Synthesis, Characterization, and Evaluation of Copolymers Based on *N*-Isopropylacrylamide and 2-Ethoxyethyl Methacrylate for the Controlled Release of Felodipine

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ABSTRACT: The free-radical copolymerization of *N*-isopropylacrylamide (NIPAAm) with 2-ethoxyethyl methacrylate (EOEMA) was carried out with 2,2′-azobisisobutyronotrile as an initiator in 1,4-dioxane at 65°C. The resulting copolymer was characterized by Fourier transform infrared and ^{1}H-NMR techniques. The composition of copolymers prepared at low conversion was determined by elemental analysis. An extended Kelen–Tudos method was used to estimate the reactivity ratios. The distribution of the monomer sequence along the copolymer chain was calculated with a statistical method based on the obtained reactivity ratios. Felodipine-loaded microspheres were prepared by the solvent evaporation technique. The effect of NIPAAm with respect to EOEMA segments on the sustained release of felodipine from the microspheres was investigated. Scanning electron micrographs of the microspheres indicated the formation of spherical microparticles in the size range 15–53 μm, even after they were loaded with the drug. The *in vitro* release studies of felodipine from the NIPAAm/EOEMA microspheres performed in a pH 7.4 medium showed that the rate of drug release was enhanced by an increase in the amount of NIPAAm; the size of the microspheres also increased with increasing NIPAAm in the copolymer. © 2008 Wiley Periodicals, Inc. J Appl Polym Sci 110: 2211–2217, 2008

Key words: copolymerization; drug delivery systems; kinetics (polym.); radical polymerization; synthesis

INTRODUCTION

Poly(*N*-isopropylacrylamide) (PNIPAAm) and *N*-substituted polyacrylamides have been used for drug-delivery applications.[1] PNIPAAm has a lower critical solution temperature at 32°C in aqueous solutions[2] because of the hydrogen-bonding effect between water and amide groups of the polymer. The behavior of acrylamide-based copolymers in water can be modified.[3–6] In the case of PNIPAAm, modification has been carried out by the copolymerization of the hydrophilic or hydrophobic monomers, by the grafting of PNIPAAm with another polymer such as poly(ethylene oxide),[7–9] or by the use of surface-active compounds such as sodium dodecyl sulfate.[10,11] *N*-Alkyl methacrylate monomers have also been used in the design of drug-delivery systems. Apart from a capability to display temperature responses that are close to that of the human body, the solubilization of hydrophobic drugs is an additional desirable property because many pharmacologically active compounds used in drug-delivery systems are amphiphilic or hydrophobic molecules.[12] The synthesis of polymers containing hydrophobic monomers is an alternative method for obtaining amphiphilic systems that can effectively encapsulate hydrophobic substances. When polymeric carriers are designed, the hydrophobic–hydrophilic balance of the cargo system is important because it regulates the interactions with proteins, cells, and other biocomponents.[13,14] This type of balance determines the biodistribution and pharmacokinetic behavior of the carrier systems.

When the thermal properties of *N*-isopropylacrylamide (NIPAAm) based copolymers or their derivatives are used, their chemical composition (in this case, the distribution of the comonomer along the

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polymer chain) is the most critical factor. For practical reasons, a random distribution of the structural units of the polymer is often assumed. Furthermore, studies on the kinetics of polymerization of NIPAAm with various comonomers have been carried out earlier.[15–19] Janne and Heikki[20] reported the determination of the reactivity ratio of NIPAAm/glycidyl methacrylate (GMA) copolymer and found a higher reactivity in GMA compared to that in NIPAAm. The polymer showed a random distribution of monomers in the copolymer. The kinetics of copolymerization and the sequence distribution of monomers are also important factors in understanding the nature of the polymer.

In this study, we synthesized a copolymer of NIPAAm with 2-ethoxyethyl methacrylate (EOEMA; a hydrophobic monomer) with 1,4-dioxane solvent and 2,2′-azobisisobutyronotrile (AIBN) initiator at 65°C. The reactivity ratios of the obtained copolymer were estimated by an extended Kelen–Tudos (EK–T) method.[21] The obtained copolymers were used to study the controlled release of felodipine, a calcium channel blocker that finds extensive applications in the treatment of hypertension. Some of the symptoms of felodipine overdose include dizziness, weakness, chest pain, shortness of breath, fainting, an unusually fast or slow heartbeat, coma, slurred speech, and confusion. To avoid such overdosing, it is necessary to extend the release time of the drug. In this study, felodipine-loaded microspheres were prepared by the solvent evaporation technique to extend the drug's release time. The formation of spherical microspheres was confirmed by scanning electron microscopy (SEM). The effect of NIPAAm with respect to EOEMA segments on the release of felodipine from the NIPAAm/EOEMA copolymer microspheres was studied *in vitro* in a pH 7.4 medium that replicated the human body system.

EXPERIMENTAL

NIPAAm, EOEMA, and AIBN were obtained from Aldrich Chemicals (Milwaukee, WI). Before use, the NIPAAm monomer was purified by recrystallization from hexane, and EOEMA was washed with dilute alkali and then distilled water, dried over anhydrous sodium sulfate, and stored below 0°C. AIBN was recrystallized from methanol and kept in a desiccator. Other solvents of 99% purity obtained from Merck Chemicals (Mumbai, India) were used as received. Felodipine was purchased from Loba Chemicals (Mumbai, India).

Synthesis of the copolymers

The copolymer (50 : 50 EOEMA/NIPAAm) was prepared by free-radical solution polymerization. AIBN (50 mg) was added to the mixture of NIPAAm (1.13 g, 10.0 mmol) and EOEMA (1.46 mL, 10.0 mmol) in the 1,4-dioxane solvent (5 mL). Copolymerization proceeded at a low conversion rate (<15%) under a nitrogen atmosphere. After polymerization, the mixture was cooled to the ambient temperature (30°C), and the polymer was precipitated by the addition of hexane. Finally, the polymer was purified through two cycles of reprecipitation from hexane and kept under reduced pressure in a desiccator.

Copolymer characterization

The copolymers were characterized with ^{1}H-NMR spectroscopy in deuterated chloroform as the solvent with a Bruker AV-300 spectrometer (University Science Instrumentation Centre, Karnatak University, Dharwad, India). Fourier transform infrared (FTIR) spectra were recorded as KBr pellets with a Shimadzu-1800S spectrometer in the range 400–4000 cm^{-1}.

Gel permeation chromatography (GPC)

Molecular weights of the synthesized copolymers were determined with a gel permeation chromatograph (Viscotek, Houston, TX) attached to a differential refractive-index detector (Viscotek, VE 3580) with two columns (Viscotek gel, GMHH R-H). The flow rate of the mobile phase, tetrahydrofuran, was set at 1 mL/min; polystyrene standards were used for calibration runs. Subsequently, the molecular weights of the copolymers were reported as the polystyrene-equivalent molecular weights.

Copolymer composition

The NIPAAm/EOEMA copolymer composition was determined by elemental analysis by the percentage of nitrogen obtained in the copolymer (results presented in Table I), which indirectly gave the amount of NIPAAm present in the copolymer.

Preparation of the microspheres

The microspheres were prepared by an emulsion solvent evaporation technique. Weighed amounts of copolymer (0.5 g) and felodipine (0.05 g) were dissolved in dichloromethane (DCM; 5 mL) and added to a 2.5% poly(vinyl alcohol) (PVA) solution under constant stirring with a Eurostar overhead stirrer (IKA Labor Technik, Germany) at a speed of 800 rpm at 30°C. The solution was stirred until DCM was completely evaporated. The microspheres were then separated with a centrifuge (Jouan, MR 23i, France). The obtained microspheres were washed three to four times to remove the PVA particles adhered to the surface of the microspheres. The microspheres were then placed in a small amount of water and

TABLE I
Reaction Conditions for the Preparation of the NIPAAm/EOEMA Copolymers

Sample code	M_1	Conversion (%)	N (%) by elemental analysis	m_1
EN-20	0.20	12.9	8.900	0.2810
EN-35	0.35	12.5	6.311	0.4892
EN-50	0.50	13.0	5.075	0.6165
EN-70	0.70	12.8	4.481	0.8033
EN-90	0.90	13.5	4.052	0.8906

The solvent was 1,4-dioxane. The temperature was 65°C, and the initiator was AIBN (0.05% on the basis of the total weight of the monomers and solvent). The monomer/solvent ratio was 1 : 3 (w/v).

lyophilized by a freeze-drier (Jouan, LP3) to obtain the dry particles.

SEM

SEM images of the microspheres were recorded at the required magnification to confirm the size and the surface morphology of the microspheres. A thin film of 10-nm gold coating was placed before the samples were subjected to SEM, which was recorded with a Leica 400 (Cambridge, UK) instrument available at the National Chemical Laboratory, Pune, India.

Particle size analysis

Particle size was measured by the laser light-scattering technique (Mastersizer 2000, Malvern, UK). The sizes of the completely dried microspheres of different formulations were measured with a dry sample adapter. The volume mean diameter was recorded.

Drug loading efficiency

Microspheres obtained by the freeze-drying method were dissolved in DCM, and the amount of felodipine encapsulated was determined by a UV spectrophotometer (Secomam, Anthelie, France) at a λ_{max} value of 263 nm. These data were collected in triplicate, but average values were used to calculate the percentage drug loading and encapsulation efficiency. The felodipine content entrapped into the microspheres was calculated from the weight of the initial drug-loaded microspheres and the amount of drug incorporated with the following equations:

$$\text{Drug loading (\%)} = \left(\frac{\text{Weight of drug in microspheres}}{\text{Weight of microspheres}}\right) \times 100 \quad (1)$$

$$\text{Encapsulation efficiency (\%)} = \left(\frac{\text{Actual drug loading}}{\text{Theoretical drug loading}}\right) \times 100 \quad (2)$$

where the theoretical drug loading refers to the amount of drug taken for loading.

In vitro drug release

The dissolution experiments were carried out in a dissolution tester provided with six paddle baskets (labIndia, Mumbai, India). Weighed amounts of felodipine-loaded microspheres (10 mg) were suspended in 100 mL of phosphate buffer at pH 7.4 and 0.1% (w/v) polysorbate 80 surfactant. The dissolution medium was stirred at a speed of 100 rpm at 37°C. Aliquots of the dissolution medium (3 mL) were withdrawn and filtered through 0.45-mm Millipore filters at predetermined time intervals. After appropriate dilution, the drug concentrations were analyzed by a UV spectrophotometer (Secomam) at a λ_{max} value of 263 nm. The dissolution medium was maintained at a constant volume by the replacement of the samples with fresh dissolution medium.

RESULTS AND DISCUSSION

Copolymer characterization

NIPAAm/EOEMA copolymers having different compositions were prepared as per the experimental details given in Table I. AIBN was used as the initiator in 1,4-dioxane solvent under an inert nitrogen atmosphere.

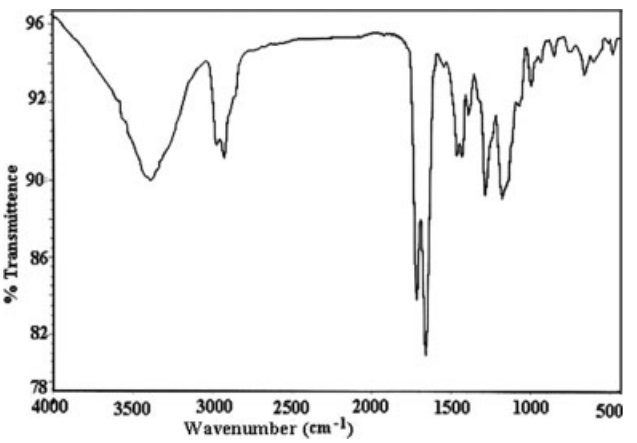

Figure 1 FTIR spectra of the NIPAAm/EOEMA copolymer.

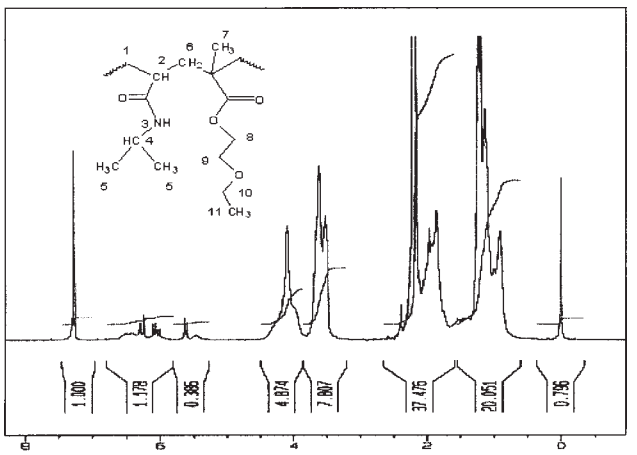

Figure 2 ^{1}H-NMR spectra of the NIPAAm/EOEMA copolymer.

FTIR spectra

The FTIR spectrum of the copolymer is shown in Figure 1. The strong absorption peak observed at 1741 cm^{-1} and the peak around 1225–1220 cm^{-1} were due to —C=O and ether C—O—C stretching vibrations in the EOEMA unit. The peaks at 3300 and 1550 cm^{-1} were due to the stretching and bending vibrations of the —NH moiety in NIPAAm. The strong absorption band at 1640 cm^{-1} was due to the >C=O peak of the NIPAAm unit.

NMR

The ^{1}H-NMR spectrum of the copolymer shown in Figure 2 confirmed the formation of the copolymers. The peaks at δ = 4.1 and 7.2 ppm were assigned to protons in the isopropyl (^{4}CH) and amide (—CONH—) groups, respectively. The main-chain methylene proton signals of both the NIPAAm and EOEMA units resonated between δ values of 2.15 and 0.90 ppm; these overlapped with different type of compositional and configurational sequences. Similarly, the methyl ($^{7}CH_3$ and $^{11}CH_3$) protons of the EOEMA signals around δ = 0.85–1.35 ppm overlapped with each other. The signals for the three —OCH_2 methylene ($^{8}CH_2$, $^{9}CH_2$, $^{10}CH_2$) protons of EOEMA appeared at δ = 3.4–3.7 ppm.

GPC

From the GPC data, we observed that the molecular weights of the prepared polymers increased with increasing amount of EOEMA with respect to NIPAAm. The weight-average and number-average molecular weights were 38,440 and 26,080, respectively. The calculated polydispersity index was 1.47, which suggested a somewhat broader molecular weight distribution.

Monomer reactivity ratio

The percentage composition of monomers incorporated was determined by the measurement of the percentage nitrogen in the synthesized copolymers with elemental analysis data. A plot of the molar fraction of EOEMA in the feed (M_1) versus the molar fraction of EOEMA in the copolymer (m_1) is shown in Figure 3(a). The copolymerization reactivity ratios of NIPAAm and EOEMA were determined with the data given in Table II by the EK–T methods as follows.

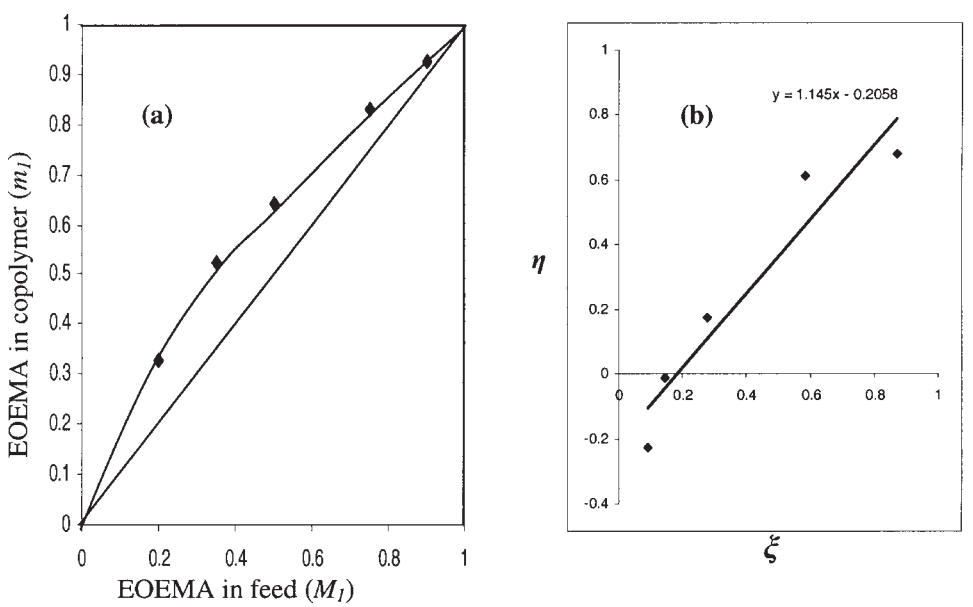

Figure 3 Elemental analysis data of the (a) plot of M_1 versus m_1 and (b) EK–T plot of η versus ξ.

TABLE II
EK–T Parameters for EOEMA and NIPAm as Determined by the Elemental Analysis Data

Sample code	ξ_{NIPAAm}	ξ_{EOEMA}	Z	G	F	ξ	η
EN-20	0.1126	0.1759	1.6191	−0.3762	0.1490	0.0897	−0.2265
EN-35	0.0937	0.1727	1.9261	0.0224	0.2579	0.1457	−0.0126
EN-50	0.0887	0.1424	1.6541	0.3653	0.5863	0.2795	0.1741
EN-70	0.0914	0.1242	1.3837	2.2230	2.1289	0.5848	0.6106
EN-90	0.0116	0.1051	0.8931	7.9398	10.143	0.8703	0.6812

$\alpha = (F_{min} \times F_{max})^{1/2} = 1.5114$.

The partial molar conversion of NIPAAm (ξ_{NIPAM}) is given as follows:

$$\xi_{NIPAM} = \frac{W(\mu + x)}{(\mu + y)} \quad (3)$$

where W is the weight conversion of polymerization, μ is the ratio of the molecular weight of NIPAAm to that of EOEMA and, $x = M_1/M_2$, $y - m_1/m_2$ where M_1, M_2 and m_1, m_2 are mole fractions of EOEMA and NIPAAm in the feed and in the copolymer, respectively. The partial molar conversion of EOEMA (ξ_{EOEMA}) is given by

$$\xi_{EOEMA} = \xi_{NIPAM}\left(\frac{y}{x}\right) \quad (4)$$

$$Z = \frac{\log(1 - \xi_{EOEMA})}{\log(1 - \xi_{NIPAM})} \quad (5)$$

where $\eta = G/(\alpha + F)$, $\xi = (\alpha + F)$, $G = (y - 1)/Z$, and $H = y/Z^2$. The EK–T parameters were calculated from the previous equations and are presented in Table II, whereas the EK–T plot for the copolymers is displayed in Figure 3(b). The reactivity ratios were found to be 0.939 and 0.311 for EOEMA and NIPAAm, respectively. This confirmed the higher reactivity of EOEMA than that of NIPAAm during the copolymerization reaction.

Copolymer microstructure

To understand the sequence distribution of monomers in the synthesized copolymers, a statistical method was used. The statistical distribution of the monomer sequences 1–1, 2–2, and 1–2 were calculated with the following equations:

$$S_{1-1} = m_1 - \frac{2m_1m_2}{1 + [(2m_1 - 1)^2 + 4r_1r_2m_1m_2]^{1/2}} \quad (6)$$

$$S_{2-2} = m_2 - \frac{2m_1m_2}{1 + [(2m_1 - 1)^2 + 4r_1r_2m_1m_2]^{1/2}} \quad (7)$$

$$S_{1-2} = \frac{4m_1m_2}{1 + [(2m_1 - 1)^2 + 4r_1r_2m_1m_2]^{1/2}} \quad (8)$$

where r_1 and r_2 are the reactivity ratios obtained by the EK–T method for EOEMA and NIPAAm, respectively, and m_1 and m_2 are the molar fractions of EOEMA and NIPAAm in the copolymers obtained from the elemental analysis data. The molar fractions of 1–1, 2–2, and 1–2 sequences are shown by S_{1-1}, S_{2-2}, and S_{1-2}, respectively. From the structural data given in Table III, the molar fraction of 1–1 increased with increasing molar fraction of EOEMA, which indicated that the copolymer formed was richer in EOEMA segments with a random nature.

SEM

The SEM micrograph of a drug-loaded single microsphere of the NIPAAm/EOEMA (50:50) copolymer shown in Figure 4 confirmed a spherical nature with a somewhat smooth surface.

Particle size analysis

The particle size of the microspheres as measured by the laser light-scattering technique suggested an

TABLE III
Structural Data of Copolymers

Sample code	Composition (molar fraction)		Blockiness (molar fraction)		Alternation (molar fraction)
	M_1	M_2	S_{1-1}	S_{2-2}	S_{1-2}
EN-20	0.2810	0.7190	0.0368	0.4748	0.4885
EN-35	0.4892	0.5108	0.1650	0.1867	0.6482
EN-50	0.6165	0.3835	0.3163	0.0833	0.6004
EN-70	0.8033	0.1967	0.6221	0.0155	0.3625
EN-90	0.8906	0.1094	0.7853	0.0042	0.2127

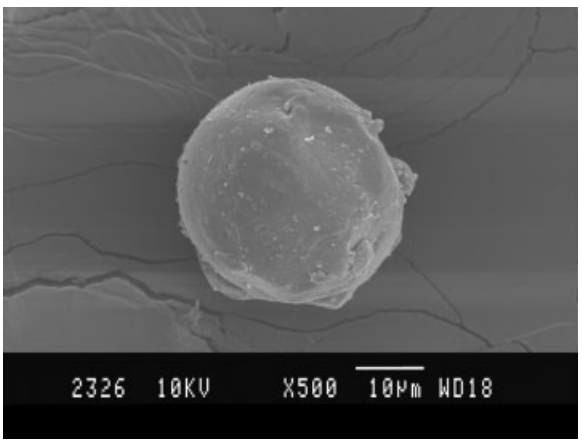

Figure 4 SEM picture of the felidopine-loaded single microsphere.

increasing trend with the increasing amount of NIPAAm in the copolymers due to the hydrophilic nature of the NIPAAm moiety, which formed hydrogen bond; thereby, it swelled more in water. The size of the microspheres increased from 15 to 53 μm, as shown in Table IV.

Drug loading efficiency

The results of the percentage drug loading and encapsulation efficiency for different formulations are presented in Table IV. A fixed amount of drug (10 wt %) was used for initial loading into the microspheres. The UV results suggest that the percentage felodipine loading decreased with increasing amount of NIPAAm of the copolymer. The loadings of felodipine in the EN-90, EN-70, EN-50, EN-35, and EN-20 formulations were 8.3, 7.9, 7.4, 6.8, and 5.9, respectively. The percentage encapsulation efficiency decreased systematically from 83 to 59% with an increasing molar ratio of NIPAAm in the copolymer. However, the percentage encapsulation efficiency showed a decreasing trend that was consistent with the increased hydrophilicity of the matrices. When 35% NIPAAm was present in the copolymer (i.e., EN-70), the encapsulation efficiency was reduced to 79%, whereas for 50, 65, and 80% NIPAAm-containing copolymers, the encapsulation efficiencies were 74, 68, and 59%, respectively. The reductions in percentage drug loading and encapsulation efficiency were attributed to the hydrophilic interaction of NIPAAm with water during the microsphere preparation.

In vitro drug release

In this investigation, felodipine was loaded into the microspheres prepared with different concentrations of NIPAAm with respect to EOEMA to investigate the *in vitro* release of felodipine in neutral pH conditions that replicated human physiological conditions. However, these copolymers were not sensitive to pH, and hence, the release studies were conducted in neutral pH. As shown by the cumulative release curves for felodipine-loaded microspheres in Figure 5, no burst effects were observed, and about 5, 9, 12, 15, and 19% felodipine were released during the first 2 h from the EN-90, EN-70 EN-50, EN-35, and EN-20 formulations, respectively. However, the release studies were continued up to 90 h; 70, 75, 83, 87, and 93% felodipine was released from the EN-90, EN-70, EN-50, EN-35, and EN-20 matrices, respectively, at longer times. An increase in the release rates were observed with increasing NIPAAm segments of the copolymers, which indicated that the release rates could be controlled by the variation of the hydrophilic (NIPAAm) and hydrophobic (EOEMA) contents of the copolymers.

Drug-release kinetics

The empirical equation, $M_t/M_\infty = kt^n$ (M_t/M_∞ represent the functional drug release at time '*t*'; '*k*' is a constant characteristic drug-polymer system and 'n' is an empirical parameter characterizing the release mechanism), was used to analyze the drug-release characteristics from both the swellable and nonswellable polymeric systems.[22] Fickian diffusion ($n = 0.5$) and case II transport ($n = 1$) are observed when drugs are released from diffusion-controlled and swelling-controlled systems, respectively. Systems controlled by

TABLE IV
Compositions of the Copolymers, Particle Size, Drug Loading, and Encapsulation Efficiencies of 10 wt % Felidopine-Loaded Microspheres

Formulation code	Monomer weight ratio in the copolymer (%)		Volume mean diameter (μm)	Drug loading (%)	Encapsulation efficiency (%)
	NIPAAm (mol %)	EOEMA (mol %)			
EN-90	10	90	15	8.3	83
EN-70	30	70	25	7.9	79
EN-50	50	50	38	7.4	74
EN-35	65	35	47	6.8	68
EN-20	80	20	53	5.9	59

both diffusion and swelling will have the n values in the range $0.5 < n < 1$. The values of n were calculated from the slope of the plot of $\ln(M_t/M_\infty)$ versus $\ln t$ with the least squares technique, and these data are given in Table V. The values of n for all of the formulations ranged between 0.55 and 0.77, which indicated almost the Fickian mode of transport. However, as the NIPAAm content of the copolymers increased, the n values also decreased.

TABLE V
Release Kinetics Data of the Drug-Loaded NIPAAm/EOEMA Copolymer Microspheres as Determined by the Power Law Equation

Sample code	Power law	
	N	r^2
EN-20	0.50	0.99
EN-35	0.54	0.98
EN-50	0.60	0.99
EN-70	0.63	0.99
EN-90	0.77	0.99

CONCLUSIONS

This study demonstrated the synthesis and characterization of EOEMA/NIPAAm copolymers and their applications in the controlled release of felodipine, an antihypertensive water-insoluble drug. The copolymers were prepared in a 1,4-dioxane solvent with an AIBN initiator. The compositions of copolymers were estimated by elemental analysis. The reactivity ratios of the monomers obtained by the EK–T method indicated that EOEMA was more reactive than NIPAAm and the copolymer formed was of a random nature. The monomer sequence distribution calculated from the statistical method clearly indicated the formation of a copolymer with a predominantly random distribution of monomers with a higher content of EOEMA units. The microspheres with various drug loading efficiencies released the drug to different extents, depending on the hydrophilic/hydrophobic balances of the copolymers; this showed a clear-cut effect in the control of the release of felodipine up to 90 h. The release kinetics data, as analyzed by an empirical equation, indicated non-Fickian anomalies.

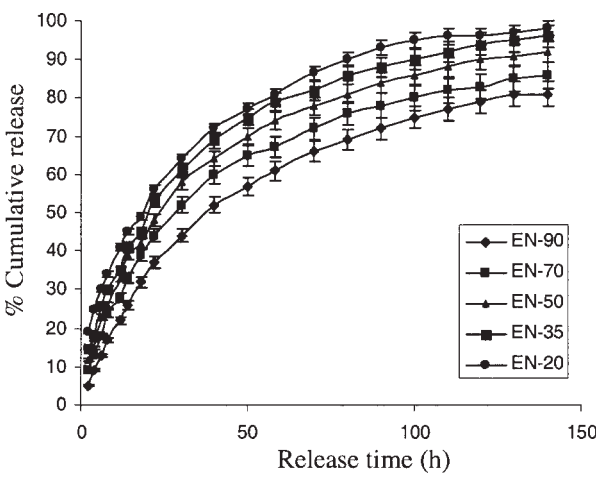

Figure 5 *In vitro* release profiles of felodipine from the formulations (◆) EN-90, (■) EN-70, (▲) EN-50, (■) EN-35, and (●) EN-20.

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