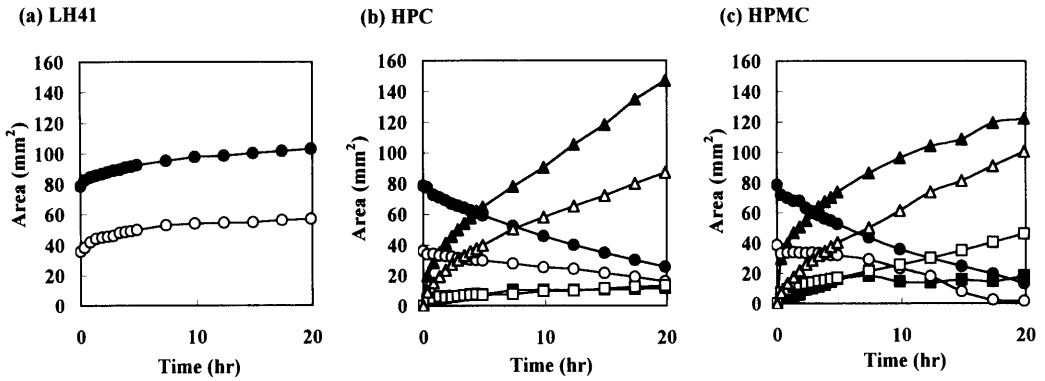

Fig. 6. Changes in Dimensions of Area *versus* Exposure Time in the Coronal and Transverse Planes

(a), LH41; (b), HPC; (c), HPMC. ●, core (coronal); ■, interface layer (coronal); ▲, gel layer (coronal); ○, core (transverse); □, interface layer (transverse); △, gel layer (transverse).

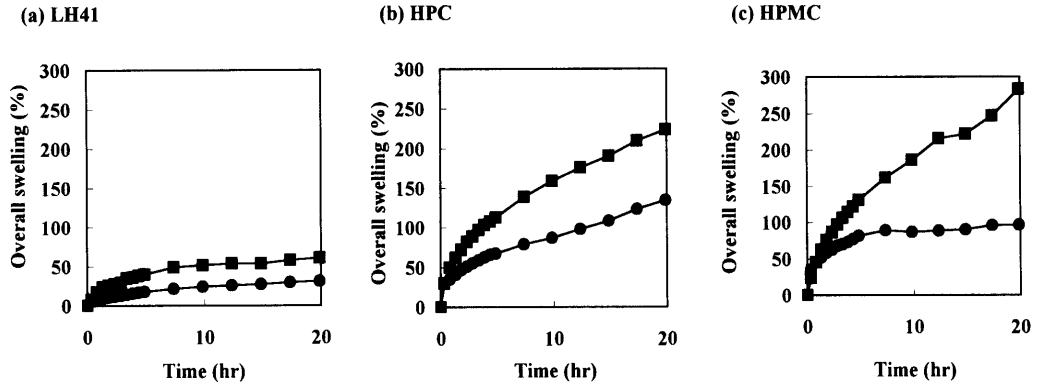

Fig. 7. Overall Swelling of Various Tablets *versus* Exposure Time in the Coronal and Transverse Planes

(a), LH41; (b), HPC; (c), HPMC. ●, coronal; ■, transverse.

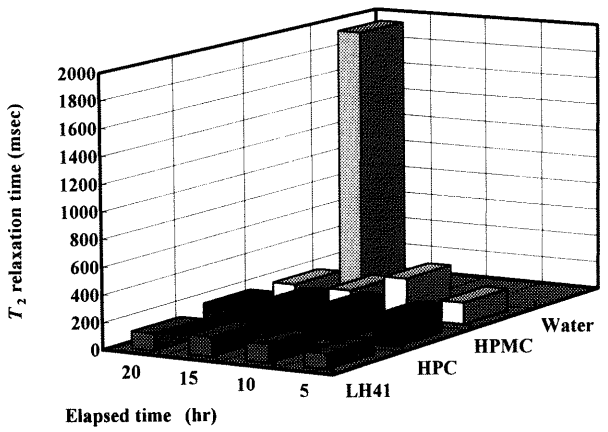

Fig. 8. T_2 Relaxation Time of Water in LH41, HPC and HPMC Tablets Undergoing Hydration

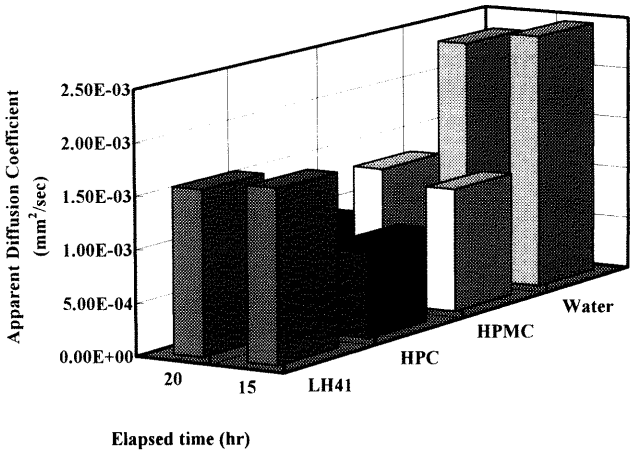

Fig. 9. ADC of Water in LH41, HPC and HPMC Tablets Undergoing Hydration

hypothesis is that the pronounced expansion of the core in the transverse direction may be a result of stress relaxation of the compressed tablet.

The Mobility of Water Absorbed into the Various Tablets Figures 8 and 9 show a coronal-averaged T_2 and ADC of the water absorbed into LH41, HPC and HPMC tablets for a typical period undergoing hydration at room temperature. In the LH41 tablet, T_2 and ADC were calculated using the average of the signal intensity of the outer pseudogel layer which became slightly brighter by degrees; in the HPC and HPMC tablets, that of the gel layer was used which can clearly be seen. The T_2 of the water in the LH41 tablet was very short compared with that of pure free water measured in a similar manner, indicating that the water is located in a highly restricted environment and suggesting that strong interaction occurs between the absorbed water and the polymer. The ADC of water absorbed into the LH41 tablet was small compared with that of pure free water similarly measured, indicating that the water diffusivity is restricted in the polymer matrix. In the other two tablets, nearly the same tendency was observed for T_2 and ADC. The values of T_2 and ADC in the three tablets changed little with

Table 1. T_2 Relaxation Time of Water Components in Various Cellulose Matrix Tablets Undergoing Hydration

Tablet	T_2 relaxation time (ms)		Population	
	15H	20H	15H	20H
LH41	—	—	—	—
	224.5	217.8	1.00	1.00
HPC	16.1	23.3	0.43	0.34
	209.3	182.9	0.57	0.66
HPMC	25.8	18.7	0.55	0.47
	124.6	149.9	0.45	0.53

exposure time. Table 1 shows the results obtained by analyzing the signal intensity decay curve *versus* TE. The T_2 analyses of the water components in almost the whole coronal section of the hydrating tablets revealed that two types of water with different mobility existed in the HPC and HPMC tablets and one type in the LH41 tablet. These results indicate that the gel layer properties may be different among the three hydrophilic polymers.

Conclusions

MRI was shown to be a useful tool for examining water properties in the matrix tablets used for controlled release. Swelling of LH41 was much less than those of HPC and HPMC. T_2 and ADC analyses indicate that water mobility in the LH41 tablet, as well as in the HPC and HPMC tablets, is highly restricted, suggesting that strong interactions occur between the absorbed water and the polymer. Further analysis of T_2 suggests that one type of restricted water exists in the LH41 tablet, whereas there are two types in the HPC and HPMC tablets.

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References and Notes

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