약제학회지(2001), 제 31 권 제 1 호
J. Kor. Pharm. Sci., Vol. 31, No. 1, 13-18 (2001)

Textural Characterization of Gel Layer Thickness and Swelling Boundary in a Hydrophilic Compact

Hyunjo Kim† and Reza Fassihi*

Bukwang Pharmaceutical Ind. Co., Ltd., Yeoeuido P.O. Box 572, Seoul, Korea
**Temple University, Philadelphia, PA 19140, U.S.A*
(Received January 2, 2001)

친수성 정제의 겔층두께와 겔팽창 영역의 조직 특성화

김현조† · 레자 파시히*

*부광약품 중앙 연구소, *템플대학교 약학대학*
(2001년 1월 2일 접수)

ABSTRACT–This study was to investigate the relationship between the gel layer thickness and swelling boundary via strength measurements using texture analysis. The novel texture analysis approach was used to examine the dynamics of swelling behavior in a ternary polymeric matrix tablet. The method permitted the characterization of the changes occurring at the peripheral as well as within interior boundary of the swelling during water ingress. The increase in gel strength for pectin, HPMC, and a ternary mixture with gelatin was found to depend on polymer concentration. Therefore, this method is further applicable to characterize the swelling behavior and provide opportunity to differentiate the gel-layer from that of swelling boundary.

Keywords–Gel layer thickness, Swelling boundry, Gel strength, Texture analyzer, Pectin, HPMC, Ternary polymeric system.

Single unit (monolithic) tablets are of great interest to the pharmaceutical industry especially when designed for controlled purposes. Currently hydrophillic matrices have been used extensively in the formulation of controlled release oral dosage forms.[1,2] One of the most interesting characteristics of the polymeric excipients used in pharmaceutical technology is the distention of polymeric chains after contact with a solvent (polymer swelling) with possible eventual disentanglement and dissolution. It has been shown that in the releasing interface, two main fronts are present : a glassy-rubbery swelling front and a rubbery-solvent eroding front.[3] It is important to be able to measure the actual nature of gellification process upon contact with aqueous or biological fluids in systems such as hydrophilic swellable matrices. Many approaches have been undertaken to measure the swelling process and characterize moving fronts during hydration. Optical microscopy[4,5] and mechanical instruments[6] have been most widely used for swelling studies of compressed water-swellable polymer matrix systems. Other techniques applied include light scattering imaging,[7] electro-spin resonance,[8] dielectric relaxation spectroscopy,[9] and Rutherford back-scattering spectrometry.[10] Cryogenic scanning electron microscopy (cryo-SEM) studies have shown that polymer in the outer layer regions of the gel is more homogeneously and extensively hydrated than the inner regions closer to the gel/core interface.[11] Pulsed-gradient spin-echo NMR[12] has also been used to measure water in swelling systems. In addition the self-diffusion coefficient (SDC) and T_2 relaxation time of water across the gel layer in the HPMC tablets has been measured using NMR-microscopy technique.[13,14] All the above methods are cumbersome to use and not readily available.

In the present work, a simple method namely micro systems texture analyzer (model TA-XT 2) is used to measure gel layer thickness and gel strength in the designed matrix system in a texture profile analysis mode. The textural property of the dosage forms such as hydrophilic swellable matrices can be utilized not only in defining dynamics of swelling and mechanisms of drug release but also in respect to the dosage form integrity within GI tract and the intragastric consequences of peristaltism including propulsion, grinding and retropulsion.

†본 논문에 관한 문의는 이 저자에게로
Tel : (031)492-0378 E-mail : hyunjokim@hotmail.com

In this study, the gel strength parameter or mechanical resistance of the gel is defined as the ratio between the force (penetrating force) and the displacement covered by the probe inside the sample. The purpose of this study was to investigate the relationship between the gel layer thickness and swelling boundary via variations in textural properties and strength measurements using texture analysis.

Experimental

Materials

Granular gelatin type B and magnesium stearate both USP grades were obtained from AMEND Drug and Chemical Co. (Irvington, NJ). Pectin type 621 [designated as high metho - xylated pectin citrus with a degree of methoxy-lation of 65-72%] obtained from Pectagel Co. (Great Neck, NY). Eudragit RS (Rhom Pharm, Germany) and Hydroxypropylmethyl cellulose (HPMC) 2208 were supplied by Dow Chemicals as METHOCEL, K4M having norminal viscosity of 4,000 cps in water at 2% w/v level. Acetone and isopropanol were obtained from Sigma Chemicals (St. Louis, MO 63178). All other chemicals were of reagent grade.

Methods

Matrix tablet preparation – Tablets containing each of pure pectin and HPMC were prepared by direct compression with a Caver press (model C, Fred S. Carver Inc., Wabash, IN) with a 7-mm flat-faced punch and die. Tablets were produced by accurately weighing 150 mg of the powder mixture. An additional batch was also produced where tablets containing the drug granulated gelatin was blended together with a pectin :HPMC (1:2) mixture and directly compressed with a 11 mm flat-faced punch and die using a Carver press. Each tablet weighed 500 mg.

Powder mixtures were blended in a V-mixer for 10 minutes. 1% w/w magnesium stearate was added to all formulations and mixed for an additional 5 minutes prior to compression. Tablets were compressed at 5,000 lbs unless otherwise stated.

Coating of tablets – Swelling experiments were undertaken on all tablets after coating either the edge or the two faces of the cylinder. The coating was achieved by holding the tablet with forceps, and applying two consecutive coats of 5% Eudragit RS in acetone and isopropanol (4:1) solution. With experience this process was standardized to produce uniform tablets after coating.

Tablet swelling thickness study

Axial swelling – Axial change determinations of tablets of pure pectin, HPMC, and the ternary polymeric combinations (pectin:HPMC:gelatin) were performed by sticking one face tablet to a glass-dish and placing individual dish in excess deionized water at 37°C immersed in water bath. Swelling of the tablets over a 5-h period was measured using a Texture Analyzer (TA-XT2, Texture technologies Corp., Scarsdale, NY) and controlled experimental conditions (see Table I).

Table I–*Experimental Conditions for Textural Analysis*

	Swelling thickness	Gel strength
Probe	2 mm flat-tipped	7 mm flat-tipped
Mode	Measure Distance in Force	Measure Force in Distance
Test Speed	2.0 mm/s	2.0 mm/s
Force	500 g	-
Distance	-	1 mm
Trigger Type	Auto-0.5 g	Auto-0.5 g
Acquisition Rate	200 pps	200 pps

Radial swelling – Individual tablets were allowed to swell in transparent glass dishes immersed in water bath with excess deionized water at 37°C for radial swelling change determinations. For this study tablets of pure pectin, HPMC, and the ternary polymeric combinations (pectin:HPMC:gelatin) were used and both faces of tablets were coated with 5% w/v coating solution (Eudragit RS dissolved in aceton and isopropanol (4:1)) and tablets were glued to the glass-dishes as described earlier. Swelling of the tablets was measured over a 5-h period.

Gel preparations – All powders (i.e., pure pectin, HPMC, and the ternary polymeric combinations (pectin:HPMC: gelatin)) which were premixed were initially dispersed in hot water (>90°C) with vigorous agitation until they were fully dissolved in the case of low powder content and thoroughly wetted and evenly dispersed at high powder content. All preparations were filled into the transparent glass dishes and left at room temperature until the entrapped air was disappeared. Thereafter samples were covered and kept at 4 °C for 2 days.

Gel strength measurement – The determinations of gel strength for pure pectin, HPMC, and ternary polymeric combinations were performed by placing individual transparent glass dishes on a stainless steel platform of the texture analyzer and gel strength was determined.

Data treatment by texture analyzer

Swelling thickness study – The system was equipped with a flaten 2 mm diameter steel probe and was able to accurately measure the travelled distance into a semi-solid material as

function of the force applied. The probe force was calibrated to determine the optimum value in order to differentiate the gel from the solid core. Tablets were immersed in dissolution medium for 2 hours and a force calibration curve was calculated for each formulation. Typical calibration curves for ternary polymeric matrix was constructed. In a Texture Analyzer calibration curve a sharp slope indicates the transition from the gel into the solid core. A force of 500 g was needed to approach the sample core as a function of distance. This force value was consistly used for different formulations tested during the tablet swelling gel thickness study.

The overall swelling thickness was measured by subtraction of the peak force at time zero from each peak force of tablets at the planned time point in a Texture Analyzer force-distance curve.

Gel strength study – The system was equipped with a 7 mm diameter steel probe whose tip was concaved shape and was able to measure the compression force required fixed at a compression distance of 1 mm on the Texture Analyzer. The probe travelled into a semi-solid material as function of the force and distance applied. In all experiments dish thickness was corrected for. Gel strength was expressed as penetration force divided by distance in a Texture Analyzer force-distance curve.

Results and Discussion

Swelling kinetics – Analysis of the swelling profile of tablets was based on studying axial and radial swelling kinetics. Measurements were done on the swollen tablet samples as described earlier. Swelling thickness values were estimated as changes of the original thickness of tablet. The increases in tablet swelling thickness were characterized by texture analyzer. Figure 1 shows a typical force-displacement profile of a complex hydrophilic tablet formulation with different extent of hydration. As seen in Figure 2 the swelling of the matrix tablets in the axial direction increased with selected time over the experiment period. Figure 2 also suggests that the axial expansion mode is in the order pectin > the ternary polymeric combinations (pectin:HPMC:gelatin) > HPMC. This result show different phenomena from the previous study (HPMC > pectin). The swelling of the ternary system falls between the two extremes of axial expansion. However, radial swelling expansion mode is in the order pectin > HPMC > the ternary polymeric combinations (pectin:HPMC :gelatin) (see Figure 2b). This indicates that a ternary polymeric matrix is more likely to maintain its cylindrical shape and expand axially. As can be seen in Figure 3, the axial expansion is approximately twice of the radial expansion in the

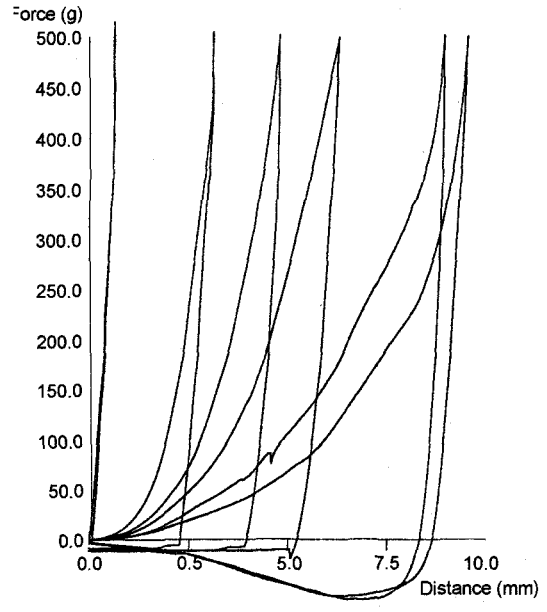

Figure 1–The representative force-distance profiles of a ternary polymeric matrices with varying times of swelling (from left to right : 0, 2, 4, 6, 8, and 10 hours).

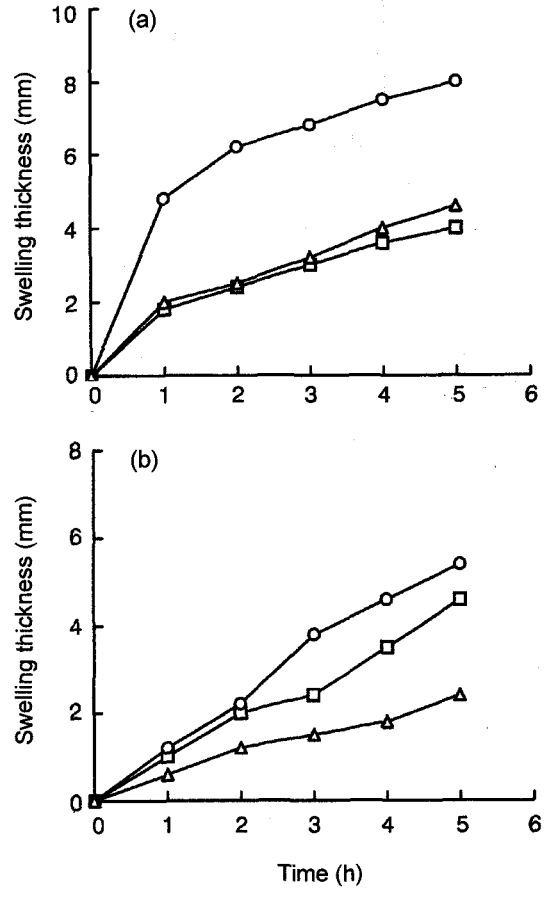

Figure 2–Swelling thickness of pectin (○) HPMC K4M (□)and a ternary mixture matrix tablets (△) in the (a) axial and Radial expansion (b).

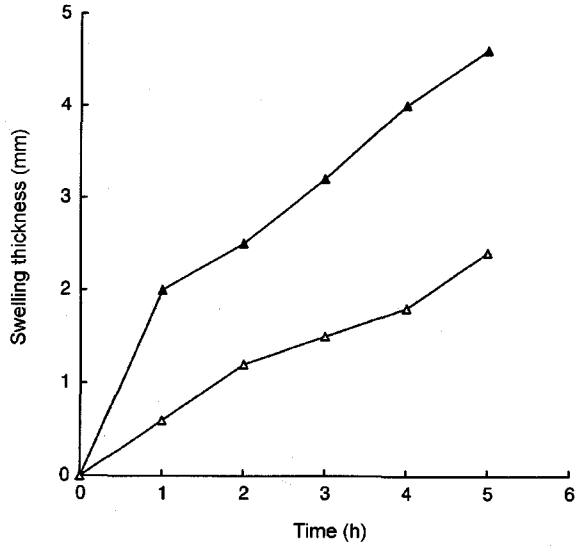

Figure 3–Swelling thickness of a ternary mixture matrix tablets in the axial (▲) and radial (△) expansion.

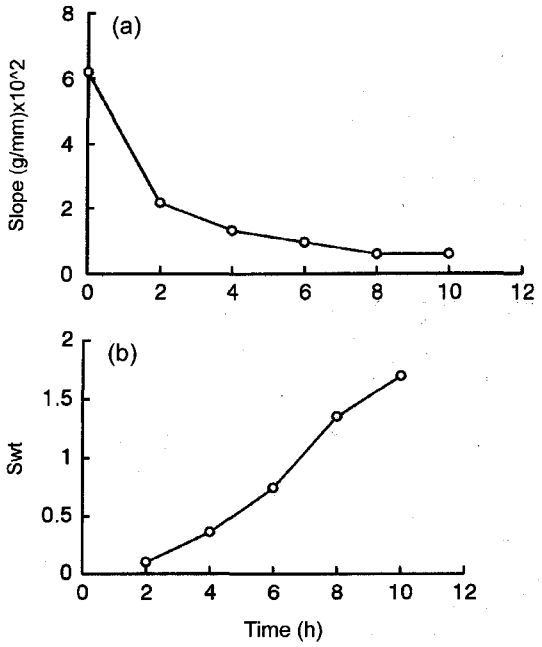

Figure 4–Slope (Force/distance) and dimensional changes in the early stages of hydration according to time in a ternary mixture matrix tablets.

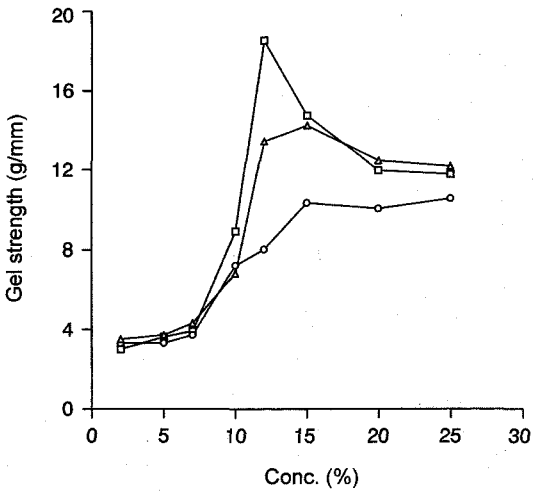

Figure 5–Gel strength (described as penetration force divided by displacement) and polymer concentration profiles of pectin (○) HPMC K4M (□) and a ternary mixture matrix tablets (△).

ternary system.

During the early stages of hydration, the characterization and measurements of the peripheral gel layer and swelling boundary were one of our main objectives. As shown in Figure 4a, the steepness of the slope (force divided by a selected distance from 100 g to 200 g, range representative for degree of swelling) changes according to the time were decreased in inverse ratio. This indicated that the swelling capacity was limited in polymeric matrix system. This phenomena is also presented in different manner as can be seen in bottom of Figure 4b.

Swelling gel strength – It has been suggested that the gel strength rather than the viscosity of the gel layer plays a major role in drug release from hydrophilic matrices. Nevertheless, the gel strength parameter is not routinely investigated in preformulation and formulation studies of such dosage forms. By using a texture analyzer it was possible to make it applicable/suitable for measuring the gel strength of pharmaceutical systems and validate its performance. In this study, the gel strength parameter or mechanical resistance of the gel system is expressed as the ratio between the penetrating force displayed on the screen at a certain time and the relative depth at which the probe has moved inside the sample at that time. Figure 5 shows the gel strength versus polymer concentration profiles obtained at three different powder dispersion. The gel strength increases as concentration increases up to 15%. This trend for HPMC can be seen in others. The increase in gel strength for pectin, HPMC, and a ternary mixture with gelatin was found to depend on polymer concentration. The increase in concentration of each polymer showed a limiting effects beyond which the gel strength declined to a plateau as concentration increased. This limiting concentration appeared to be around approximately 15% w/v for each polymer or the ternary mixture.

Thus, it indicates that the gel strength (mechanical resistance) of the sample is affected by the gel layer thickness induced by a texture analyzer curve.

Gel layer thickness determination upon dissolution – The transient development of gel layer thickness for different

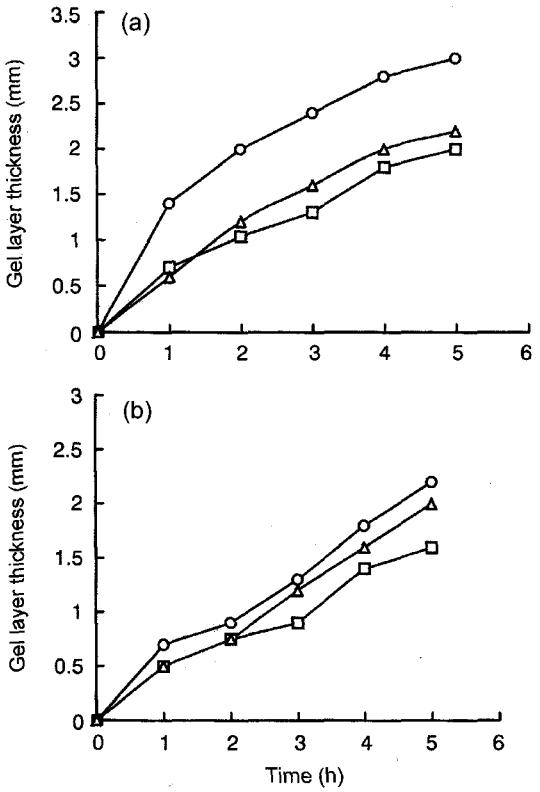

Figure 6–Gel layer thickness of pectin (○) HPMC K4M (□) and a ternary mixture matrix tablets (△) in the (a) axial and Radial expansion (b).

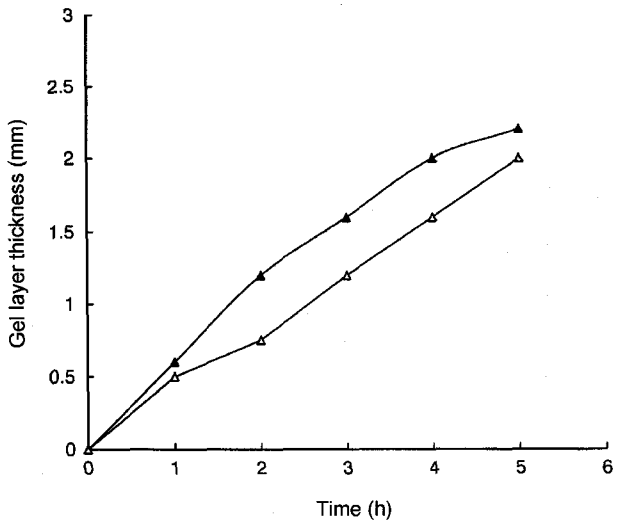

Figure 7–Gel layer growth of a ternary mixture matrix tablets in the axial (▲) and radial (△) expansion.

formulations is shown in Figure 6. The transient gel layer thickness increases considerably with time period. Since the gel layer development in the dissolution study is a result of competition between two process, namely swelling and dissolution, it is possible for their actual rates to remain differ for all formulations The gel thickness 3 mm, 1.8 mm and 2.3 mm 5 hour after water immersion, representing transient gel development for pure pectin, HPMC and their ternary matrix, respectively shown in Figure 6. For pure HPMC tablets a very thin gel layer remains and more or less constant since polymer swelling and erosion rate are similar in this case. Gel layer thickness for ternary polymeric matrix is quiet constantly increases, 2 mm and 2.3 mm for radial and axial growth, respectively over 5 hour-period (see Figure 7). This persistent and slow increase of gel layer growth gives more controlled drug release profile as can be seen in previous study.

Conclusion

The texture analyzer study was investigated to get relationship between the gel layer thickness and swelling boundary via strength measurements. This novel approach was used to characterize the swelling behavior in pectin, HPMC, and a ternary mixture with gelatin hydrophilic matrix. Gel strength depend on polymer concentration was investigated. The increase in concentration of each polymer showed a limiting effects beyond which the gel strength declined to a plateau as concentration increased. This limiting concentration appeared around approximately 15% w/v each polymer or their ternary mixture. The technique was proved to be simple and accurate. Thus, it can be used for analysis of polymer concentration threshold and gel structure.

References

1) H. Kim and R. A. Fassihi, application of binary polymer system in drug release rate modulation. 1. Characterization of release mechanism, *J. Pharm. Sci.*, **86**, 316-322 (1997).
2) H. Kim and R. A. Fassihi, A new ternary polymeric matrix system for controlled drug delivery of highly soluble drug : I. Diltiazem hydrochloride, *Pharm. Res.*, **14**, 1415-1421 (1997).
3) P. I. Lee. Influence of formulation variables and hydrodynamic conditions on release kinetics, *J. Membrane Sci.*, **7**, 255-275 (1980).
4) P. Colombo, R. Bettini, G. Massimi, 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) C. D. Melia, J. S. Binns, M. C. Davies, Hydrophyllic matrix sustained release system based on polysaccharide carriers, *J. Pharm. Pharmacol.*, **42**, 125P (1990).
6) P. I. Lee, Swelling and dissolution kinetics during peptide release from erodibleanionic gel beads, *Pharm. Res.*, **10**, 980-985 (1993).
7) P. Gao and R. H. Meury, Swelling of hydroxylpropylmethy-

lcellulose matrix tablets. 1. Charaterization of swelling using a novel optimal imaging method, *J. Pharm. Sci.,* **7**, 725-731 (1996).

8) C. Caramella, F. Ferrari, A. Gazzaniga, U. Conte and A. La Manna, Swelling activated delivery system, *Drug Dev. Ind. Pharm.,* **14**, 2167-2177 (1988).

9) L. S. Cutts, S. Hibberd, J. Alder, M. C. Davis and C. D. Melia, Hydrophyllic matrix sustained release system based on polysaccharide carriers, *J. Controlled Release,* **42**, 115-124 (1996).

10) D. Li. S. Zhu and A. E. Hamielec, Efficacy of sustained release verapamil, *Polymer.,* **34**, 1383-1387 (1993).

11) P. J. Mills, C. J. Palmstrom and E. j. Kramer, Controlled release delivery system, *J. Mater. Sci.,* **21**, 1479-1486 (1986).

12) P. Gao and P. E. Fagerness, Swelling of hydroxypropyl methylcellulose matrix tablets. 2. Mechanistic study of the influence of formulation variables on matrix performance and drug release, *Pharm. Res.,* **12**, 955-964 (1995).

13) A. R. Rajabi-Siahboomi, R. W. Bowtell, P. Mansfield, A. Henderson, M. C. Davis and C. D. Melia, Structure and behavior in hydrophyllic matrix sustained release dosage forms:2. NMR imaging studies of dimensional changes in the gel layer and core of HPMC matrices undergoing hydration, *J. Controlled Release*, **31**, 121-128 (1994).

14) A. R. Rajabi-Siahboomi, R. W. Bowtell, P. Mansfield, A. Henderson, M. C. Davis and C. D. Melia, Structure and behaviour in hydrophilic matrix sustained release dosage forms: 4. Studies of water mobility and diffusion coefficient in the gel layer of HPMC tablets using NMR imaging, *Pharm. Res.,* **11**, 471-477 (1994).

15) C. A. Fype and A. I. Blazek, Influence of drug solubility in the formulation of hydrophilic matrices, *Macromolecules,* **30**, 6230-6237 (1997).

16) 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).

17) E. Papadimitriou, G. Buckton and M. Efentakis, Probing the mechanism of the drug release from hydroxypropyl methylcellulose matrices, *Int. J. Pharm.,* **98**, 57-62 (1993).