Determination of Continuous Changes in the Gel Layer Thickness of Poly(ethylene oxide) and HPMC Tablets Undergoing Hydration: A Texture Analysis Study

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INTRODUCTION

Gel layer thickness has been considered as one of the key parameters affecting drug release from the swelling-controlled matrix system. Continuous increase in gel thickness of the rate-controlling polymer will lead to declining release rate irrespective of the system geometry, while it is argued that maintenance of constant gel layer thickness might produce zero-order release kinetics from a planar surface (1,2). It has also been demonstrated that the profile of gel layer thickness versus time consists of three stages: i) initial increase due to polymer swelling; ii) maintenance of constant gel-layer thickness between the swelling and dissolution fronts, often referred to as front synchronization; iii) reduction in gel-layer thickness as the glassy core is depleted (2). However, fronts synchronization is rarely encountered in the actual fabrication of oral controlled drug delivery systems, and therefore additional explanations pertaining to swelling and release mechanisms have to be considered if constant release rate is the objective. Hence, understanding the time-dependent polymer gel growth behavior will assist the formulation scientist in selecting the rational polymer.

The investigation of matrix swelling behavior generally involves the determination of front movement during dissolution process, from which gel layer thickness and core dimensional changes are calculated. Optical microscopy has been widely used to detect the movement of water advancing front based on the significant change in the refractive index at the interface of polymer gel and glassy core (3–6). However, the intermediate regions and polymeric domains that do not contain sufficient amount of water to affect the optical properties may not be distinguishable. Additionally, a significant disadvantage of optical microscopy is that often the matrix is refrained from axial expansion and the swelling studies are usually conducted by sandwiching the matrix with special devices (commonly plexiglass disks) which limits water penetration and the subsequent swelling in the radial direction only (3,4). It is also reported that on many occasions hydrophilic polymeric systems primarily swell in the axial direction (5,6), therefore the information derived from optical microscopy might not reflect the true nature of matrix swelling process. More recently, several non-invasive imaging techniques have been adapted to perform swelling studies of polymeric tablets, including ^{1}H NMR imaging (7), confocal laser scanning microscopy (CLSM) (8), Cryogenic scanning electron microscopy (Cryo-SEM) (9) and light scattering imaging (LSI) (10). These sophisticated techniques were capable of demonstrating the existence of polymer concentration and water mobility gradients across the gel regions. For example, in ^{1}H NMR imaging the local variations in the hydration extent of polymer matrix were visualized and water state was differentiated in terms of proton relaxation times and self-diffusion coefficients (11). When the matrix was loaded with drug, the transport and distribution of the drug within the gel-layer was also characterized using CLSM (8). From these studies, it is concluded that drug distribution and water mobility within the polymer gel predominantly depend on the inherent hydration properties of the polymer and the solubility of the formulation components. The routine application of sophisticated techniques such as NMR, CLSM, Cryo-SEM and LSI are often time consuming and difficult to perform despite their high accuracy and precision, thus impose limitations. Consequently easy and accurate determination of dimensional changes associated with matrix hydration and swelling of complex formulation on a routine bases still remains a challenge in formulation research and development.

In this report, a new approach to monitor water advancement, swelling process and gel growth is presented using a laboratory scale texture analyzer. Furthermore, the accuracy of the technique and data collection is compared and validated with NMR imaging results of recently published work (7).

MATERIALS AND METHODS

Sample Preparation

The compacts of pure hydroxypropylmethylcellulose (Methocel™, K100-LV, K4M and K15M, Dow Chemical Company, with average moisture content of 3.4% as determined by Karl Fischer analysis) and poly(ethylene oxide) (PEO, M_w: 0.6×10^6, 1×10^6, 2×10^6 and 5×10^6, Union Carbide, with moisture content of 0.58%, 0.45%, 0.34% and 0.63%, respectively as determined by Karl Fischer analysis) were prepared by directly compressing 500 mg polymer into a 10 mm diameter die using Carver press (Model C, Fred S. Carver Inc., Wabash, IN) and flat faced punch. To minimize processing variables, all tablets were produced under identical conditions. One planar base of the compact was covered with organic coating (14 g Eudragit® RS in the mixture of 50 mL acetone and 50 mL isopropanol) impermeable to water in order to prevent deformation during the determination of core/gel interface and it was subsequently glued to a glass petridish. For the determination of radial gel layer thickness, the compacts were cut in half diametrically, and the flat end of hemisphere-shaped compact was glued to a glass petridish with the same organic coating solution. The samples prepared in this manner were then placed in dissolution vessels filled with 900 mL deionized water at room temperature.

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The paddle speed was 50 rpm to simulate the actual tablet dissolution process. The swollen compacts were taken out at predetermined time intervals for textural profiling and the determination of water penetration front and gel layer thickness.

Texture Analyzer Profiling

The movement of water penetration front and the increase in gel layer thickness were determined on a TA. XT2 Texture Analyzer (Texture Technologies Corp., Scarsdale, NY/Stable Micro Systems, Godalming, Surrey, UK). Texture Analyzer instrument is a microprocessor-controlled texture analysis system that captures the complete profile of stress-strain behavior for material under test. It consists of an analyzer and a personal computer equipped with Texture Expert™ software that automates data acquisition and analysis. A probe is connected to a force transducer within the analyzer which measures the force of resistance encountered by the probe during the test. The motion of the probe is controlled by a stepping motor that records the displacement up to the accuracy of 25 μm.

During the test, the sample was positioned in the center of the testing platform. A flat-tipped, round steel probe of 2 mm in diameter and 30 mm in length was used in this study. The probe traveled at 2.0 mm/s until the surface of the matrix was detected at 0.7 g of force (threshold value for triggering the texture analyzer), at which point the probe penetrated the swollen matrix at a speed of 0.2 mm/s. Once the predetermined force was detected, the probe was automatically withdrawn at 0.2 mm/s. The predetermined force was established in such a manner that it could differentiate the glassy polymer from polymer gel. This force was optimally determined to be 500 gram. At a starting point, an initial indentation of 75 μm was made on the dry compacts with 500 gram force, and this distance was considered and corrected for in the actual calculation of the gel layer thickness. Data were collected at a rate of 200 points per second by Texture Expert™ software for further analysis.

RESULTS AND DISCUSSION

The glass transition temperature (T_g) of hydrophilic polymers, at which molecular mobility dramatically changes, depends significantly on the water content in the polymer. For example, the T_g of HPMC E5 was shown to decrease from 175°C to room temperature at water content of about 20% (12). It was also demonstrated by Rutherford backscattering spectrometry (13) that the water penetration front preceded the phase transition front during the swelling process of polymer. In addition, the diffusive and heterogeneous nature of phase transition front (i.e., absence of microscopically sharp boundaries) makes the physical description of core/gel interface inexact, which might be further complicated by the presence of entrapped air bubble or gas inside the gel (14). Consequently the accuracy of detecting core/gel interface and calculation of gel layer thickness depend greatly on the resolution power of the analytical techniques used. As mentioned earlier, the glassy core and rubbery gel in pharmaceutical matrices have been either characterized by relying on the optical characteristics of the swollen gel and glassy polymer (3–6) or alternatively, the magnetic resonance signal intensity of ^1H due to the presence of water at the phase transition front and the ability of polymer gel to scatter light have been reported in NMR and light scattering spectrometry respectively (7,10). In the present work, the glassy core/rubbery gel interface and nature of intermediate regions have been detected by the accurate measurement of variations in the textural and physicomechanical properties associated with changes in gel layer growth and glassy core.

Figure 1 shows a typical force-displacement profile of PEO compact with different extent of hydration. Pure polymer was used to exclude the influence of the formulation additives since such additives may enhance or suppress the swelling behavior of the polymer within the matrix microenvironment depending on their solubility and interaction. As shown in Figure 1, the resistance force encountered by the probe penetration is a function of the traveled distance into the gel and gel consistency/strength. Low resistance as reflected by the low initial slope indicates that the gel strength is weak while sharp increase in force (i.e., higher slope) as probe moves deeper into the swollen phase corresponds to a much stronger gel. At the periphery (i.e., outer edge) of the swollen compact the mobility and concentration of water is close to that of free water as has been reported by NMR studies (11), indicating that polymer concentration is negligible; while at the glassy front where the mobility of water approaches zero, the polymer concentration is at its maximum. The overall change in polymer and water concentration gradients is found between the two extremes. It is apparent that the mechanical strength of polymer gel reflected as resistance to force in this study is proportional to the polymer concentration in the gel. More appropriately, the force-displacement profile of the loading phase is qualitatively indicative of the polymer concentration profile within the swollen region. From Figure 1 it is evident that the probe encountered little resistance near the periphery of the matrix (i.e., low initial force detected at different time intervals, <100 gram force), however the resistance to the probe penetration monotonically increased as the probe approached the glassy core/gel interface. It is also observed from Figure 1 that the gradient of the force-displacement curves specifically in the region from zero to 200 gram force progressively decreased with the time of hydration,

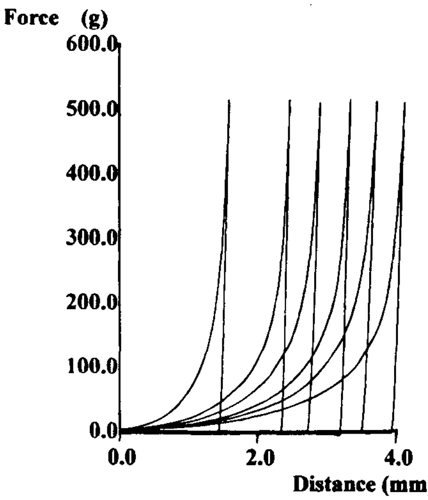

Fig. 1. The representative force-displacement profiles of PEO (M_w: 2×10^6) matrices with varying time of swelling (from left to right: 0.5, 1.0, 2.0, 3.0, 4.0, 5.0 hours).

indicating greater degree of polymer chain mobility and disentanglement/dissolution as well as the decrease in polymer concentration. A sharp increase in the slope of the force-displacement (F-D) profile beyond 200 gram force as the probe moved into the swelling front suggests the discontinuity of material consistency (i.e., the regional detection of core/gel interface/boundary). Based on the approximation of the force-displacement slope to infinity, the glassy core and rubbery gel interface as well as the overall gel strength can be precisely determined. It should be noted that the magnitude of such forces and changes in the F-D profiles are dependent on the probe size and shape.

The growth of hydrophilic polymer gel depends on the swelling rate at the water penetration front and the erosion rate at the outer surface of the gel. However, gel erosion often lags behind since the polymer concentration has to reach a threshold value before erosion or disentanglement occurs (3). In general, the maintenance of polymer gel thickness is governed by the relative rates of water penetration and polymer chain disentanglement at the periphery of the gel. Continuous growth of polymer gel layer will result if water penetration is more rapid than polymer chain disentanglement. On the contrary, when water penetration is retarded by the increasing gel layer thickness while polymer chain disentanglement proceeds steadily, little or no change in polymer gel thickness may occur and constant gel layer thickness will be observed. It should be noted that both water penetration into polymer and polymer chain disentanglement heavily depend on the molecular weight of polymer assuming that other inherent characteristics of the polymer are accounted for. In the present study, the gel thickness is defined as the distance between the outer surface of the swollen compact (i.e., periphery) and the core/gel interface. Figure 2a and b show the increase in gel layer thickness dynamics versus time for tablets made of HPMC and PEO of various molecular weights. HPMC and PEO were chosen due to their popularity in fabricating swelling-controlled dosage forms (6,15,16). The gel thickness reported here is the average of three independent measurements (i.e., on three tablets). It is evident that initial growth in gel thickness occurred fairly rapidly ($t \leq 1$ hour), followed by continuous but relatively slow advancement depending on polymer gel structure and water interaction. Figure 2a indicates that the growth in gel layer thickness for HPMC tablets is associated with their molecular weight. High molecular weights HPMC K4M and K15M showed similar pattern in the rate and extent of swelling, whereas the growth rate of HPMC K100-LV gel layer was slowed down significantly probably due to the more rapid erosion process. It is also evident that no front synchronization occurred for all molecular weights of HPMC studied. With regard to PEO (Figure 2b), the three grades behaved alike until 3 hours after the initiation of dissolution process, at which time the increase in gel layer thickness for PEO 0.6×10^6 began to level off, while the gel layer thickness of PEO 1×10^6 and 2×10^6 continued to increase. Thus front synchronization seemed to be only achieved for PEO of molecular weight 0.6×10^6. Overall comparison of the gel layer growth behavior of HPMC and PEO matrices further suggests that during the same time period PEO possesses higher degree of swelling capacity than HPMC.

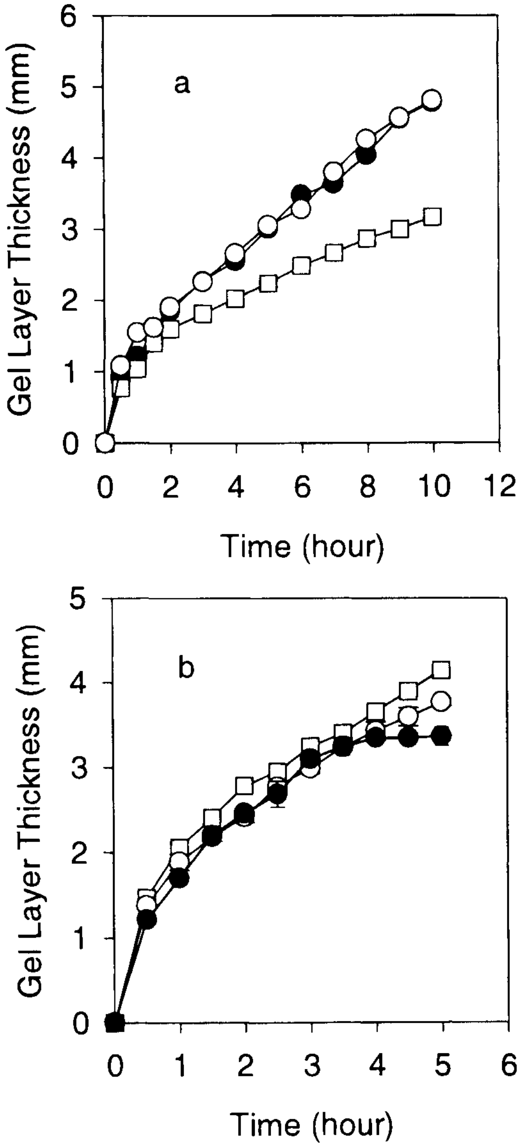

Fig. 2. Dynamic changes in gel layer thickness for HPMC and PEO matrices of various molecular weight as a function of time. (a) HPMC matrices (□, K100-LV, O, K15M, ●, K4M), (b) PEO matrices (●, 0.6×10^6; O, 1×10^6, □, 2×10^6). (Standard deviations have been shown in every case, however, in most cases they are smaller than the symbol size).

From a practical point of view, it is known that water penetration into the polymer matrix and drug solubility are the key events in regulating swelling and drug release. Thus the kinetics of water penetration could be used as a predictive measure of swelling behavior and drug release from polymeric matrix. As shown in Figure 3a, both the axial and the radial movement of water penetration front is dependent on the square root of time, signifying that water ingress into high molecular weight PEO (5×10^6) matrices is a Fickian diffusion process. It is interesting to note that the movement of water penetration front in low molecular weight PEO (0.6×10^6) matrices (see Figure 3b) is a Fickian diffusion in the first three hours followed by relaxation-controlled process resulting in front synchronization. In addition, Figure 3 also demonstrates that the dynamics of gel growth and thickness for PEO (0.6×10^6 and 5×10^6)

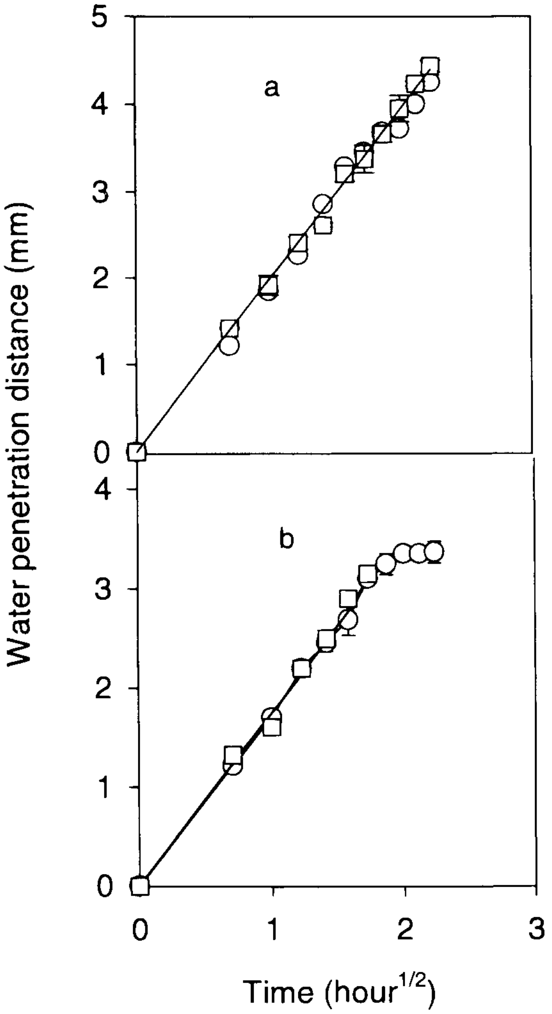

Fig. 3. The distance water penetrated into PEO matrices as a function of time. (a) PEO M_w:5 × 10^6, (b) PEO M_w: 0.6 × 10^6 (O, axial direction; □, radial direction).

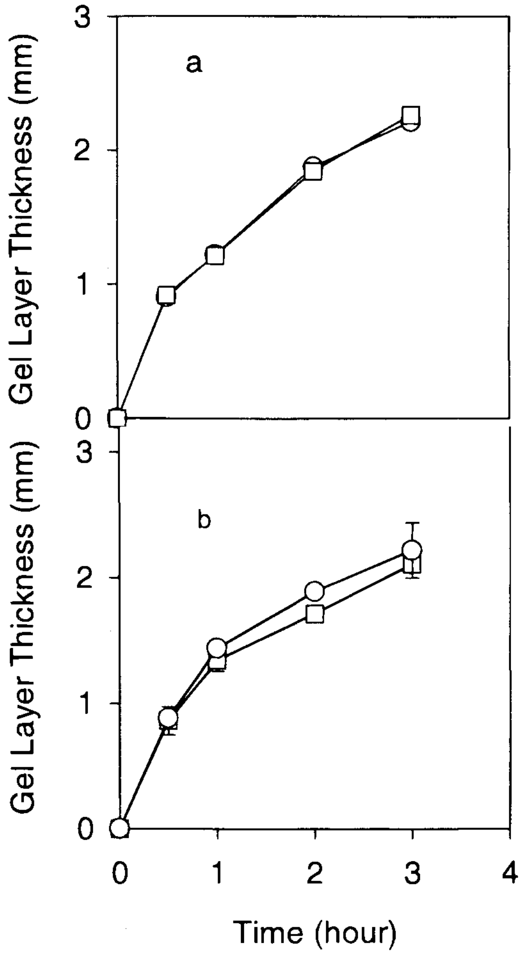

Fig. 4. Correlation of increase in (a) axial and (b) radial gel layer growth for HPMC K4M tablets derived from Texture analyzer study (□) and NMR microscopy (O) reported by Rajabi-Siahboomi *et al.*(1994). (Standard deviations have been shown in every case, however, in most cases they are smaller than the symbol size).

was comparable in both axial and radial directions. Similar behaviors have also been observed for HPMC K4M compacts by others (7,17).

In order to verify the accuracy of data, correlation between the results generated from texture analyzer and that of NMR imaging technique was established. The dynamics of change in both axial and radial gel layer thickness for HPMC K4M compacts studied in this work were correlated with the results of NMR imaging reported by Rajabi-Siahboomi *et al.* (7). This correlation was considered since in our laboratory we have shown that variation in compression force in a certain range does not significantly affect the swelling of KPMC K4M compacts (6). Figure 4 shows that the data are essentially superimposed, suggesting that excellent agreement exists between the two techniques for HPMC K4M compacts.

In conclusion, the present study has demonstrated the potential and application of texture analysis in characterization of the swelling behavior of hydrophilic polymeric matrices. The results show that the gel layer thickness of HPMC matrices increased continuously over the time period studied without fronts synchronization. On the other hand, high molecular weight PEOs (1 × 10^6, 2 × 10^6, 5 × 10^6) manifested greater capacity and growth potential in gel layer thickness, while low molecular weight PEO (0.6 × 10^6) demonstrated the capacity to achieve front synchronization (i.e., the moving velocity of polymer swelling front equals that of polymer dissolution front, leading to constant gel layer thickness). The results further indicated that water penetration into high molecular weight PEO (5 × 10^6) matrix appeared to be a diffusion-controlled process, whereas both diffusion and relaxation were present in controlling water penetration into low molecular weight PEO (0.6 × 10^6) matrix. Additionally, the gel growth is symmetrical in both the axial and radial directions for PEO (0.6 × 10^6 and 5 × 10^6) matrix. This method offers the advantage that the glassy core/rubbery gel interface could be precisely detected based on the approximation of the force-displacement profile slope to infinity. Finally the results of texture analysis profiling appears to be comparable to techniques such as NMR imaging in the investigation of polymer matrix swelling behavior and front movement with excellent reproducibility as demonstrated from correlation study of HPMC K4M data. It appears that the application of texture analyzer on the routine bases might be of great value to scientist involved in formulation design and dosage form development.

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REFERENCES

1. P. I. Lee. Diffusional release of a solute from a polymeric matrix. Approximate analytical solutions. *J. Membrane Sci.* **7**:255–275 (1980).
2. R. S. Harland, A. Gazzaniga, M. E. Sangalli, P. Colombo, and N. A. Peppas. Drug/polymer matrix swelling and dissolution. *Pharm. Res.* **5**:488–494 (1988).
3. Y.-O. Tu and A. C. Ouano. Model for the kinematics of polymer dissolution. *IMB J. Res. Develop.* **21**:131–142 (1977).
4. P. Colombo, R. Bettini, G. Massimo, P. L. Catellani, P. Santi, and N. A. Peppas. Drug diffusion front movement is important in drug release control from swellable matrix tablets. *J. Pharm. Sci.* **84**:991–997 (1995).
5. E. Papadimitriou, G. Buckton, and M. Efentakis. Probing the mechanism of swelling of hydroxypropylmethylcelloluse matrices. *Int. J. Pharm.* **98**:57–62 (1993).
6. H. Kim and R. A. Fassihi. Application of a binary polymer system in drug release rate modulation. I. Characterization of release mechanism. *J. Pharm. Sci.* **86**:316–322 (1997).
7. A. R. Rajabi-Siahboomi, R. W. Bowtell, P. Mansfield, A. Henderson, M. C. Davis, and C. D. Melia. Structure and behavior in hydrophilic matrix sustained release dosage forms: 2. NMR imaging studies of dimensional changes in the gel layer and core of HPMC matrices undergoing hydration. *J. Contr. Rel.* **31**:121–128 (1994).
8. L. S. Cutts, S. Hibberd, J. Adler, M. C. Davis, and C. D. Melia. Characterizing drug release process within controlled release dosage form using the confocal laser scanning microscope. *J. Contr. Rel.* **42**:115–124 (1996).
9. C. D. Melia, A. C. Hodsdon, M. C. Davis, and J. R. Mitchell. Polymer concentration profiles of the surface gel layer of Xanthan, alginate and HPMC matrix systems. *Proceed Int'l Symp. Control. Rel. Bioact. Mater.* **21**:724–725 (1994).
10. P. Gao and R. H. Meury. Swelling of hydroxypropylmethylcellulose matrix tablets. 1. Characterization of swelling using a novel optical imaging method. *J. Pharm. Sci.* **85**:725–731 (1996).
11. A. R. Rajabi-Siahboomi, R. W. Bowtell, P. Mansfield, M. C. Davis, and C. D. Melia. 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. *Pharm. Res.* **13**:376–380 (1996).
12. B. C. Hancock and G. Zografi. The relationship between the glass transition temperature and the water content of amorphous pharmaceutical solids. *Pharm. Res.* **11**:471–477 (1994).
13. C.-Y. Hui, K.-C. Wu, R. C. Lasky, and E. J. Kramer. Case-II diffusion in polymers. I. Transient swelling. *J. Appl. Phys.* **22**:1885–1900 (1987).
14. C. A. Fyfe and A. I. Blazek. Complications in investigation of hydrogel matrices due to the presence of trapped gas. *J. Contr. Rel.* **52**:221–225 (1998).
15. U. Conte, L. Maggi, P. Colombo, and A. La Manna. Multi-layered hydrophilic matrices as constant release devices (Geomatrix™ systems). *J. Contr. Rel.* **26**:39–47 (1993).
16. L.-B. Yang and R. Fassihi. Zero-order release kinetics from a self-correcting floatable asymmetric configuration drug delivery system. *J. Pharm. Sci.* **85**:170–173 (1996).
17. C. A. Fyfe and A. I. Blazek. Investigation of hydrogel formation from hydroxypropylmethylcellulose (HPMC) by NMR spectroscopy and NMR imaging techniques. *Macromolecules* **30**:6230–6237 (1997).