A Novel Nuclear Magnetic Resonance (NMR) Imaging Method for Measuring the Water Front Penetration Rate in Hydrophilic Polymer Matrix Capsule Plugs and Its Role in Drug Release

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An NMR imaging method was developed to estimate the rate of water movement in slow-release capsule matrices of pseudoephedrine HCl and hydroxypropyl cellulose (HPC). Test capsules were first placed in a USP method 2 (paddles, 50 rpm) dissolution apparatus. Each plug was removed from the dissolution medium at predetermined times, blotted dry, and placed within the magnetic field of a General Electric 400-MHz wide-bore NMR spectrometer equipped with a microimaging accessory. Images were recorded along the transverse plane of each plug. The water penetration rate was determined by comparison of the cut and weighed contour plots of the images acquired. After 1 hr, the plugs tamped to 200 N exhibited water penetration to the center, while only 45% of the drug was released. The percentage dry matrix was fitted to the Jost equation to obtain a diffusion coefficient of 4.15×10^{-6} cm^2/sec. NMR imaging is set forth as an important and practicable technique to investigate drug formulations. In the HPC matrix system of this study, the NMR imaging results convincingly revealed the rate of hydration front penetration not to be a rate-limiting step in the drug release process.

KEY WORDS: nuclear magnetic resonance (NMR) imaging; hydroxypropyl cellulose matrix; water penetration rate; slow-release formulation.

INTRODUCTION

The introduction of water-soluble gel-forming polymeric matrix systems for sustained delivery of water-soluble drugs has brought forth new challenges in drug development. The dissolution data from such hydrophilic matrices have been classically analyzed using Higuchi's square-root-of-time equation (1). However, this approach has been criticized for the assumption of a pseudo-steady state and for the fact that the model was derived for an inert matrix with fixed geometry (2,3). Gel-forming hydrophilic matrices do not conform to these criteria. Upon hydration, they swell and eventually erode at the surface. Moreover, they do not have an immutable porosity. Alternative models have been proposed but have achieved limited success (4,5).

In the development of slow-release matrix formulations containing a hydrophilic polymer, the following factors have been investigated to ascertain a rate-determining process. These include the rate of penetration of the hydration front and its importance in drug release, diffusion of the dissolution medium and the drug through the matrix after it changes to a rubbery state upon gelatinization, relative importance of matrix erosion and diffusion in drug release, and comparison of first-order mechanisms versus diffusion in these matrices. One or more of these processes possibly could be responsible for the overall drug release rate.

The precise role of hydration front penetration in capsule matrix formulations containing a hydrophilic polymer is not well understood. Carstensen *et al.* reported a method to determine the rate of water penetration in tablets formulated with hydrophilic polymers that involves the mechanical removal of the gelatinized layer by careful scraping with a spatula and weighing the dry core at predetermined times (6). Their findings suggest the rate of penetration of the water front, along with back diffusion of the dissolved drug through the gel, to be rate-determining in the drug release process, rather than the gelation rate or the actual drug dissolution rate. Obviously a technique that employs physical manipulation may introduce considerable errors in measurement and generally would not be applicable to the capsule matrices of our study due to their greater fragility. Furthermore, the ability to correlate the amount of drug release directly with the rate of penetration of the hydration front could be an important tool for the formulator. Therefore, the development of an improved method to assess the penetration rate in matrix formulations is of practical significance.

In the present study, a method that employs nuclear magnetic resonance (NMR) imaging was developed to measure the rate of penetration of the hydration front in a swellable hydrophilic polymer matrix system. NMR imaging, which has gained widespread recognition as a diagnostic and research tool, provides a noninvasive method to examine internal structures. Image voxels are generated from intrinsic NMR properties, namely, spin density, spin-lattice relaxation, and spin-spin relaxation, whose influence on signal intensity characterizes water mobility (7). Since NMR imaging is sensitive to mobile protons, it is a technique ideally suited for tracking the hydration front.

The use of proton NMR imaging to obtain spatial information has been investigated for other swollen polymer systems (8–10). A primary advantage of such a noninvasive technique is that it permits the study of physical processes such as diffusion without mechanical interference. Consequently, the use of NMR imaging to determine dynamic characteristics of polymer matrices may be applied to fragile capsule formulations.

The specific objectives of this study were (i) to develop an NMR imaging method to track the penetration of the hydration front in wet hydrophilic polymer matrices; (ii) to obtain, at predetermined times, images of the capsule matrices containing 35% hydroxypropyl cellulose to estimate the rate of water uptake; and (iii) to investigate the role of water

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uptake or hydration rate in the release of pseudoephedrine HCl from these capsule matrices.

MATERIALS AND METHODS

Materials. Fine-particle size, high-viscosity hydroxypropyl cellulose (HPC) NF was supplied by Aqualon Co. (Wilmington, DE), anhydrous lactose was from Sheffield Products (Norwich, NY), and magnesium stearate was from Mallinckrodt Inc. (St. Louis, MO). Pseudoephedrine HCl was generously supplied by Burroughs Wellcome Co. (Research Triangle Park, NC).

Capsule Formulation. The following formulation was used to make capsule plugs for this study.

Pseudoephedrine HCl	45 mg
HPC NF	35%
Anhydrous lactose	Q.S.
Magnesium stearate	1%

A 12-g blend of the capsule formulation was prepared. The capsules were filled by the plug formation and transfer method, a commonly employed principle in modern capsule manufacture. A specially designed compaction simulator which closely replicates the tamp fill principle (11) was used for this purpose. The target capsule fill weight was 250 mg.

Dissolution Method. The dissolution rate was determined by means of USP method 2 (paddle) at a stirring rate of 50 rpm. Three randomly selected capsules of the matrix formulation were tested, and three individual measurements were averaged to obtain each data point. The capsules were inserted into standard stainless steel spirals to prevent floating. Dissolution was carried out in an automated dissolution apparatus consisting of a multidrive stirrer (Vanderkamp 600, Vankel Industries, Chatham, NJ) coupled to a multiflow cell dissolution spectrophotometer (Model 25-7, Beckman Instruments, Silver Spring, MD). The uv absorbance of pseudoephedrine HCl was determined spectrophotometrically at 254.6 nm.

Novel NMR Imaging Method to Track the Rate of Penetration of the Water Front in a Hydrophilic Matrix. The test capsules were evaluated via dissolution as already described. At a predetermined time, each capsule plug was gently removed from the dissolution medium and immediately blotted dry after removing the steel spiral. Care was taken while handling the wet plugs so as not to distort their shape. The plug was then placed in the capsule-shaped cavity, 6.5-mm ID, of a Delrin cylindrical holder specially designed to be inserted into a 10-mm-OD NMR glass tube and secured by a rubber ring. The entire sample apparatus was suspended from an elongated tube and placed inside the bore of the magnet by an upper stack entry so that the capsule plug was positioned in the center of a 10-mm-ID shielded radiofrequency (RF) coil designed for microimaging. The 9.4-T spectrometer employed was accessorized with actively shielded Microstar gradients and interfaced to an Omega operating system (GE NMR Instruments, Fremont, CA).

NMR imaging experiments were performed using a conventional spin-warp imaging sequence (12). The temperature inside the RF coil was maintained at 19°C. The proton observation frequency was 400.16 MHz, and the spectral width was 166,667 Hz. The strengths of the slice-selection, phase-encoding, and read gradients were of the order of 130 Gcm^{-1}. Multislice data were collected in the transverse plane with a field of view of 20 mm. The pulse sequence parameters were optimized for imaging pharmaceutical formulations at SPRI with the GE Omega PSG-based instrument. The key parameters selected for pulse sequence generation (PSG) were a phase encode time of 400 μsec, a gradient ramp time of 50 μsec, and a crusher slice gradient time of 200 μsec. The number of sinc pulse cycles was 2.0, and the selective 90 and 180° amplitude-modulated pulses each were applied for 1 msec. The imaging parameters were chosen as follows: number of scans, 2; echo time, 3.4 msec; repetition time, 500 msec; slice thickness, 2.0 mm; number of slices, 4; slice separation, 2.0 mm; and in-plane matrix resolution, 256 × 256. Total scan time per capsule plug was 4 min 16 sec.

The images were processed at a SPARCstation IPC with SunOS 4.1.1 (Sun Microsystems, Mountainview, CA) using GE Omega software. Contour plots of the transverse slices were used for determining the penetration rate of the water front (described in the Data Analysis section). The image data files were subsequently exported and transferred in binary form from the SPARCstation to a Macintosh IIcx computer to be imported with Image, v. 1.22, analysis software (National Technical Information Services). In gray-scale images, the voxel intensity is brightest wherever the greatest number of mobile protons is contributing to the overall NMR signal. Displaying the images in color highlights the distinction between wet and dry parts of the capsule matrices; therefore, a pseudocolor scale was applied prior to implementing the graphical presentation features of Microsoft PowerPoint (Redmond, WA). Final photographic images were captured with Image Q, v. 2.0 (Presentation Technologies, Sunnyvale, CA), which allows direct imaging onto a Montage FRI bit-mapped high-resolution film recorder.

Data Analysis. The central dry core area was determined by a cut and weigh technique applied to contour plots of these eight image time points. The image display size was enlarged by positioning each pair of horizontal and vertical cursors 100 data points apart, thus a uniform zoom region was defined for all contour plots. The rate of hydration front penetration was calculated by comparing the inner dry area weight to the total area weight of the plug recorded at time 0. For each image time point, the percentage drug remaining to be released was plotted as a function of the corresponding percentage dry core weight. The percentage dry core was plotted according to the following diffusion equation of Jost (13), modified by Pitkin and Carstensen (14) for this purpose,

$$\ln(m) = -(D\pi/r_o^2)t \quad (1)$$

where r_o is the radius of the equivalent sphere and m represents the percentage dry core. The diffusion coefficient of water in the gel was obtained from the slope of this plot.

RESULTS AND DISCUSSION

The representative images in Fig. 1 (printed in black and white) and the plot in Fig. 2 reveal that in 1 hr, water penetrated to the center of the capsule matrix in plugs tamped to 200 N, while only about 45% of the drug was released during this time.

The NMR imaging method presented here tracks the

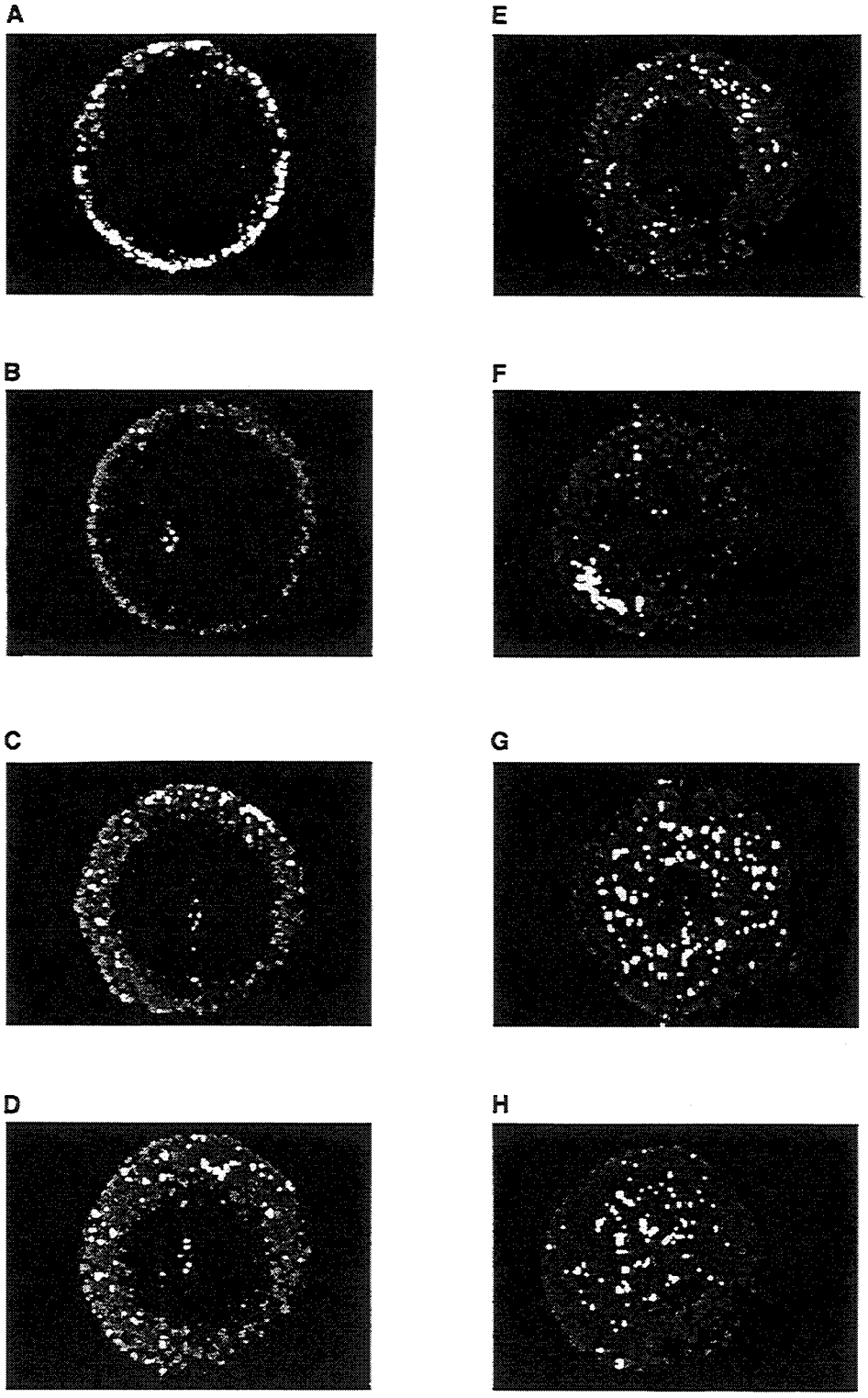

Fig. 1. NMR images of wet capsule plugs removed from the dissolution medium at predetermined times: (A) 0, (B) 10, (C) 15, (D) 20, (E) 30, (F) 40, (G) 50, and (H) 60 min. The diameter of the plug imaged at time 0 was 6 mm as measured with the contour plot scale.

water penetration front in intact hydrophilic matrix capsules and provides a potentially more accurate approach than mechanical removal of the gel. The dry core area can be measured noninvasively even when greater swelling in the plugs examined at later time points requires minimal removal of the gelled surface to accommodate insertion into the capsule holder cavity. By defining the hydration front at the boundary of the outermost dry area, an indirect estimate of the

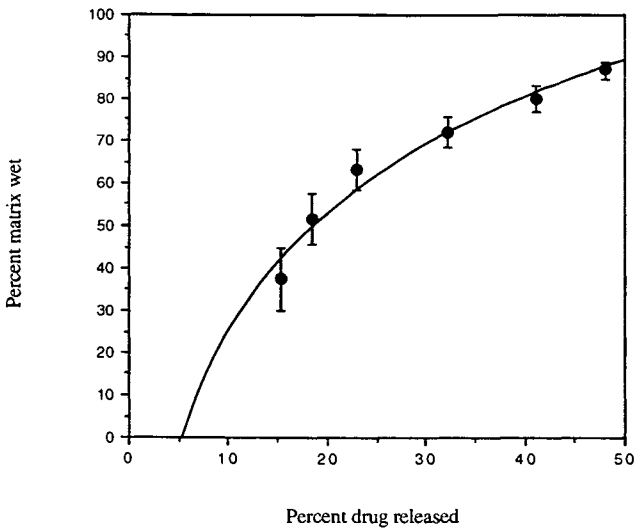

Fig. 2. Plot of percentage drug released as a function of percentage matrix wet.

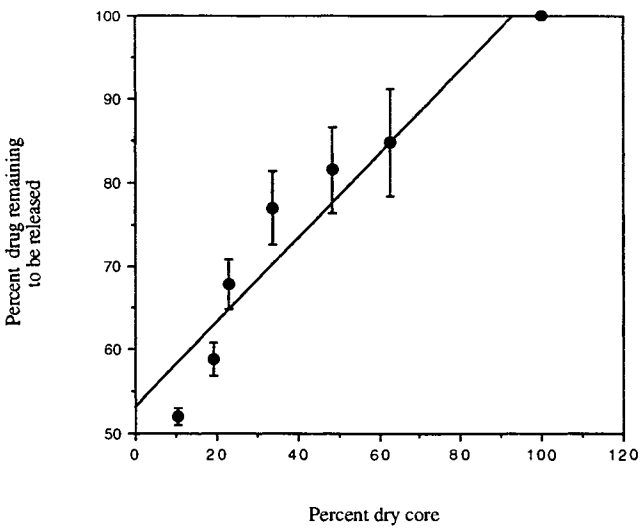

Fig. 3. Plot of percentage drug remaining to be released as a function of percentage dry core. The regression line has a slope of 0.5 and an intercept of 53.1.

percentage wet matrix can be made by comparison with the total image area determined for the plug examined at time 0. Thus, the ability of NMR imaging to delineate and measure the dry inner portion not yet penetrated by water gives this technique its advantage for testing hydrophilic matrix capsules. Extrapolation from area percentage to volume percentage is simplified by exclusion of any end effects, which are negligible since each set of multislice images in this study represents data for the centermost 8 mm of the total capsule plug length. The experiment parameters were selected such that the water penetration at the ends of each plug was not detected during NMR imaging.

Although NMR methods cannot discriminate perfectly among the NMR-sensitive protons, varying degrees of spin relaxation influence signal detection (15). Net magnetization from macromolecular or polymeric protons decays rapidly and yields very short relaxation times. The NMR imaging sequence employed in this study relies on spin-echo generation with a short echo time and significantly longer repetition time, such that only those protons with intrinsically long relaxation times will contribute to the NMR image data. The relaxation times of the swollen polymer protons are very likely too short to render them NMR visible. Through exchange processes, however, any mobilized protons of the polymer matrix may exert their influence by affecting the relaxation behavior of the penetrating water protons, whose rapid molecular motions contribute to the NMR signal.

If water penetration were the only rate-limiting step in drug release from hydrophilic matrix capsules, then the percentage wet matrix should correspond to the percentage drug released, or the percentage drug remaining to be released should correspond to the percentage dry matrix. In this case, a plot of percentage wet versus percentage released should be linear with a unit slope and an intercept of 0. However, in Figs. 2 and 3, the slope is not 1 and the intercept is not 0. This clearly suggests that the water penetration rate is not a rate-controlling factor in these formulations.

The plot in Fig. 4 shows that the percentage dry core is log linear with respect to time. The slope of this plot, as defined by Eq. (1), yields a diffusion coefficient of water equal to 4.15×10^{-6} cm^2/sec (% CV = 11), which is in the usual range of such measurements, although too much emphasis should not be placed on the absolute value due to assumptions in the calculation (6). The exponential decline in the rate of penetration by the hydration front could arise from the progressive development of the gel phase and the associated swelling, which blocks the pores in the matrix. This in turn retards the water penetration and back diffusion. Initially these pores provide the dissolution medium rapid access into the superficial layers of the loosely tamped matrix and lead to rapid drug release. It is important to note that sufficient water penetration is necessary for Higuchi's model to hold (16). As the matrix swells, the pores are blocked and free access to the dissolution medium is decreased accordingly. The relative insensitivity of such formulations to tamp-

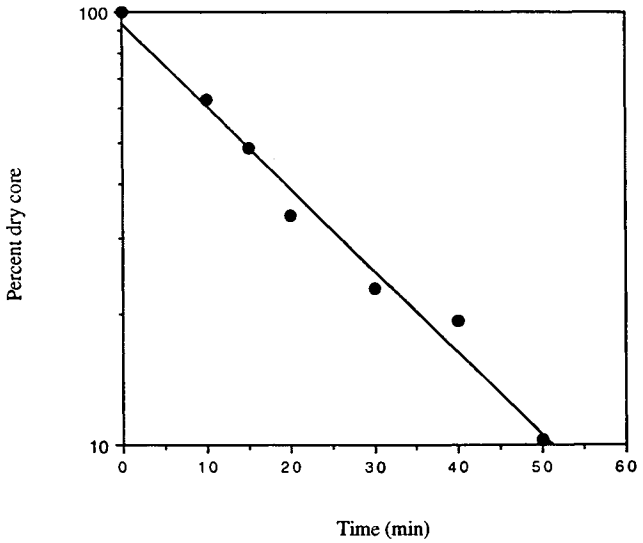

Fig. 4. The log of percentage dry core as a function of time.

ing force, as observed previously (11), may be attributed to this same phenomenon as well.

In conclusion, these observations indicate that the rate of penetration of the water front in a hydrophilic polymer matrix system is not the rate-limiting step in drug release. This study clearly demonstrates that NMR imaging provides a novel and noninvasive method to measure the rate of hydration front penetration in polymer matrix systems. In the future, NMR imaging should prove to be a valuable research tool in formulation development and evaluation.

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