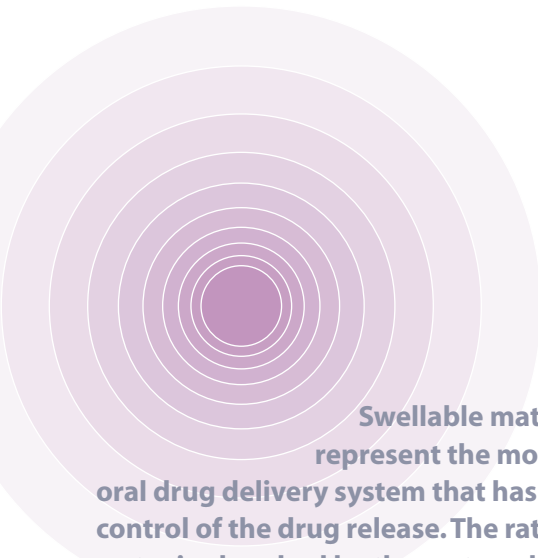


A Novel Method for the Study of Water Absorption Rates by Swellable Matrices

S.R. Parakh,* A.V. Gothoskar, and M.T. Karad



Swellable matrices represent the most popular oral drug delivery system that has temporal control of the drug release. The rate at which water is absorbed by the system decides the pattern of drug release; therefore, the study of water absorption kinetics plays a vital role in predicting and explaining the drug release pattern. In this article, a novel method is developed to study the water absorption rate. This method allows for the study of accurate actual water content determination. The results obtained in this study show a good correlation with the swelling behavior of the matrices. The authors observed that the rate of water absorption depends on the ratio of polymer:hydrophilic excipient and polymer viscosity.

S.R. Parakh, PhD, is a principal and professor in pharmaceuticals; **A.V. Gothoskar** is a senior lecturer in pharmaceuticals; and **M.T. Karad** is the executive president, all at Maharashtra Academy of Engineering Research and Education, Maharashtra Institute of Pharmacy, S. No. 124, Ex-Servicemen Colony, MIT Campus, Paud Road, Pune 411 038, Maharashtra, India, tel. +91 020 5431795, fax +91 020 5442770.

*To whom all correspondence should be addressed.

The focus of pharmaceutical research is being steadily shifted from the development of new chemical entities to the development of novel drug delivery systems of existing drug molecules to maximize their effectiveness in terms of therapeutic action and patent protection. This shift has been made possible by the discovery of various compatible polymers. These polymers, when used in the formulation, control the temporal and/or spatial delivery of a drug.

The majority of oral drug delivery systems are matrix-based. In such systems, the tablet is in the form of a compressed compact that contains an active ingredient, a lubricant, an excipient, and a filler or binder (1). Erosion, diffusion, and swelling of the matrix are the various methods through which the systems control drug delivery. The polymer properties invariably play an important role in the release pattern of the drug. If the polymer is predominantly hydrophilic, the swelling process chiefly controls the drug release. The swellable matrices are monolithic systems prepared by compressing a powdered mixture of a hydrophilic polymer and a drug. The success of these drug delivery systems is attributed to the established tablet manufacturing technology.

Hydroxypropyl methylcellulose (HPMC) is a dominant vehicle used for the preparation of oral controlled drug delivery systems (2). HPMC is a semisynthetic ether derivative of cellulose that has been used extensively as a hydrophilic polymer in oral drug delivery systems since the early 1960s. Its popularity can be linked to its nontoxic nature, the small influence of processing variables on drug release, its ease of compression, and its applicability to accommodate high levels of a drug (3).

HPMC matrices represent swellable matrix drug delivery systems, which are porous in nature. When an HPMC matrix comes in contact with water or aqueous gastrointestinal fluid, the polymer absorbs the water and undergoes swelling or hydration. The rapid formation of a viscous gel layer upon hydration has been regarded as an essential step in achieving controlled drug release from HPMC matrices (4). This process leads to the relaxation of the polymeric chain with a reduction in the value of the glass transition temperature of the polymer. Subsequently, the polymer undergoes a glassy-to-rubbery phase transition, the chains disentangle, and as a result of increased distance of separation between the chains, the drug diffuses. Lowering the

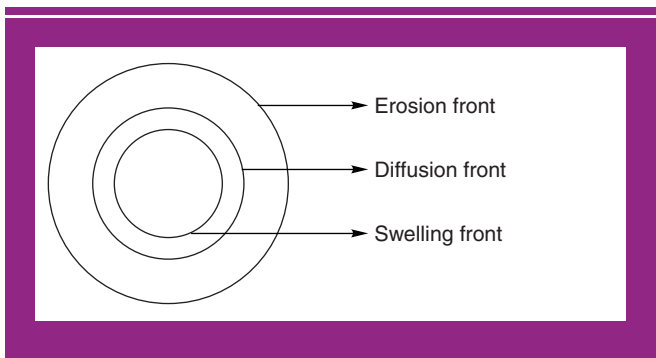


Figure 1: Different front positions in a swellable matrix.

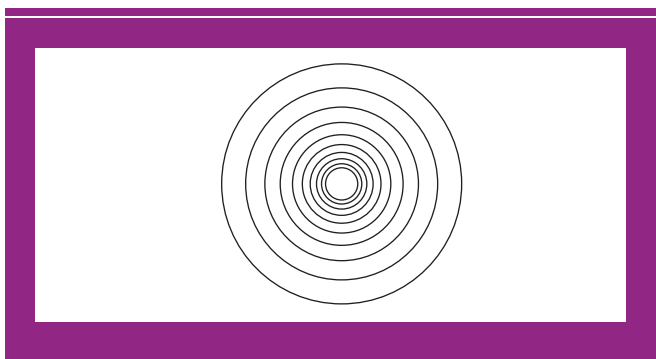


Figure 2: Representation of a novel method for the study of water absorption kinetics.

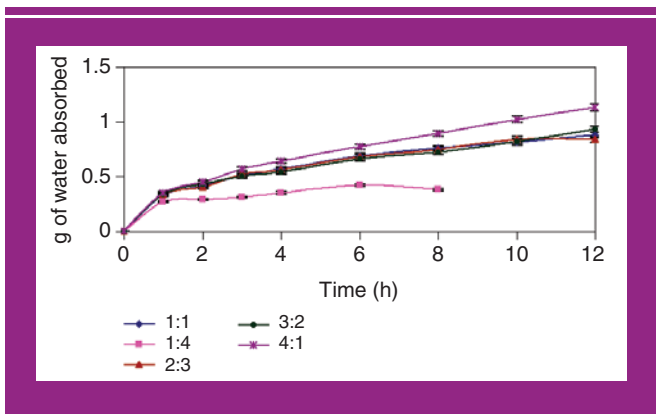


Figure 3: Water absorption rate for HPMC K15M.

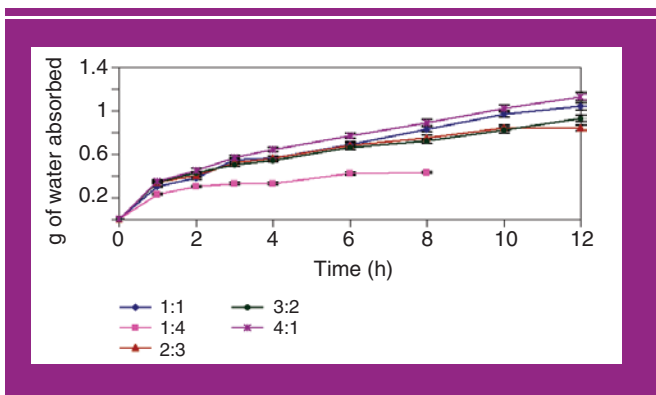


Figure 4: Water absorption rate for HPMC K100M.

glass transition temperature of the polymer is controlled by the characteristic concentrations of polymers in the matrix and depends upon the temperature and thermodynamic interactions of the water–polymer system (5).

Mechanistically, two distinctive processes, swelling and true dissolution, generally occur during the overall dissolution of glassy polymers (6). The transport phenomena involved in drug release from HPMC matrices are complex because the micro- and macrostructure of HPMC exposed to water are very time dependent (2).

The swelling behavior of heterogeneous swellable matrices is mechanistically described by front positions. *Front* indicates the position in the matrix where the physical conditions sharply change (7–10). In a macroscopic observation of the swelling process, a swelling front that separates the rubbery region can be identified and is in fact the water penetration front, which is responsible for lowering the glass transition temperature of the polymer in the matrix. A second front, the erosion front, separates the matrix from the solvent, and the diffusion front is located between the swelling and the erosion fronts (see Figure 1).

The rate of drug release depends on the rate at which the polymer swells, which in turn depends on the rate of water uptake by the matrix. Hence, one should study the water absorption rate of the matrix to gain an insight into the release mechanism of the drug from the matrix and predict its release rate.

Several methods are described in the literature for the investigation of matrix-swelling behavior (which is the result of water absorption). These methods include two types of techniques: optical microscopy (e.g., polarized microscopy, photomicrography, and optical imaging) and nuclear magnetic resonance imaging (11). However, seldom is any attempt made to study the kinetics of water absorption. The study of water absorption kinetics forms an integral part of the investigation of any hydrophilic matrix used as an oral drug delivery system.

In this article, the authors describe a novel yet simple method for following the water absorption kinetics of hydrophilic matrices containing HPMC. This method not only allows for the determination of unidirectional swelling behavior without disturbing the gel layer, but also aids in the quantitation of the water absorption pattern on the basis of the concentration of the polymer, hydrophilic excipient, and the viscosity grade of the polymer.

Experiment

Materials. Methocel Premium HPMC with viscosity grades K100LV (batch ML23012N21), K4M (batch ND24012N02), K15M (batch LL01012N01), and K100M (batch NE14012N02) were all obtained from Colorcon Asia Ltd (Mumbai, India). According to the specifications of the manufacturer, the nominal viscosities of 2% aqueous solution of the polymers at 20 °C are 100, 4000, 15,000, and 100,000 cps, respectively. Methocel K grade has a methoxyl content of 22.1% and a hydroxypropyl content of 8.1%. Alprazolam (lot RP 9541), lactose anhydrous (lot RP 9598), and magnesium stearate (lot RP 9628) were all obtained from LiTaka Pharmaceuticals Ltd. (Pune, Maharashtra, India). Lactose was used as filler, and magnesium stearate was used as a lubricant.

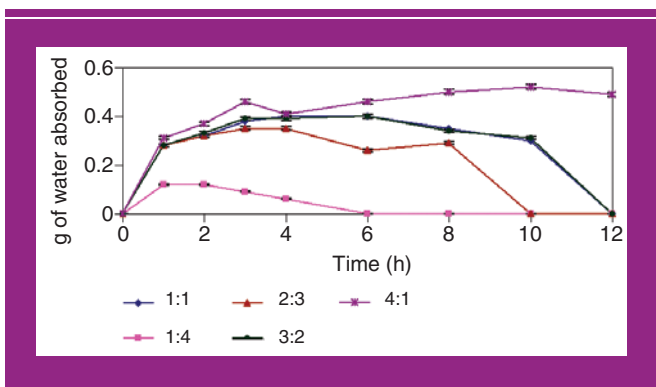


Figure 5: Water absorption rate for HPMC K100LV.

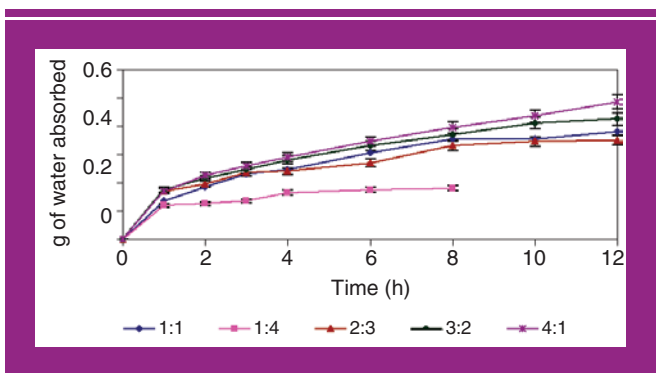


Figure 6: Water absorption rate for HPMC K4M.

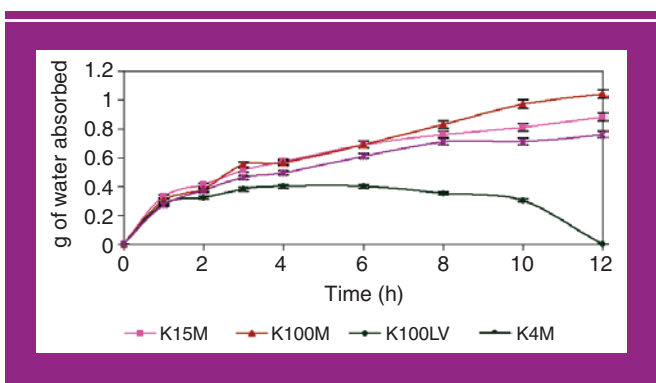


Figure 7: Water absorption rate for HPMC:lactose ratio 1:1.

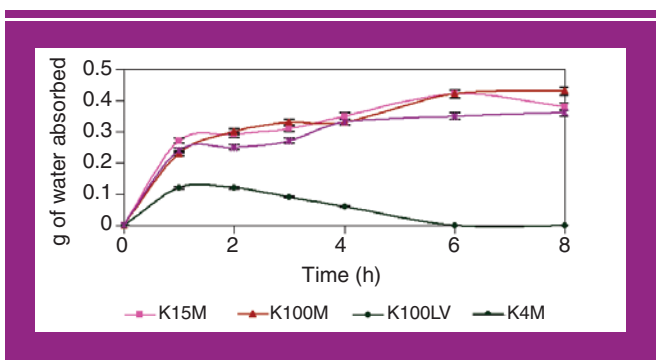


Figure 8: Water absorption rate for HPMC:lactose ratio 1:4.

Matrix formulation and preparation. Flat, circular tablet matrices that have varying HPMC:lactose ratios were made using different viscosity grades of the polymer. The formulations were thus categorized into two groups: the one in which the concentration of the HPMC was varied (concentration series) and the second in which the viscosity of the polymer was varied (viscosity series). The matrices were prepared using HPMC:lactose ratio of 1:1, 1:4, 2:3, 3:2, and 4:1. The same ratios were followed irrespective of the viscosity of the polymer. Each matrix weighed 100 mg and contained 1.0 mg of alprazolam and 1.0 mg of magnesium stearate. The matrices were directly compressed using a 16-station single rotary tablet machine (Cadmach, India) at a pressure of 4000 lb applied in an axial direction to obtain the tablets with a diameter of 7 mm. The thickness of the tablets varied between 2.27–2.45 mm.

Method for the study of water absorption kinetics. The matrices obtained were circular in shape with 7-mm diameters. Hence, using computer-aided design software, concentric circles were drawn with diameters of 7, 8, 10, 12, 14, 16, 18, 20, 22, 25, and 30 mm as shown in Figure 2. The printout of this figure was laminated to make it hydrophobic. On either side of this piece, special arrangements were made to facilitate the raising and lowering of the assembly. The concentric circles are drawn to measure the increase in the radial direction, which makes it unnecessary to disturb the gel layer that formed, and the diameter of the outermost circle arbitrarily was fixed at 30 mm as the matrices underwent dissolution above this parameter. The area A of the circular face was determined using the equation

$$A = \pi r^2 \quad [1]$$

in which π is the constant and r is the radius of the circle.

The tablet matrix under investigation was placed in the center so that it occupied the innermost circle with a 7-mm diameter. The assembly was weighed and then lowered in a 100-mL glass beaker containing 35 mL of deionized water that was maintained at $37 \pm 0.5^\circ\text{C}$.

After predetermined time periods, this assembly was raised out of the beaker and was reweighed after wiping off the water droplets that adhered to the surface of the assembly. The difference in the two weight values gives the amount of water absorbed by the matrix. The amount of water absorbed by the matrix is plotted against the time to determine the water absorption pattern.

The average velocity of water penetration front was determined using the equation

$$u = \left(\frac{dW_g}{dt} \right) \times \left(\frac{1}{\rho_w 2A} \right) \quad [2]$$

in which dW_g/dt is the weight of water absorbed by the matrix per unit time, ρ_w is the density of water at 37°C , A is the area of the matrix, and the factor 2 accounts for diffusion taking place through both the faces.

Results and discussion

When the water absorption commences, the water penetration front initially will develop and move inward. This inward movement of water causes the relaxation of polymeric chains, which begin reptating. This relaxation is attributable to the glassy-to-

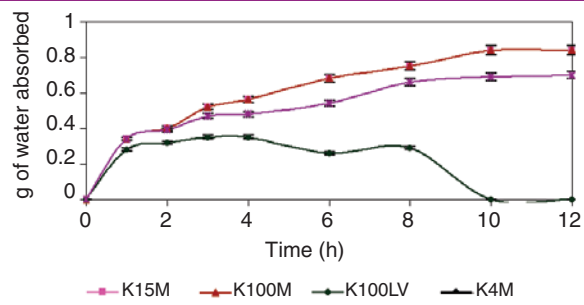


Figure 9: Water absorption rate for HPMC:lactose ratio 2:3.

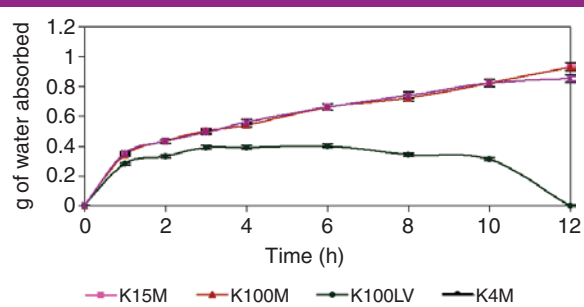


Figure 10: Water absorption rate for HPMC:lactose ratio 3:2.

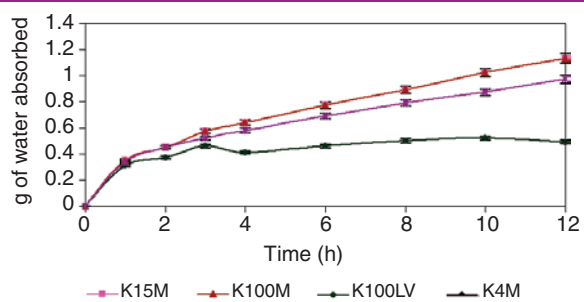


Figure 11: Water absorption rate for HPMC:lactose ratio 4:1.

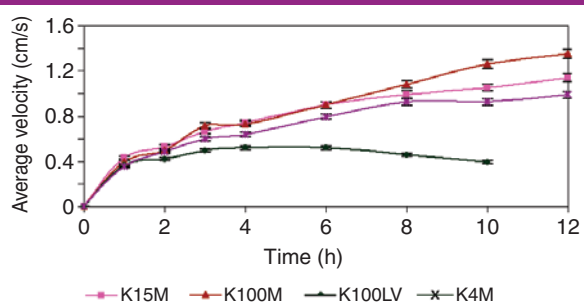


Figure 12: Average water penetration front velocity for HPMC:lactose ratio 1:1.

rubbery phase transition. In other words, as time passes, the glassy core diminishes and the tablet dimensions change in the axial and radial directions.

Detecting the true water penetration front is difficult. Hence, water absorption can be discussed in terms of diminishment in the size of the glassy core, the distance of water movement toward the center of the matrix, or the increase in the weight of the matrix.

The forward movement of the water penetration front leaves behind a rubbery region in which the polymeric chains are now free to rotate. As time increases, the chains become totally disentangled and ultimately pass to the erosion front and are cleaved off. Figures 3–16 show distinct patterns of the water absorption rate that are characteristic of the polymer viscosity and the polymer:lactose ratio. Figures 3–6 show the water absorption rate plotted as a function of polymer viscosity, and Figures 7–10 depict the water absorption rate as a function of the ratio of polymer:lactose concentration, which is nothing but the concentration of the lactose.

In the concentration series (see Figures 7–11), the rate of water absorption initially is slow, followed by an intermediate rate, and then maximum water absorption toward the end. Also, where the concentration of lactose is higher (see Figure 8), the polymer is so relaxed that such tablets completely dissolve within 8 h. This dissolution is attributable to the hydrophilic nature of the lactose that hastens the process of water absorption. The same fact is confirmed by the study of the average water penetration front velocity (see Figure 13), which is the highest velocity for the maximum lactose content.

In the viscosity series, HPMC K100LV (see Figure 5) undergoes disintegration faster. In other words, less water is absorbed to relax the polymeric chains that have low viscosity. As the viscosity grade increases (see Figures 3, 4, and 6), the water absorption rate increases, and at the end of the experiment the polymer of the highest viscosity shows the maximum absorption (see Figure 4).

When the lactose concentration is high and the polymer viscosity is low, the radial and axial dimensions of the matrix diminish along with a reduction in the matrix's weight as the water absorption rate increases. The dimensions diminish because the polymer chains undergo a rapid phase transition and become relaxed as a result of the water absorption. The diminishment further the matrix's passage from the swelling front to the erosion front where the polymer chains are cleaved off. These findings are in accordance with works reported by Gao and Meury (6), Lee and Kim (12), and Ju et al. (13).

Conclusion

The water absorption behavior of HPMC depends on its viscosity as well as the presence of a hydrophilic excipient (lactose, in this case). The lowest viscosity grade of HPMC with the highest concentration of lactose undergoes swelling and dissolution at a faster rate compared with other combinations because it absorbs water at a faster rate, which causes the polymer to transition from a glassy to a rubbery state, thereby facilitating chain movements.

The rate of water absorption and the water penetration front velocity increase in direct proportion with the increasing conc-

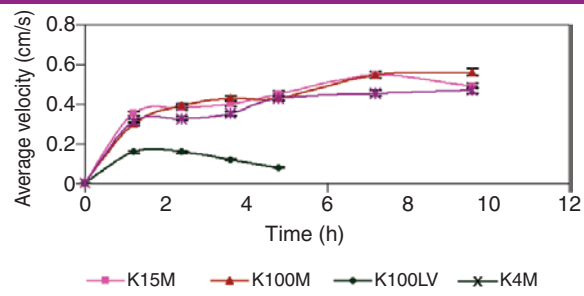


Figure 13: Average water penetration front velocity for HPMC:lactose ratio 1:4.

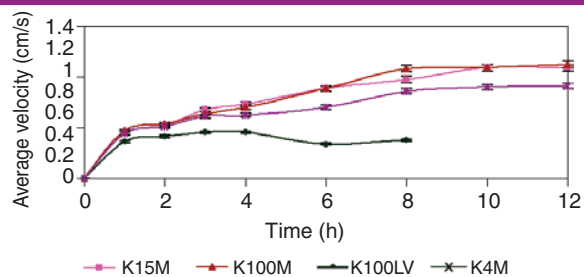


Figure 14: Average water penetration front velocity for HPMC:lactose ratio 2:3.

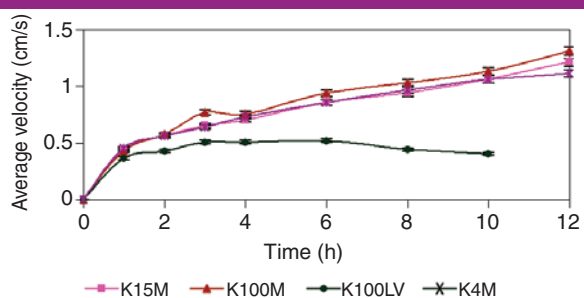


Figure 15: Average water penetration front velocity for HPMC:lactose ratio 3:2.

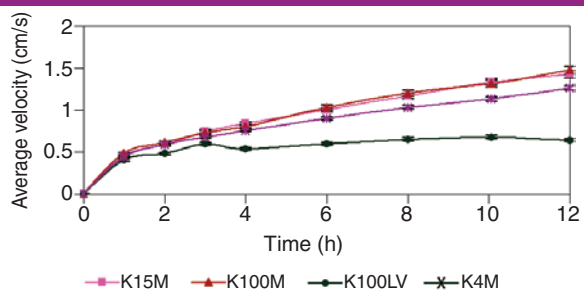


Figure 16: Average water penetration front velocity for HPMC:lactose ratio 4:1.

centration of lactose in the formulation and is a result of the hydrophilic nature of the lactose, which hastens the rate at which water is absorbed. In the matrices with the highest lactose concentration, the matrix undergoes complete dissolution within 8 h.

In the viscosity series, the water absorption rate increases as the polymer viscosity increases. However, this increase in the absorption rate does not necessarily lead to the diminishment of the tablet dimensions by the process of erosion or the dissolution of the polymeric chains because a gel layer is formed in case the high viscosity polymer is resistant to erosion. At the same time, the hydrophilic nature of the polymer facilitates the water absorption.

Because the results obtained by the newly developed method are in excellent agreement with the reported findings, one can conclude that this method can be successfully used for studying the swelling behavior of the swellable matrices. This method is economical and easy to set up and follow.

References

1. J.E. Hogan, "Hydroxypropyl Methylcellulose Sustained-Release Technology," *Drug Dev. Ind. Pharm.* **15** (6,7), 975–999 (1989).
2. J. Siepmann et al., "HPMC-Matrices for Controlled Drug Delivery: A New Model Combining Diffusion, Swelling, and Dissolution Mechanisms and Predicting the Release Kinetics," *Pharm. Res.* **16** (11), 1748–1756 (1999).
3. A.T. Pham and P.I. Lee, "Probing the Mechanisms of Drug Release from Hydroxypropyl Methylcellulose Matrices," *Pharm. Res.* **11**, 1379–1384 (1994).
4. D.A. Alderman, "A Review of Cellulose Ethers in Hydrophilic Matrices for Oral Controlled-Release Dosage Forms," *Int. J. Pharm. Tech. Prod. Mfr.* **5**, 1–9 (1984).
5. P. Colombo et al., "Swellable Matrices for Controlled Drug Delivery: Gel-Layer Behavior, Mechanisms, and Optimal Performance," *Pharm. Sci. Technol. Today* **3** (6), 1–8 (2000).
6. P. Gao and R.H. Meury, "Swelling of Hydroxypropyl Methylcellulose Matrix Tablets, Part I: Characterization of Swelling Using a Novel Optical Imaging Method," *J. Pharm. Sci.* **85** (7), 725–731 (1996).
7. R. Bettini et al., "Moving Fronts and Drug Release from Hydrophilic Matrices," *Proc. 21st Int. Symp. Controlled Release Bioact. Mater.* **21**, 19–20 (1994).
8. P. Colombo et al., "Drug Diffusion Front Movement Is Important in Drug Release Control from Swellable Matrix Tablet," *J. Pharm. Sci.* **84** (8), 991–997 (1995).
9. R. Bettini, P. Colombo, and N.A. Peppas, "Drug Concentration Profiles During Drug Release from Hydrophilic Matrices," *Proc. 24th Int. Symp. Controlled Release Bioact. Mater.* **24**, 635–636, (1997).
10. R. Bettini, N.A. Peppas, and P. Colombo, "Polymer Relaxation in Swellable Matrices Contributes to Drug Release," *Proc. 25th Int. Symp. Controlled Release Bioact. Mater.* **25**, 36–37 (1998).
11. P.I. Lee and N.A. Peppas, "Prediction of Polymer Dissolution in Swellable Controlled-Release Systems," *J. Controlled Release* **6**, 207–215, (1987).
12. P.I. Lee and C.J. Kim, "Effect of Geometry on Solvent Front Penetration in Glassy Polymers," *J. Membr. Sci.* **65**, 77–92 (1992).
13. R.T.C. Ju, P.R. Nixon, and M.V. Patel, "Drug Release from Hydrophilic Matrices, Part I: New Scaling Laws for Predicting Polymer and Drug Release Based on the Polymer Disentanglement Concentration and the Diffusion Layer," *J. Pharm. Sci.* **84** (12), 1455–1463 (1995). **PT**