Polymeric Blend Microspheres for Controlled Release of Theophylline

Anita G. Sullad,[1] Lata S. Manjeshwar,[1] Tejraj M. Aminabhavi[2]

[1]*Department of Chemistry, Karnatak University, Dharwad 580 003, India*
[2]*CSIR Emeritus, Scientist SET College of Pharmacy, Dharwad 580 008, India*

Received 27 February 2009; accepted 23 November 2009
DOI 10.1002/app.31866
Published online 29 March 2010 in Wiley InterScience (www.interscience.wiley.com).

ABSTRACT: Microspheres of poly(vinyl alcohol) (PVA) and hydroxyethyl cellulose (HEC) were prepared as semi-interpenetrating networks (IPNs), crosslinked with glutaraldehyde and used in controlled release of theophylline (THP), an anti-asthmatic drug. Formulations were characterized by X-ray diffraction (XRD) to understand uniform distribution of THP, Fourier transform infrared (FTIR) spectroscopy to understand chemical interactions, universal testing machine (UTM) for mechanical stability, and scanning electron microscopy (SEM) for investigating the morphology of the microspheres produced. SEM indicated smooth surfaces of the microparticles and sizes of around 10–15 μm giving high encapsulation efficiency up to 69%. Equilibrium uptake performed in double distilled water and *in vitro* release studies performed in 1.2 and 7.4 pH buffer media indicated the effect of extent of crosslinking and HEC content of the semi-IPN matrix on the release of THP that was extended up to 12 h. Analysis of i*n vitro* results using empirical equation suggested a deviation from the Fickian transport. Drug diffusion was estimated from the Fick's diffusion equation for spherical geometry. Kinetics of drug release followed the Higuchi square root equation, indicating that release is diffusion-controlled. © 2010 Wiley Periodicals, Inc. J Appl Polym Sci 117: 1361–1370, 2010

Key words: microspheres; poly(vinyl alcohol); hydroxyethyl cellulose; controlled release; crosslinking agent; semi-IPN; theophylline

INTRODUCTION

Controlled release (CR) of drugs through polymeric devices is important to increase the plasma half life of drugs that are short-acting. In the pharmaceutical literature, different types of drug delivery devices have been developed and tested for *in vitro* and *in vivo* studies.[1–4] Such systems incorporate the drugs without altering their original properties and exhibit tunable time release kinetics by selecting a combination of suitable polymers, copolymers or graft copolymers.[5–7] Particularly, development of micro/or nanoparticles derived from biodegradable polymers have been widely used in recent years because of their inherent advantages over the conventional dosage forms.[2,3]

Poly(vinyl alcohol) (PVA), because of its hydrophilicity and semicrystalline nature as well as its availability in highly hydrolyzed (degree of hydrolysis above 98.5%) and partially hydrolyzed grades (degree of hydrolysis of 80.0 to 98.5%), exhibits different chemical properties, solubility, and crystallizability.[8] Cellulose ethers are the commonly used water soluble and swellable polymers and their availability in different forms[9] such as hydroxypropylcellulose (HPC), hydroxyethyl cellulose (HEC), hydroxypropylmethylcellulose (HPMC) and methylcellulose (MC) exhibit different release characteristics. Of these, HEC is a hydrophilic and most erodible polymer demonstrating synchronization between erosion and diffusion to achieve zero-order release. HEC is a nonionic water-soluble, odorless, tasteless, and nontoxic carbohydrate polymer used extensively in pharmaceutical area.[10] The polymer exhibits a wide range of viscosity grades and poor solubility in organic solvents compared to cellulosic derivatives, such as HPC and HPMC. Additionally, HEC shows pH-independent release because of its nonionic nature.[11]

In our previous study, we have developed the IPNs of PVA and methyl cellulose to investigate the CR characteristics of THP.[12] In continuation of this study, we now propose to develop semi-IPN hydrogel microspheres of PVA with HEC to achieve an increased encapsulation efficiency of THP, a water-soluble drug, having plasma half time of 5–6 h; even though its frequent doses are toxic, but the drug is effective in the treatment of asthma.[13] In the previous literature, THP was used as a model drug[12–18] wherein its therapeutic effects required the plasma concentration of at least 5–10 μg/mL; however, its toxicity[19] was apparent at 15–20 μg/mL. Hence,

Correspondence to: L. S. Manjeshwar (latamanjeshwar@yahoo.com).

Contract grant sponsor: University Grants Commission (UGC), New Delhi, India; contract grant number: KU/SCH/UGC/RFSMS/2008-09.

TABLE I
Formulation Parameters of the Microspheres of PVA and HEC and Results of Encapsulation, % Equilibrium Swelling

Formulation codes	PVA (% w/w)	HEC (% w/w)	THP loading (%)	GA (mL)	OH/CHO Molar ratio	% EE (eq.1)	% Water uptake (eq.2)
F1	90	10	25	2	0.1890	63 ± 0.35[a]	312 ± 0.50[a]
F2	90	10	25	4	0.0940	65 ± 0.25	275 ± 0.64
F3	90	10	25	6	0.0630	66 ± 0.34	264 ± 0.48
F4	90	10	25	8	0.0472	69 ± 0.21	260 ± 0.62
F5	90	10	10	4	0.0940	62 ± 0.15	477 ± 0.78
F6	90	10	40	4	0.0940	69 ± 0.39	285 ± 0.55
F7	80	20	25	4	0.0858	65 ± 0.22	283 ± 0.69
F8	70	30	25	4	0.0751	63 ± 0.45	305 ± 0.40
F9	60	40	25	4	0.0644	61 ± 0.18	357 ± 0.60
Placebo	90	10	–	4	0.0940	–	269 ± 0.50

[a] Least squares analysis was done at 95% confidence limit to give standard deviations.

developing CR formulations of THP are needed in pharmaceutics area, as the drug has immense value in controlling the asthmatic related problems. The semi-IPN matrices prepared in this study from PVA and HEC are found to be suitable to increase the plasma life time of the drug, giving a sustained release effect.

EXPERIMENTAL

Materials and methods

Theophylline and Tween-80 were purchased from Loba Chemicals, Mumbai, India. Poly(vinyl alcohol) (M_w = 125,000) of degree of hydrolysis 86–89 % and hydroxyethyl cellulose (viscosity of 200 mPa·s) were purchased from s.d. fine Chemicals, Mumbai, India. Analytical reagent grade glutaraldehyde solution 25% (v/v), petroleum ether, and liquid paraffin oil were all purchased from s.d. fine Chemicals, Mumbai, India. Water used was of high purity grade after double distillation and deionization.

Preparation of semi-IPN microspheres

Semi-IPN microspheres of PVA and HEC were prepared by the emulsion-crosslinking method.[20] Briefly, 2 wt % of PVA solution was prepared by dissolving solid PVA powder in double-distilled deionized water and stirring continuously until a homogeneous solution was obtained. HEC was then dispersed in PVA solution and stirred for overnight to get a homogeneous solution. THP was dissolved in the above blend polymer solution and this solution was then added slowly to light liquid paraffin (100 g, w/w) containing 1% (w/w) Tween-80 under a constant stirring speed of 400 rpm for about 15 min. To this w/o emulsion, different amounts i.e, 2, 4, 6, and 8 mL of glutaraldehyde (GA), as a cross-linking agent, containing 0.5 mL of 0.1 N HCl was added slowly and stirred for 3 h.

The hardened microspheres were separated by filtration, washed with petroleum ether and water to remove the unreacted GA. The residual GA was removed completely by washing and the aldehydic test was done to the filtrate; the repeated washing was done using 20 mL of double distilled water until the test gives negative result; this confirmed the absolute absence of GA. Every time, the same amount of water was used for washings. The use of GA in developing CR formulations has been suggested to be toxic,[21] yet very small amount of GA present in the matrix to affect the cross-linking would not pose any problems as discussed before in the literature.[13,20,21] Solid microspheres obtained were vacuum dried at 40°C for 24 h and stored in a desiccator until further use. Totally, nine formulations were prepared as per the formulation codes given in Table I. In the preparation of all these formulations, same protocols were used to achieve a required level of encapsulation efficiency. A schematic chemical representation of the formation of semi-IPN structure is given in Figure 1. The compositions of placebo microspheres are included in Table I.

Fourier transform infrared (FTIR) spectral measurements

FTIR spectral data were obtained using a Nicolet (Model Impact 410, Milwaukee, WI) instrument to confirm the formation of IPN structure and also to find out any possible chemical interaction of the drug with the semi-IPN matrix. For FTIR measurements, samples were crushed with KBr to make pellets using 600 kg/cm^2 pressure. FTIR spectra of plain PVA, plain HEC, placebo semi-IPN microspheres, drug-loaded microspheres and plain THP were all scanned between 4000 and 500 cm^{-1}.

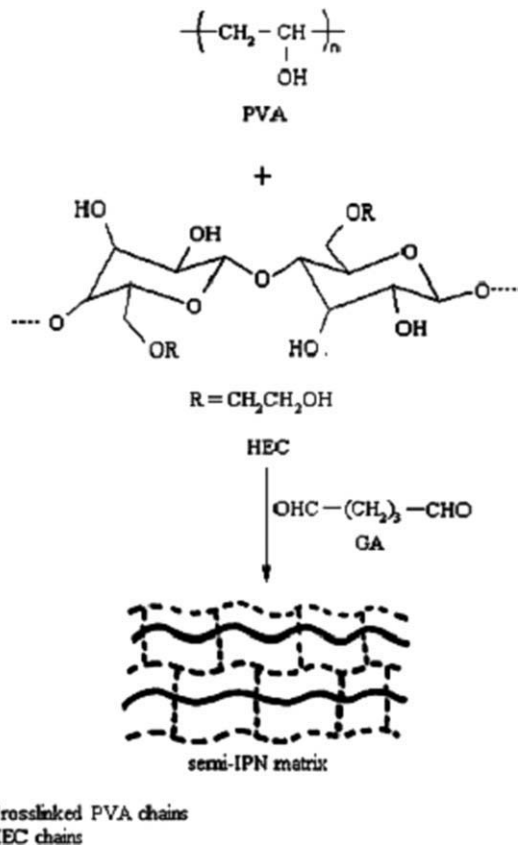

Figure 1 Formation of semi-IPN structure between PVA and HEC.

X-ray diffraction (XRD)

Crystallinity of theophylline after encapsulation was examined by X-ray diffraction (XRD) measurements (x-Pert, Philips, UK) recorded for placebo microspheres, THP-loaded microspheres and plain THP. Scanning was done at ambient temperature (25°C) up to the angle $2\theta = 50^{o}$.

Scanning electron microscopy (SEM)

SEM images were taken using JEOL model JSM-840A, Japan instrument available at Indian Institute of Science, Bangalore, India. Microspheres were sputtered with gold to make them conducting and placed on a copper stub. Thickness of the gold layer accomplished by gold sputtering was around 15 nm.

Encapsulation efficiency (EE)

Estimation of drug concentration was done according to the method adopted by Mundargi et al.[22] Microspheres of known weight (~10 mg) were ground to powder using an agate-mortar, extracted with 50 mL of 7.4 pH buffer solution and sonicated for 30 min (UP 400s, Dr.Hielscher, GmBH, Germany). The solution was centrifuged (Jouan, MR23i, France) to remove polymeric debris and washed twice to extract the drug completely. The clear solution was then analyzed by UV spectrophotometer (Secomam, Anthelie, France) at the fixed λ_{max} of 273 nm. The % encapsulation efficiency was calculated as:

$$\% \text{ Encapsulation efficiency} = \left(\frac{\text{Actual drug loading}}{\text{Theoretical drug loading}}\right) \times 100 \quad (1)$$

Theoretical drug loading is the percentage of amount of drug taken during the formulation. At least, three sample tests were done for studying the encapsulation efficiency of all the formulations. The percentage standard deviations were computed by the least squares analysis at 95% confidence limit. These data for various formulations are included in Table I.

Water uptake measurements

Water uptake of the microspheres was determined by measuring the extent of swelling of the microspheres in distilled water. To ensure complete equilibration, samples were allowed to swell for about 24 h in the selected media and excess surface-adhered liquid drops were removed by blotting with soft tissue paper wraps. The sorbed microspheres were weighed to an accuracy of ±0.01 mg using an electronic microbalance (Mettler, AT120, Greifensee, Switzerland). The microspheres were dried in an oven at 60°C for 5 h until no further change in weight gain of the dried samples was observed. The % water uptake was calculated using the following equation after attainment of equilibrium swelling as indicated by no more weight uptake of the microspheres:

$$\% \text{ Water uptake} = \left(\frac{\text{Weight of swollen microspheres} - \text{Weight of dry microspheres}}{\text{Weight of dry microspheres}}\right) \times 100 \quad (2)$$

Experiments were performed in triplicate, but the average data are considered for data analysis and graphic display. The percentage of water uptake data along with standard deviations are also included in Table I.

Tensile strength measurements

In actual practice, formulations are prepared as tableted microspheres, in which state, it is important to maintain their mechanical stability. For determining

TABLE II
Tensile Test Data of Various Formulations

Formulation codes[a]	ρ (g/cm^3)	E (MPa)	M_c (kg/mol)	$V_e \times 10^5$ (mol/cm^3)
F1	1.0019	0.121 ± 0.008	61.60 ± 3.35	1.63 ± 0.11
F2	1.0019	0.134 ± 0.006	55.41 ± 2.74	1.81 ± 0.08
F3	1.0019	0.158 ± 0.004	47.25 ± 1.09	2.12 ± 0.05
F4	1.0019	0.173 ± 0.004	43.17 ± 0.90	2.32 ± 0.05
F7	1.0022	0.183 ± 0.004	40.64 ± 0.92	2.47 ± 0.06
F8	1.0024	0.200 ± 0.008	37.25 ± 1.43	2.69 ± 0.11
F9	1.0025	0.219 ± 0.009	34.04 ± 1.60	2.94 ± 0.13

[a] As per details given in Table I.

the strength of the formulated microspheres, its powder form is not possible for the measurement and hence, films of the polymers were prepared by the solution casting method on a clean glass plate. The formed films were peeled off from the glass plate and crosslinked with GA. The crosslinking time (i.e., 3 h) was kept the same as used during microsphere preparation; this presumably would not change the release kinetics data.[20,23] Films were dried at ambient temperature (25°C) and used for mechanical testing.

Test specimens were prepared by cutting the membranes to 10 mm width and 100 mm length using a fine razor cutter. Testing was done using Hounsfield Universal Testing Machine, UTM (Model H25KS, Surrey, UK). In the actual measurement, two ends of the specimen were placed between the upper and lower jaws of the instrument, leaving a length of 50 mm of the film in between the two jaws. Extension speed of the instrument was maintained at 10 mm/min. The film thicknesses as measured by the micrometer screw gage were around 0.2 ± 0.02 mm.

Young's modulus of PVA and HEC films were measured to estimate the average molar mass (M_c) between network crosslinks and the effective crosslink density (V_e). For the measurement of Young's modulus, films were prepared from aqueous solutions of PVA and HEC as per the compositions (without drug) given in Table II. In all cases, triplicate data were collected, but only the average values with standard deviations are included in Table II.

In vitro release experiments

Microspheres equivalent to daily dosage of THP (100 mg) were used in release experiments. Drug release from the semi-IPN microspheres at different percentage drug loading, polymer blend compositions and different extent of crosslinking were investigated in 0.1 *N* HCl initially for 2 h, followed by phosphate buffer solution at pH 7.4, until completion of the dissolution process. These experiments were performed using a tablet dissolution tester (LabIndia, Mumbai, India) equipped with eight baskets (glass jars) at the stirring speed of 100 rpm. Weighed quantity of each sample was placed in 500 mL of dissolution medium maintained at the body temperature of 37°C. At regular intervals of time, 5 mL of sample aliquots were withdrawn and analyzed by UV spectrophotometer (Secomam, Anthelie, France) at the fixed λ_{max} of 273 nm. The utilized solvent media was replenished by adding 5 mL of fresh solvent. Triplicate data were collected, but the curves are drawn through the average points, giving the standard deviations around 3% in all the formulations.

Drug release kinetics

To describe the kinetics of drug release from the formulations, various empirical equations are used.[24] Applicability of all the equations was tested for all the drug-loaded formulations. The respective equations are given below:

Zero order equation

$$Q = Q_0 - K_0 t \tag{3}$$

where Q is the amount of drug remaining at time, t, Q_0 is the amount of drug remaining at $t = 0$ and K_0 is zero order release constant.

First order equation.

$$\ln\ Q = \ln\ Q_0 - K_1 t \tag{4}$$

where K_1 is first order release constant

Higuchi square root equation.

$$M_t = K_H t^{1/2} \tag{5}$$

where M_t is the amount of drug released at time t and K_H is Higuchi rate constant.

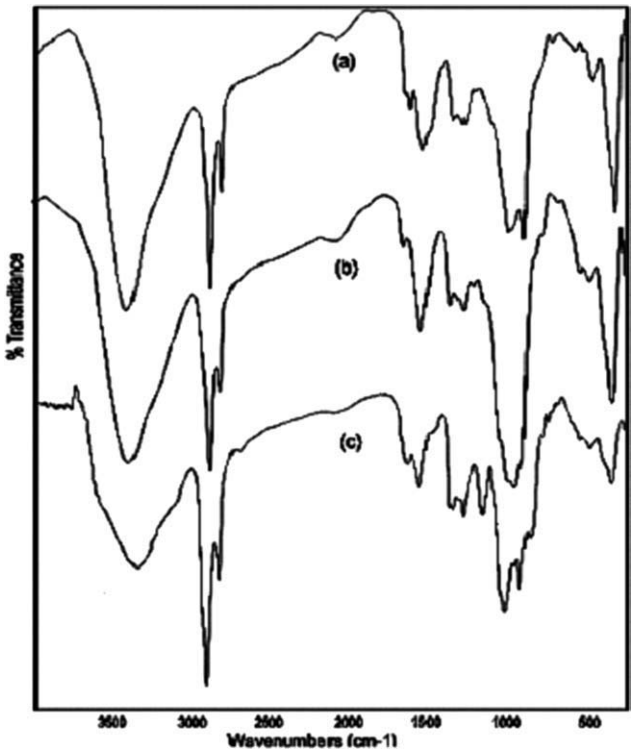

Figure 2 FTIR spectra of (a) plain PVA, (b) plain HEC and (c) placebo microspheres.

Hixson-Crowell cube root equation:

$$Q^{1/3} = Q_0{}^{1/3} - K_c t \quad (6)$$

where K_c is cube root law release constant. All these equations were tested using the release data. A similar approach was used before.[25]

RESULTS AND DISCUSSION

Fourier transform infrared spectra

FTIR spectra of the plain PVA, plain HEC, placebo semi-IPN microspheres, drug-loaded microspheres and plain THP were all taken to investigate the stability of THP after encapsulation. Figure 2 displays the FTIR spectra of (a) plain PVA, (b) plain HEC, and (c) placebo microspheres. In case of plain PVA, a broad band observed at 3432 cm^{-1} is attributed to O—H bond stretching vibrations. Two bands observed at 2924 and 2854 cm^{-1} represent the presence of C—H aliphatic stretching vibrations. HEC has a characteristic band at 3419 cm^{-1} because of O—H stretching vibrations, whereas the bands at 2923 and 2858 cm^{-1} are attributed to C—H aliphatic stretching vibrations. In case of placebo microspheres, all the characteristic bands of both PVA and HEC are observed in addition to a new band at 1112 cm^{-1}, because of the presence of acetal group formed from the reaction of GA with hydroxyl group of PVA. The decrease in the intensity of the OH peak in the placebo microspheres because of the reaction of hydroxyl groups of PVA with GA also confirm successful crosslinking of PVA chains by GA.

FTIR spectra were used to confirm the chemical stability of THP in the semi-IPN microspheres as displayed in Figure 3 for (a) placebo microspheres, (b) drug-loaded microspheres (F2) and (c) plain THP. In case of THP, a broad band at 3434 cm^{-1} is because of N—H stretching vibrations. Bands at 3122, 3060, 2985, 2916 and 2826 cm^{-1} are attributed to both aromatic and aliphatic C—H stretching vibrations. Band at 1715 cm^{-1} is characteristic of the imide stretching of heterocyclic moiety[13] of THP (see Fig. 4). A sharp band at 1670 cm^{-1} is because of tertiary amide group stretching vibrations. The N—H bending vibration is shown at 1567 cm^{-1}, while the band at 1242 cm^{-1} is because of C—N stretching vibrations. Spectra of drug loaded are not characteristically different from the spectra of placebo microspheres. The peaks appearing at 1712, 1665, 1567, and 1246 cm^{-1} for THP have also appeared in drug loaded microspheres, indicating the chemical stability of THP even after encapsulation; this suggests no chemical interactions between THP and the semi-IPN matrix.

X-ray diffraction (XRD)

X-ray diffractograms of (a) placebo microspheres, (b) drug-loaded microspheres and (c) plain THP are

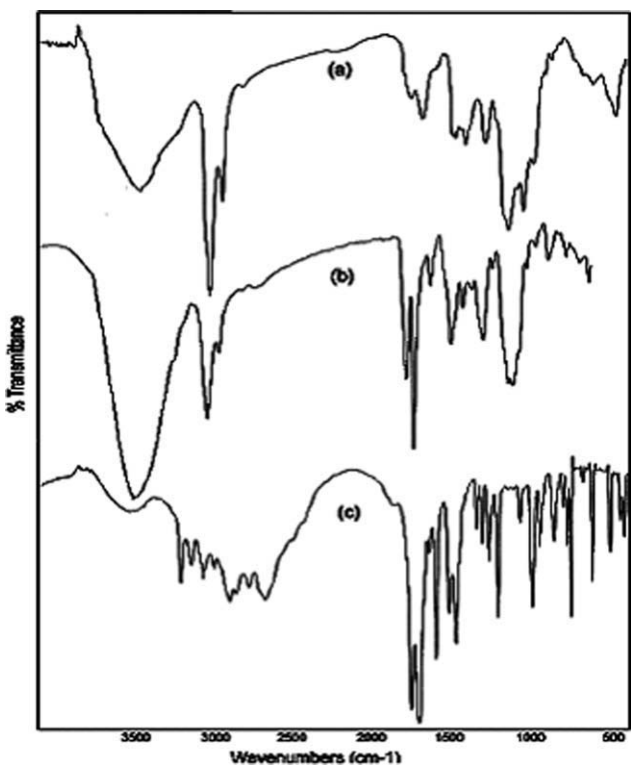

Figure 3 FTIR spectra of (a) placebo microspheres, (b) drug-loaded microspheres (F2), and (c) plain THP.

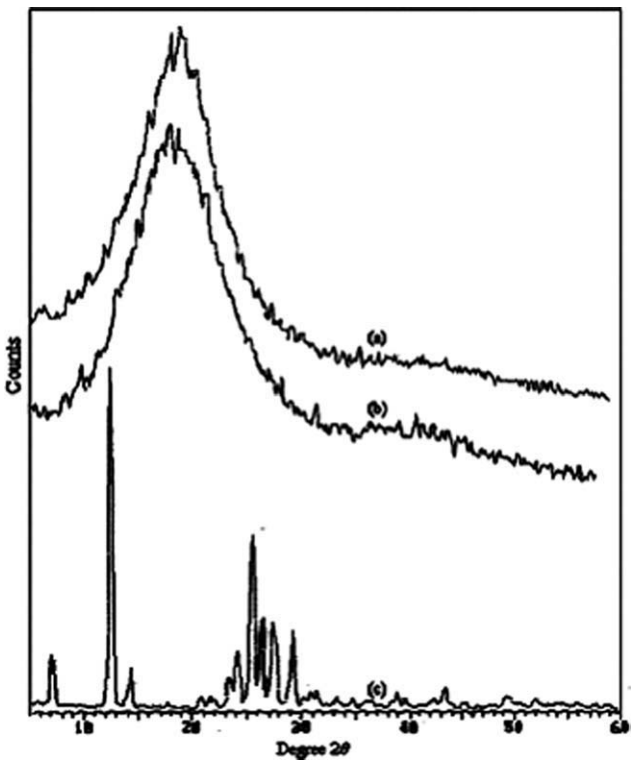

Figure 4 XRD spectra of (a) placebo microspheres, (b) drug-loaded microspheres, and (c) plain THP.

presented in Figure 4. Diffraction pattern of THP has characteristic intense peaks at 2θ of 12.4° that is identical to stable anhydrous theophylline crystal. This peak has disappeared in the THP–loaded microspheres, but only peaks observed in placebo matrix were seen. The XRD peak depends on the crystal size, but in this study, for all the drug–loaded matrices, characteristic peak of THP has overlapped with the noise of the polymer. Further, even after encapsulation, THP is in an amorphous form and hence, it is difficult to study its crystallinity at the detection limit of the crystal size. This indicates that THP is dispersed molecularly in the polymer matrix and hence, no crystals were found in the drug-loaded matrices.

Scanning electron microscopic (SEM)

SEM images of the microspheres taken at 1,000×, 1,500× and 3,000× and 2,000× magnifications are shown in Figs. 5(a), (b), (c) and (d), respectively for group of placebo microspheres, drug-loaded microspheres and some individual placebo microspheres as well as individual drug-loaded microspheres. For drug-loaded microspheres, the formulation F2 i.e., 90% PVA + 10% HEC with 4 mL GA (as per the Table I), we observe more dents compared with placebo microspheres. Microspheres are all spherical in nature with smooth surfaces. The sizes of the individual microspheres are around 10–15 μm. However, the polymeric debris seen around some of the microspheres are probably due to the method of particle production (i.e., simultaneous particle production and formation of semi-IPN blend matrix).

Encapsulation efficiency

To develop successful formulations containing THP in polymeric matrices, it is important to achieve high encapsulation efficiency (EE). As reported before,[12] the EE values are dependent on process variables like drug-polymer ratio, blend composition and extent of crosslinking. Results presented in Table I clearly display the dependence of EE values on these parameters. For instance, in case of F5, F2, and F6 formulations containing 90 wt % of PVA, 10 wt % of HEC, and 4 mL of GA, the EE values increased systematically from 62, 65, to 69% with increasing THP loadings. For decreasing blend compositions of 80 to 60 wt % PVA, keeping THP loading (25 wt %) and amount of GA (4 mL) as constants, the EE values decrease from 65 to 61% because of varying crosslinking (rather cross-link density) of the semi-IPN matrix. On the contrary, for the blend of 90 wt % PVA (i.e., F1, F2, F3 and F4) with a constant THP loading of 25 wt % and varying amounts of GA from 2 to 8 mL, we observed a systematic increase of EE values from 63 to 69%, because of increased rigidity of the network, thereby reducing the leaching of THP out of the polymer matrix. It is thus evident that EE values are affected greatly by process variables as reported before.[26]

Water uptake

Drug release rates are influenced by the extent of water uptake of the liquid due to swelling of the crosslinked microspheres.[23,26] The percentage of uptake data of the completely swollen (at the attainment of equilibrium sorption) crosslinked microspheres presented in Table I indicate that, as the amount of GA in the matrix is increased from 2 to 8 mL, the % equilibrium uptake decreased significantly from 312 to 260 because of the formation of a more rigid semi-IPN matrix at higher crosslink density (i.e., at higher amount of GA in the matrix). Notice that formulations containing the highest amount of HEC exhibited higher equilibrium uptake (higher swelling) i.e., formulation F9 (40 wt % of HEC) exhibited higher equilibrium uptake than F8 (30 wt % of HEC), F7 (20 wt % of HEC) and F2 (10 wt % of HEC) because of increased hydrophylicity induced by the presence of HEC, which facilitates higher absorption of water compared with PVA.

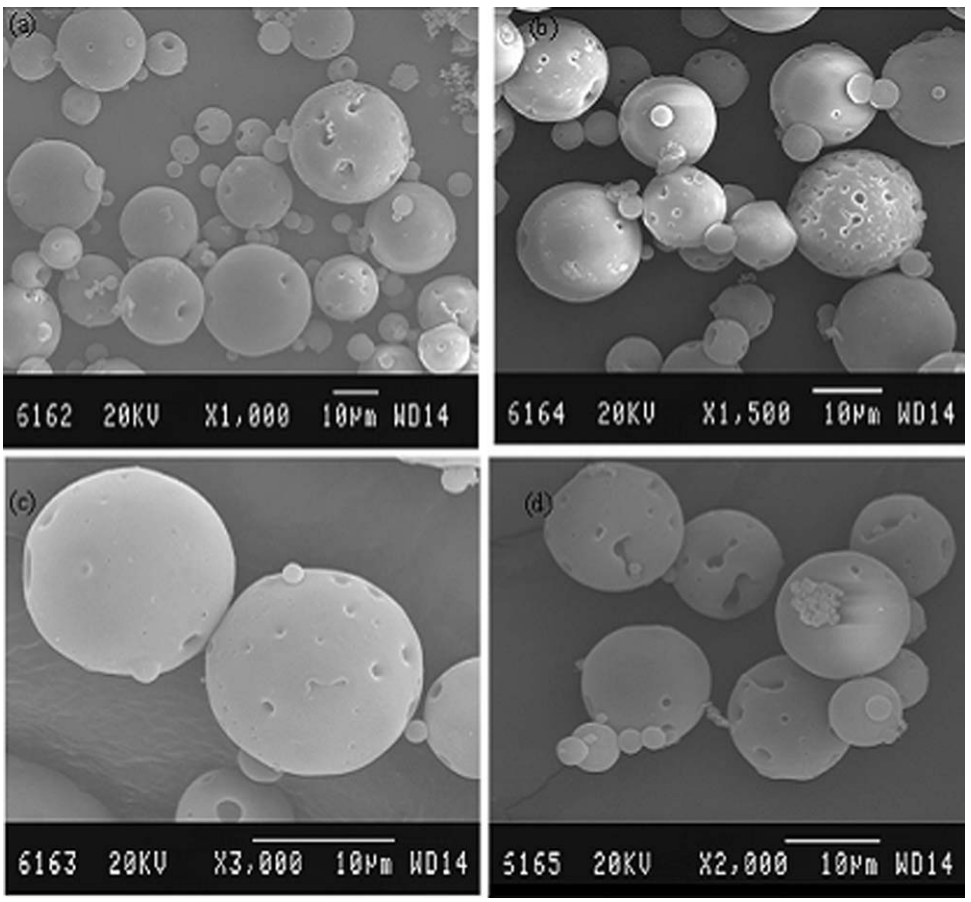

Figure 5 Scanning electron micrograph of (a) group of placebo microspheres, (b) group of drug-loaded microspheres, (c) individual placebo microspheres and (d) individual drug-loaded microspheres.

Molar mass between cross-links and effective crosslink density

Young's modulus of the crosslinked PVA and HEC films was measured to estimate the average values of molar mass (M_c) between crosslinks and the effective crosslink density (V_e) of the semi-IPN network. The M_c value was determined using eq. (7) derived from rubber elasticity theory.[27,28]

$$M_c = \frac{3\rho RT}{E} \tag{7}$$

where ρ is specific density (g/cm^3), which is measured using a density meter (Anton Peer, Austria), R is universal gas constant, T is absolute temperature and E is Young's modulus. The value of V_e was calculated as:[27,29]

$$V_e = \frac{\rho}{E} \tag{8}$$

The results of Young's modulus, M_c and V_e estimated for PVA and HEC films are compiled in Table II. Since the E values are greatly affected by the water content of the tested films, the samples were conditioned at 37°C in an incubator before these tests were done. The M_c values decrease with increasing GA content of the formulation, since the network becomes denser. Also, M_c values decrease with increasing HEC content of the formulation, further indicating a dense network structure. Similarly, GA and HEC contents of the formulations have significantly affected the M_c and V_e values of the semi-IPNs. Thus, one can establish a correlation of these data with percentage of uptake data. Moreover, such data are meaningful in predicting the fate of drug-loaded microspheres in the bio-environment.

In vitro release and drug diffusion parameter

In vitro release of THP from semi-IPN microspheres of PVA and HEC was investigated in gastric (pH 1.2) and intestinal (pH 7.2) conditions to understand its release in stomach as well as intestine. Each experiment was conducted in triplicate and the plotted data are the averages of the corresponding determinations at each time point. The percentage of cumulative release vs. time plots for drug-loaded microspheres in case of formulations F1, F2, F3 and F4 are compared in Figure 6 to understand the

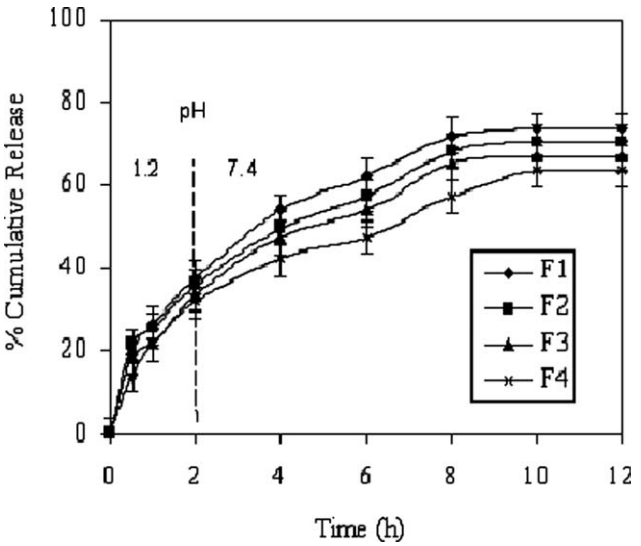

Figure 6 Effect of crosslinking on the *in vitro* release for formulations F1 (2 mL), F2 (4 mL), F3 (6 mL) and F4 (8 mL) at 37°C.

extent of crosslinking on *in vitro* release profiles. The release curves clearly indicate a dependence on the extent of crosslinking. For instance, formulation F3 exhibited higher release than F4 and similarly, F2 exhibited higher release than either F3 or F4, and in the same way, F1 exhibited higher release than F2, F3, or F4. Notice that F4 contains higher amount of GA (8 mL) compared with F1, F2 and F3, thus making it more rigid compared with F1, F2 and F3. This has resulted in a decreased percentage of cumulative release of THP. In fact, F1 i.e., the matrix containing smaller amount of GA (2 mL) exhibited higher release rates. In all cases (F1, F2, F3 and F4), the release trends follow identical patterns and the release of THP occurred up to 12 h.

Figure 7 displays the effect of polymer blend composition on the release rates as per formulations F2, F7, F8, and F9. The percentage of cumulative release is higher for of F9 than F8, which is because of an increase in hydrophilicity of the semi-IPN with increasing HEC content. There is thus a clear-cut dependence on blend composition of the formulation. Similarly, F8 showed higher release than F7 and F2. In all cases, complete release of THP occurred in 12 h. However, slower or delayed release rates with more hydrophilic microspheres resulted in a delayed penetration of drug-containing aqueous solution through the matrix. It is thus, obvious that diffusion path in the matrix might be filled with water molecules to facilitate more of drug diffusion. SEM pictures shown in Figure 5 also confirm this effect.

The effect of percentage drug loading on *in vitro* release for formulations F5, F2, and F6 are displayed in Figure 8, wherein formulation F6 has a higher release than F2. Similarly, F2 has a higher release than F5, which clearly indicates the dependence of THP release on the amount of drug loaded in the matrix, i.e., release is higher for those formulations having higher amount of drug and vice versa. Notice that during the first two hours of drug release, dissolution was performed in 0.1 *N* HCl, wherein the burst release was observed for all formulations and the release was extended up to 12 h. Thus, it is important to simultaneously adjust appropriately the process parameters to develop a formulation giving optimal release profiles. In all, nearly 75% of THP was released from the developed formulations.

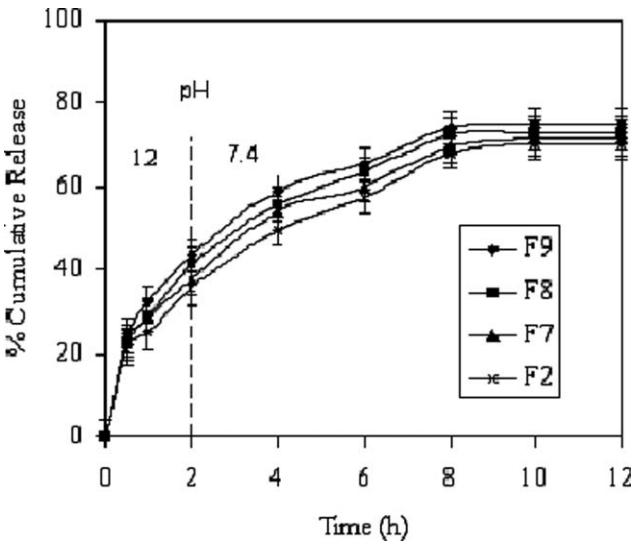

Figure 7 Effect of polymer blend ratio on *in vitro* release for formulations F2 (10 wt % HEC), F7 (20 wt % HEC), F8 (30 wt % HEC), and F9 (40 wt % HEC) at 37°C.

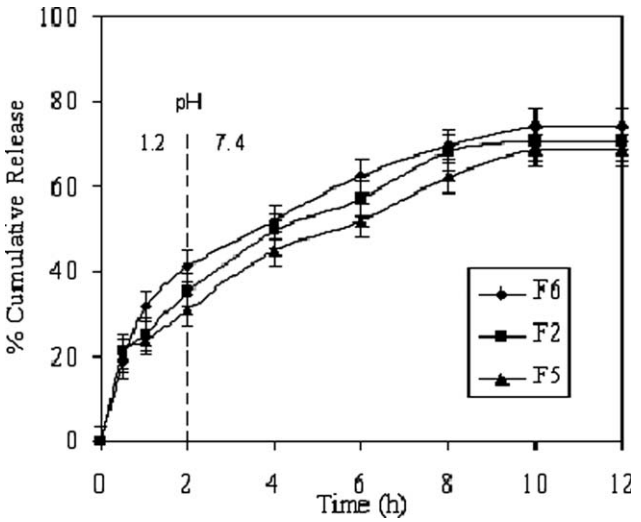

Figure 8 Effect of percent of drug loading on *in vitro* release of formulations F5 (10 wt %), F2 (25 wt %), and F6 (40 wt %).

TABLE III
Dissolution Rate Constants and Correlation Coefficient (*r*) Values of All the Formulations for Different Equations

Formulation codes[a]	Zero order rate constant (eq. 3)	First order rate constant (eq. 4)	Higuchi square root rate constant (eq. 5)	Hixson-Crowell rate constant (eq. 6)
F1	0.5337, $r = 0.9541$	0.0504, $r = 0.9658$	2.2361, $r = 0.9918$	0.0672, $r = 0.9458$
F2	0.5778, $r = 0.9279$	0.0568, $r = 0.9642$	2.4091, $r = 0.9904$	0.0743, $r = 0.9426$
F3	0.5308, $r = 0.946$	0.0467, $r = 0.9648$	2.1737, $r = 0.9927$	0.0634, $r = 0.9473$
F4	0.5153, $r = 0.9417$	0.0517, $r = 0.9529$	2.2549, $r = 0.9841$	0.0681, $r = 0.9276$
F5	0.5372, $r = 0.9155$	0.0551, $r = 0.9457$	2.3472, $r = 0.9811$	0.0789, $r = 0.9559$
F6	0.5131, $r = 0.9825$	0.0459, $r = 0.9769$	2.103, $r = 0.9941$	0.0621, $r = 0.9613$
F7	0.5419, $r = 0.9273$	0.0551, $r = 0.9628$	2.337, $r = 0.9845$	0.0719, $r = 0.9355$
F8	0.4909, $r = 0.9542$	0.04, $r = 0.9691$	1.9874, $r = 0.9954$	0.0557, $r = 0.9528$
F9	0.5296, $r = 0.9074$	0.0576, $r = 0.9386$	2.3796, $r = 0.9738$	0.0741, $r = 0.9028$

[a] As per details given in Table I.

Drug release is controlled by the diffusion phenomenon as per Fick's second law of diffusion.[30] This equation can be simplified to give a solution where diffusional resistance within the polymer matrix is predominant. Thus, apparent diffusion coefficient, D of the drug can be computed using:

$$D = \pi\left(\frac{r\theta}{6M\infty}\right) \quad (9)$$

where Θ is the slope of linear portion of the plot of M_t/M_∞ vs $t^{1/2}$, r is the radius of spherical particles and M_∞ is the maximum value of drug release. Diffusion coefficients are given in Table IV, which range from 1.78×10^{-5} to 14.52×10^{-5} cm^2/s and these values are dependent on the extent of crosslinking. For instance, D values decrease with increasing crosslinking of the matrix. This is obvious because of the increased rigidity of the chain due to increased crosslinking, thereby prohibiting the transport of more drug solution. It is also noticed that D values increased with increasing HEC content of the semi-IPN matrix. This could be due to the hydrophilic nature of HEC, thereby leading to higher matrix swelling.

Empirical analysis of cumulative release

Cumulative release data were analyzed by an empirical equation[30] of the type:

$$M_t/M_\infty = kt^n \quad (10)$$

Here, M_t/M_∞ represents fractional drug release at time t, k is a kinetic parameter characteristic of the drug-polymer system and n is an empirical parameter, characterizing the release mechanism. Using the regression analysis, we have estimated the values of n and k for all formulations at 95% confidence limit; these data along with the estimated correlation coefficients (r) are also included in Table IV. For the values of $n = 0.5$, drug diffuses and releases out of the polymer matrix following a Fickian diffusion. If $n > 0.5$, then anomalous or non-Fickian transport is operative. If $n = 1$, non-Fickian or more commonly called Case II transport occurs. If the values of n vary between 0.5 and 1.0, then transport is classified to be anomalous type.[22]

In this study, the values of n and k are dependent on the extent of crosslinking and % loading of THP. The plot of k values vs percent of THP loading shown in Figure 9 indicates that k increases with increasing loading of THP, but decreases with increasing crosslinking of PVA/HEC semi-IPN matrix, suggesting varying interactions. The n values for microspheres crosslinked with 2 mL of GA are smaller than those prepared with 4, 6, and 8 mL of GA because of the formation of loosely crosslinked network, which gave somewhat higher % uptake. Thus, the values of n are higher for microspheres that are crosslinked with 8 mL of GA because of the formation of a rigid semi-IPN matrix and vice-versa. In this study, the n values ranged from 0.32 to 0.42,

TABLE IV
Results of Empirical Parameters *n*, *k*, Correlation Coefficient (r^2) and Diffusion coefficients (*D*)

Formulation codes[a]	n (eq. 10)	k (eq. 10)	r^2	$D \times 10^5$ (cm^2/s) (eq. 9)
F1	0.346	0.411	0.926	5.41
F2	0.361	0.390	0.936	2.36
F3	0.394	0.370	0.931	2.11
F4	0.415	0.345	0.938	1.94
F5	0.366	0.379	0.950	1.78
F6	0.359	0.401	0.919	2.85
F7	0.333	0.430	0.936	2.58
F8	0.327	0.445	0.923	8.67
F9	0.323	0.452	0.922	14.52

[a] As per details given in Table I.

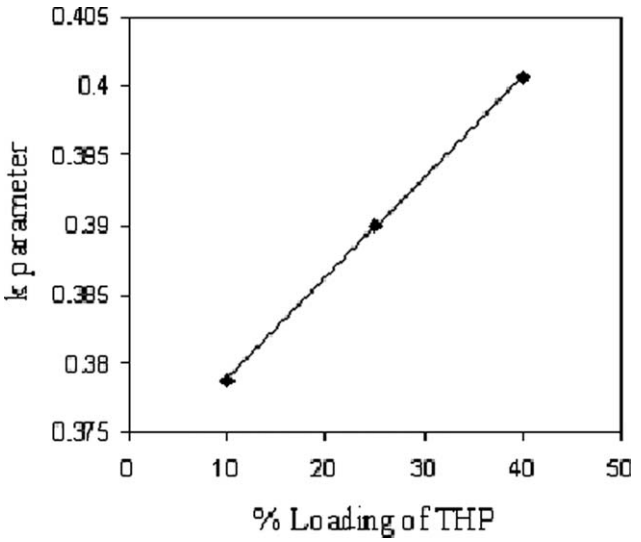

Figure 9 Effect of % loading of THP on *k* parameter calculated from Eq. (10).

indicating that THP release from the microspheres deviates somewhat from the Fickian trends.

Dissolution profiles of all the formulations have been fitted to eqs. (3)–(6). It was found that the fit was better with Higuchi kinetic model, suggesting that the release kinetics follows more of the Higuchi square root equation than the other equations. This also proves that the release is diffusion-controlled. However, additional insight into the release mechanism was obtained by fitting the dissolution data into Hixson-Crowell cubic root equation. Results of release kinetics for all the models are displayed in Table III.

CONCLUSIONS

This work is a continuation of our earlier research efforts on the development of semi-IPN microspheres to achieve higher encapsulation efficiency and better controlled release of theophylline using PVA and HEC polymers. The sizes of microparticles obtained by water-in-oil emulsion method are in the range 10–15 μm with percent of encapsulation efficiency of 69%. The release of water-soluble drug like theophylline was described by the diffusion and kinetics models. It was found that the kinetics of drug release followed Higuchi square root equation, indicating the release as diffusion-controlled. The crosslink density was significantly affected by the amount of GA and the HEC content of the drug-loaded formulations. FTIR confirmed the formation of semi-IPN as well as chemical stability of THP in the microspheres. In all formulations, the release was extended up to 12 h. The initial release data were analyzed using an empirical equation, which indicated a slight deviation from the Fickian transport. The percentage of swelling data are well correlated with the crosslink density data computed from the Young's modulus results.

References

1. Martinez, M.; Rathbone, M.; Burgess, D.; Huynh, M. J Control Release 2008, 129, 79.
2. Soppimath, K. S.; Aminabhavi, T. M.; Rudzinski, W. E. J Control Release 2001, 70, 1.
3. Soppimath, K. S.; Kulkarni, A. R.; Aminabhavi, T. M.; Rudzinski, W. E. Drug Metab Revs 2001, 33, 149.
4. Agnihotri, S. A.; Mallikarjuna, N. N.; Aminabhavi, T. M. J Control Release 2004, 100, 5.
5. Hameed, N.; Guo, Q. Polymer 2008, 49, 5268.
6. Pitarresi, G.; Palumbo, F. S.; Albanese, A.; Licciardi, M.; Calascibetta, F.; Giammona, G. Eur Polym J 2008, 44, 3764.
7. Mundargi, R. C.; Patil, S. A.; Aminabhavi, T. M. Carbohyd Polym 2007, 69, 130.
8. Peppas, N. A. Hydrogel in Medicine and Pharmacy 2; CRC Press: Boca Raton, Florida, 1986.
9. Ferrero, R. C.; Bruneau, N.; Barra, J.; Alfonso, D.; Doelker, E. Handbook of Pharm Control Release Technology, Donald, L. W., Ed.; Marcel Dekker: New York, Basel, 2000; 1–30.
10. Fayazpour, F.; Lucas, B.; Alvarez-Lorenzo, C.; Sanders, N. N.; Demeester, J.; De Smedt, S. C. Biomacromolecules 2006, 7, 2856.
11. Matsuo, M.; Arimori, K.; Nakamura, C.; Nakano, M. Int J Pharm 1996, 138, 225.
12. Sullad, A. G.; Manjeshwar, L. S.; Aminabhavi, T. M. J Appl Polym Sci 2010, 116, 1226.
13. Rokhade, A. P.; Shelke, N. B.; Patil, S. A.; Aminabhavi, T. M. Carbohyd Polym 2007, 69, 678.
14. Yu, Z.; Schwartz, J. B.; Sugita, E. T. Biopharm Drug Dispos 1996, 17, 259.
15. Antal, I.; Zelko, R.; Roczey, N.; Plachy, J.; Racz, I. Int J Pharm 1997, 155, 83.
16. Coviello, T.; Grassi, M.; Lapasin, R.; Marino, A.; Alhaique, F. Biomaterials 2003, 24, 2789.
17. Katime, I.; Novoa, R.; Zuluaga, F. Eur Polym J 2001, 37, 1465.
18. Miyazaki, S.; Kubo, W.; Attwood, D. J Control Release 2000, 67, 275.
19. Shaheen, S. M.; Yamaura, K. J Control Release 2002, 81, 367.
20. Rokhade, A. P.; Agnihotri, S. A.; Patil, S. A.; Mallikarjuna, N. N.; Kulkarni, P. V.; Aminabhavi, T. M. Carbohyd Polym 2006, 65, 243.
21. Zeiger, E.; Gollapudi, B.; Spencer, P. Mutat Research/Rev Mutat Res 2005, 589, 136.
22. Mundargi, R. C.; Shelke, N. B.; Rokhade, A. P.; Patil, S. A.; Aminabhavi, T. M. Carbohyd Polym 2008, 71, 42.
23. Rokhade, A. P.; Patil, S. A.; Aminabhavi, T. M. Carbohyd Polym 2007, 67, 605.
24. Maswadeh, H. M.; Semreen, M. H.; Abdulhalim, A. Acta Pol Pharm – Drug Res 2006, 63, 63.
25. Toti, U. S.; Aminabhavi, T. M. J Control Release 2004, 95, 567.
26. Agnihotri, S. A.; Aminabhavi, T. M. Drug Dev Ind pharm 2005, 31, 491.
27. Flory, P. J. Principles of polymer chemistry; Cornell University Press: New York, 1953; 266: 432.
28. Ward, I. M.; Hadley, D. W. An Introduction to Mechanical Properties of Solid Polymers; Wiley: Chichester, 1993.
29. Uzun, C.; Hassnisaber, M.; Sen, M. Nucl Instrumental Methods Phys Res B: Beam Interaction Mater At 2003, 208, 242.
30. Ritger, P. L.; Peppas, N. A. J Control Release 1987, 5, 37.