Lamotrigine-Loaded Polyacrylate Nanoparticles Synthesized Through Emulsion Polymerization

Sunil Shah,[1] Angshuman Pal,[1] Tushar Rajyaguru,[2] R. S. R. Murthy,[2] Surekha Devi[1]

[1]*Department of Chemistry, Faculty of Science, The Maharaja Sayajirao University of Baroda, Vadodara 390002, India*
[2]*G. H. Patel Pharmacy Building, TIFAC-CORE in NDDS, The Maharaja Sayajirao University of Baroda, Vadodara 390002, India*

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ABSTRACT: A series of copolymeric nanoparticles of the partially water-soluble monomer ethyl methacrylate and the water-soluble monomer 2-hydroxyl ethyl methacrylate were synthesized from emulsions containing sodium dodecyl sulfate via free-radical polymerization. Lamotrigine, as a model drug, was loaded in nanoparticles during *in situ* polymerization. A stable and transparent poly(ethyl methacrylate-*co*-hydroxyl ethyl methacrylate) nanolatex was produced for all compositions and characterized for particle size by dynamic light scattering and transmission electron microscopy. Particles were found to be smaller than 50 nm in size. Structural characterization of copolymers was done by infrared spectrometry, gel permeation chromatography, and NMR spectroscopy. Drug encapsulation efficiency was determined by ultraviolet (UV)–visible spectrometry and was found to be 26–62% for copolymers with different compositions. UV data suggest molecular-level dispersion of the drug in the nanoparticles. *In vitro* drug-release studies showed the controlled release of lamotrigine. © 2007 Wiley Periodicals, Inc. J Appl Polym Sci 107: 3221–3229, 2008

Key words: emulsion polymerization; nanoparticles; nanotechnology

INTRODUCTION

Since the original discovery by Folkman and Long in 1964 regarding the diffusion of drug molecules, which are hydrophobic and small in size, through the wall of silicone tubing at a controlled rate; polymers have occupied a central status in control drug release and in the fabrication of drug-delivery systems. With the emergence of the genomic era, new drug targets have been identified; because of these, controlled release (CR) and targeted drug-delivery systems have become popular research areas.[1] Polymeric nanoparticles serve as carriers for both hydrophilic and hydrophobic drugs and have acquired technological importance in research because of their multifaceted specific properties, such as their effective targeting of hydrophilic and hydrophobic drugs at the site of action, long shelf life, and high encapsulation efficiency of drugs, unlike liposomes.[2]

In search of an ideal system, a number of carrier systems have been investigated for the controlled delivery of biomolecules/drugs.[3–6] The materials used for the production of the polymeric network are natural polymers, such as albumin, collagen, chitosan, and gelatin, or synthetic polymers, such as polyalkylcyanoacrylates or polyalkylmethacrylates, polyesters like poly(lactic acid), poly(glycolic acid), and their copolymers.[7,8] Since the pioneering works of Peehmann and Rohm in the late 1930s, the industrial use of acrylic polymers has gained popularity.[9] Acrylic polymers, such as Eudragit and Carbapol, are currently being used worldwide in the pharmaceutical industry for controlled drug release and for the development of specific drug-delivery systems.

Most of the reported methods produce nanoparticles with diameters of greater than 100 nm with high polydispersity values.[10,11] This size of the nanoparticles is quite large compared to the histology of the endothelial barrier,[12] and hence, nanoparticles below 100 nm with hydrophilic surfaces can act as better carriers with the added advantage of CR and longer circulation time. The use of amphiphilic polymers such as poly(ethylene glycol) and surfactant molecules such as polaxamers and polaxamines significantly increase the blood circulation time.[13–16] Kim et al.[17] suggested an alternative use of hydrophilic and hydrophobic monomers with appropriate composition in CR studies of bioactive molecules.

In the literature, the preparation of polymeric nanoparticles via the dispersion of the preformed polymer or by *in situ* polymerization has been

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Correspondence to: S. Devi (surekha_devi@yahoo.com).

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reported. Several methods, such as solvent evaporation, spontaneous emulsification/solvent–diffusion, and salting out/emulsification diffusion, require the use of organic solvents for the dispersion of preformed polymers, which could be hazardous to the biological environment. Hence, the encapsulation of hydrophilic/hydrophobic drug molecules through the w/o or o/w micellar polymerization of monomers where the drug is simultaneously present in w/o or o/w micelles can be a better alternative. It is also possible to adhere drug molecules to polymeric particles after polymerization. These methods are known for the imparting of high specific surface areas, spherical morphologies, and lower particle sizes to polymeric nanoparticles, which enable a large variety of drugs to be successfully associated, including cytostatics, antibodies, antiparasitic compounds, hormones, and antiviral drugs. Polyalkylacrylate nanoparticles have been reported to show slow biodegradability. Biodegradability of the polymer can be improved by its copolymerization with more biodegradable stimuli-responsive monomers, such as hydroxyl ethyl methacrylate (HEMA), acrylamide, *N*-isopropyl acrylamide, and *N*-vinyl caprolactam.[18,19] Recently, Rameshbabu et al.[20] carried out the polymerization of acrylamide and methyl methacrylate to produce novel core–shell microspheres and investigated the release of the anticancer agent 5-fluorouracil with respect to the absorption–adsorption technique and a crosslinking agent. An improved release profile with a higher entrapment of drug was reported for a 3 : 1 ratio of acrylamide to methyl methacrylate core–shell microparticles prepared by an *in situ* polymerization method.

As a part of our ongoing research on the development of novel CR systems[21,22] we attempted to synthesize nanoparticles of different compositions through the emulsion copolymerization of ethyl methacrylate (EMA) and HEMA to entrap the lipophilic antiepileptic drug lamotrigine and to investigate its release pattern. To our knowledge, these copolymeric nanoparticles were used for the first time to load the antiepileptic drug lamotrigine.

EXPERIMENTAL

Materials

Lamotrigine (99.9%) was obtained as a gift sample from Alembic Chemicals, Ltd. (Baroda, India). EMA (Fluka, Buchs, Switzerland) was purified by vacuum distillation under reduced pressure and stored at 4°C for further use. HEMA (Aldrich, Deutschland, Germany) was used as received. L-Ascorbic acid, hydrogen peroxide (30%w/v, Merck, Mumbai, India), and sodium dodecyl sulfate (SDS; SD Fine Chem, Baroda, India) were used as received, and double-distilled deionized water (0.22 μm nylon filtered) was used throughout the experiments.

Synthesis of poly(ethyl methacrylate-*co*-hydroxy ethyl methacrylate) nanoparticles

Copolymeric nanoparticles of various compositions with and without lamotrigine were prepared by an emulsion polymerization technique. The ternary emulsions comprising the EMA–HEMA monomer mixture (6% w/w) containing 1% w/w lamotrigine, 2% w/w SDS, and 91% w/w water were used in a three-necked reaction vessel equipped with a nitrogen inlet, thermometer, water condenser, and magnetic stirrer. Polymerization was initiated by the redox initiator hydrogen peroxide and L-ascorbic acid at 40 ± 1°C for 4 h to achieve complete conversion. The final latex obtained was allowed to purify at the Kraft temperature of the surfactant to achieve a surfactant-free latex, and the latex was lyophilized (Heato Dry, Winner, Germany) to separate the nanoparticles. The adsorbed surfactant was removed by the redispersion of the lyophilized nanoparticles containing drug in a 30 : 70 methanol–water mixture and the relyophilization of the filtered nanoparticles for further studies.

Characterization

Infrared (IR) spectra

The IR spectra of the purified copolymer, drug-loaded copolymer, and drug were recorded on a PerkinElmer Rx_1 IR spectrophotometer with KBr pellets 1 cm in diameter.

NMR spectroscopy

Dried nanoparticles were dissolved in $CDCl_3$, and ^{1}H-NMR spectra were recorded with a 400-MHz NMR spectrometer (Bruker Specrospin Avance Ultra-Shield, Germany) at room temperature. The spectra were obtained after 16 scans were accumulated with a 1% sample in $CDCl_3$, and the copolymer compositions derived are given in Table S.I.

Dynamic light scattering (DLS)

A Brookhaven 90 plus DLS instrument with a solid-state laser source operated at 688 nm was used to measure the particle size and size distribution of the polymerized latex in a dynamic mode. The particle size was obtained from the Stokes–Einstein relation $D = KT/(3\pi\eta d)$, where d is the particle diameter, D is the translational diffusion coefficient, K is Boltzmann constant, T is the temperature (°C), and η is the viscosity of the medium. The scattering inten-

TABLE I
Effects of the Monomer Ratio on the Particle Size, %EE of Lamotrigine, and Swelling

EMA : HEMA	Particle size (nm)	PDI	Equilibrium swelling (Q)	n	r^2	%EE
90 : 10	24 ± 0.34	0.11	10.1	0.28	0.93	42.66 ± 2.16
80 : 20	26 ± 0.69	0.22	12.1	0.29	0.88	54.28 ± 2.88
70 : 30	25 ± 0.85	0.19	23.6	0.38	0.97	62.87 ± 3.44
60 : 40	36 ± 0.71	0.16	34.5	0.41	0.97	35.72 ± 2.69
50 : 50	30 ± 0.60	0.18	41.5	0.45	0.98	26.88 ± 1.65

PDI, polydispersity index.

sities from the samples were measured at 90° with a photomultiplier tube. To minimize the interparticle interactions, the analysis of the latex was done after 10× dilution with the refractive index and viscosity of water considered as that of latex. All of the measurements were performed in triplicate.

Transmission electron microscopy (TEM)

TEM analyses of the copolymeric nanoparticles and drug-loaded nanoparticles were performed with a Jeol 1200 EX transmission electron microscope at an accelerating voltage of 80 kV. One drop of latex was dispersed in 5 mL of water and was placed on the carbon-coated copper grid. The grid was dried under an IR lamp, and then, the images of representative areas were captured at suitable magnifications.

Estimation of the percentage encapsulation efficiency

The UV spectra of the purified copolymer, drug, and drug-containing polymer were recorded on a PerkinElmer Lambda 35 ultraviolet–visible (UV–vis) spectrophotometer. The drug-loaded nanoparticles were purified by successive washing with methanol to remove the adsorbed drug and were then relyophilized. Ten milligrams of nanoparticle were dissolved in 10 mL of alcohol, and the spectrum was scanned. The entrapment efficiency (%EE) of lamotrigine in the nanoparticles was calculated from the calibration plot constructed at 306 nm. The data is compiled in Table I.

Swelling study

The swelling study of the lamotrigine-loaded copolymeric nanoparticles was done in a simulated gastric environment with 0.1*M* HCl. The swelling of the copolymeric nanoparticles was measured by the equilibrium weight gain method[23] up to 15 h until an equilibrium was attained in an incubator (Stuart Orbital Incubator, model S150, Staffordshire, United Kingdom) maintained at 37°C. Liquid droplets adhered on the surface of the particles were removed with tissue paper, and the swollen particles were weighed on an electronic balance (Mettler, model AE 240, Griefensee, Switzerland) with an accuracy of ±0.1 mg. The nanoparticles were dried in an oven at 60°C for 5 h until there was no change in the dry weight of the samples. From the weight of the dry particles (W_1) and the weight of the swollen particles (W_2; i.e., the equilibrium weight percentage), water uptake (Q) was calculated with the following equation:

$$Q = \left(\frac{W_2 - W_1}{W_1}\right) \times 100 \quad (1)$$

Measurements were done in triplicate, and the results are given in Table I.

In vitro release

The *in vitro* release study for the drug-loaded polymeric nanoparticles of various compositions was carried out in a dialysis bag (cutoff = 10,000; Hi-Media, India). Drug release from the nanoparticles was studied in 0.1*M* HCl, which is a dissolution medium for lamotrigine according to the U.S. Food and Drug Administration. Aliquots of samples were withdrawn at regular time intervals, and the same volume was replaced with fresh dissolution medium. The samples were analyzed with a UV spectrophotometer at 306 nm against a reagent blank. All experiments were repeated three times, and the average values were considered, where k_o, k_1, and k_h are kinetics constants. Data for kinetics of drug release are compiled in Table II.

Stability studies

Short term stability studies were carried out for all batches. The formulations were stored in air-tight sealed vials at 2–8 and 30 ± 2°C. The preparations were sampled at regular intervals of 0, 10, 20, and 30 days and tested for particle size and percentage drug retained. Lyophilized powder was vortexed with aliquots (2 mL) of the distilled water and subjected to centrifugation on a laboratory centrifuge (Remi C24, Mumbai, India) at 5000 rpm. The clear supernatant was carefully siphoned off to separate out free lamotrigine from the nanoparticles, if any, on storage. Absolute alcohol (2 mL) was added to

TABLE II
Comparative Account of the Kinetic Data for Lamotrigine Release

		Zero-order		First-order		Higuchi		Peppas	
EMA : HEMA		k_o	r^2	k_1	r^2	k_h	r^2	n	r^2
First step	90 : 10	0.23	0.99	0.028	0.98	2.43	0.98	1.37	1.00
	80 : 20	0.36	0.97	0.027	0.91	3.7	0.94	1.66	0.99
	70 : 30	0.15	0.97	0.021	1.00	1.57	0.94	1.29	0.99
	60 : 40	0.19	1.0	0.019	1.00	2.00	0.92	1.22	0.99
	50 : 50	0.23	0.96	0.028	0.98	2.38	0.99	1.71	1.00
Second step	90 : 10	0.017	0.99	0.0003	0.98	0.62	0.98	0.24	0.93
	80 : 20	0.024	0.99	0.0004	0.98	0.91	0.97	0.25	0.95
	70 : 30	0.026	0.99	0.0005	0.98	1.01	0.99	0.34	0.98
	60 : 40	0.024	0.99	0.0003	0.96	0.90	0.98	0.22	0.96
	50 : 50	0.022	0.99	0.0003	0.99	0.83	0.95	0.22	0.91

the supernatant to lyses the nanoparticles, and the absorbance was recorded at 306 nm. The observations are recorded in Table III.

RESULTS AND DISCUSSION

IR spectrometry

The methacrylate copolymeric nanoparticles were prepared through a free-radical emulsion polymerization technique with the redox initiator hydrogen peroxide and ascorbic acid. To achieve a high percentage conversion, temperature, time, and initiator concentration were optimized at 2% SDS concentration. After the separation of the nanoparticles from the nanolatex through successive freeze drying, the IR spectra of drug-loaded copolymeric nanoparticles, copolymeric nanoparticles without drug, and free lamotrigine were recorded and are given in Figure 1. The IR spectra of copolymeric nanoparticles [Fig. 1(B)] showed a > C=O stretching band due to both EMA and HEMA units in the copolymer at 1728 cm^{-1}, and the broad band observed at 3500 cm^{-1} was due to O—H stretching vibrations. The bands at 2852, 2923, 1482, and 1389 cm^{-1} were attributed to stretching vibrations of —CH_2 and —CH groups and the bending vibration of —CH_2, —CH groups, respectively, and bands appearing at 1045 and 1245 cm^{-1} corresponded to the —C—O ester stretching band of acrylate copolymer. However, in the case of the drug-loaded copolymeric nanoparticles [Fig. 1(C)], the broad hydroxyl band of copolymer was partially replaced by a sharp band due to N—H stretching at 3451 cm^{-1}, and an additional new band appeared at 1620 cm^{-1}, corresponding to N—H bending vibration. The appearance of ring-stretching bands due to —C=C and —C≡N bands of lamotrigine around 1300–1500 cm^{-1} confirmed drug entrapment in the polymeric matrix [Fig. 1(A)].

NMR spectroscopy

The signal that appeared at 4.064 ppm corresponded to the protons of the —O—CH_2 ester group of the methacrylate units, and the one appearing at 3.86 ppm corresponded to the protons of the —CH_2—OH of the HEMA, which confirmed copolymer formation. The copolymer composition and representative spectra are given as supplementary data (Table S.I and Fig. S.1).

Determination of particle size

The particle size of the drug-loaded copolymeric nanoparticle latex was determined through the DLS technique and TEM (Figs. 2 and 3). A representative particle size histogram obtained through DLS for a 90 : 10 EMA : HEMA ratio is given in Figure 2. The particle size was observed to be between 25 and 35 nm for all of the copolymer compositions, and the data are compiled in Table I. TEM was used to

TABLE III
Effects of Temperature and Storage Time on the Stability of the Nanoparticles

	Particle size (nm)							
	2–8°C				30 ± 2°C			
EMA : HEMA	Initial	1 month	2 months	3 months	Initial	1 month	2 months	3 months
90 : 10	24 ± 3	26 ± 3	27 ± 4	30 ± 2	24 ± 3	27 ± 1	32 ± 2	37 ± 2
80 : 20	26 ± 2	28 ± 3	29 ± 2	31 ± 2	26 ± 2	33 ± 4	40 ± 3	42 ± 2
70 : 30	25 ± 2	28 ± 2	30 ± 2	32 ± 3	25 ± 2	38 ± 5	42 ± 3	49 ± 5
60 : 40	35 ± 2	46 ± 5	52 ± 5	52 ± 5	36 ± 2	50 ± 3	54 ± 5	62 ± 4
50 : 50	30 ± 3	39 ± 5	58 ± 4	60 ± 4	30 ± 3	67 ± 1	70 ± 4	76 ± 5

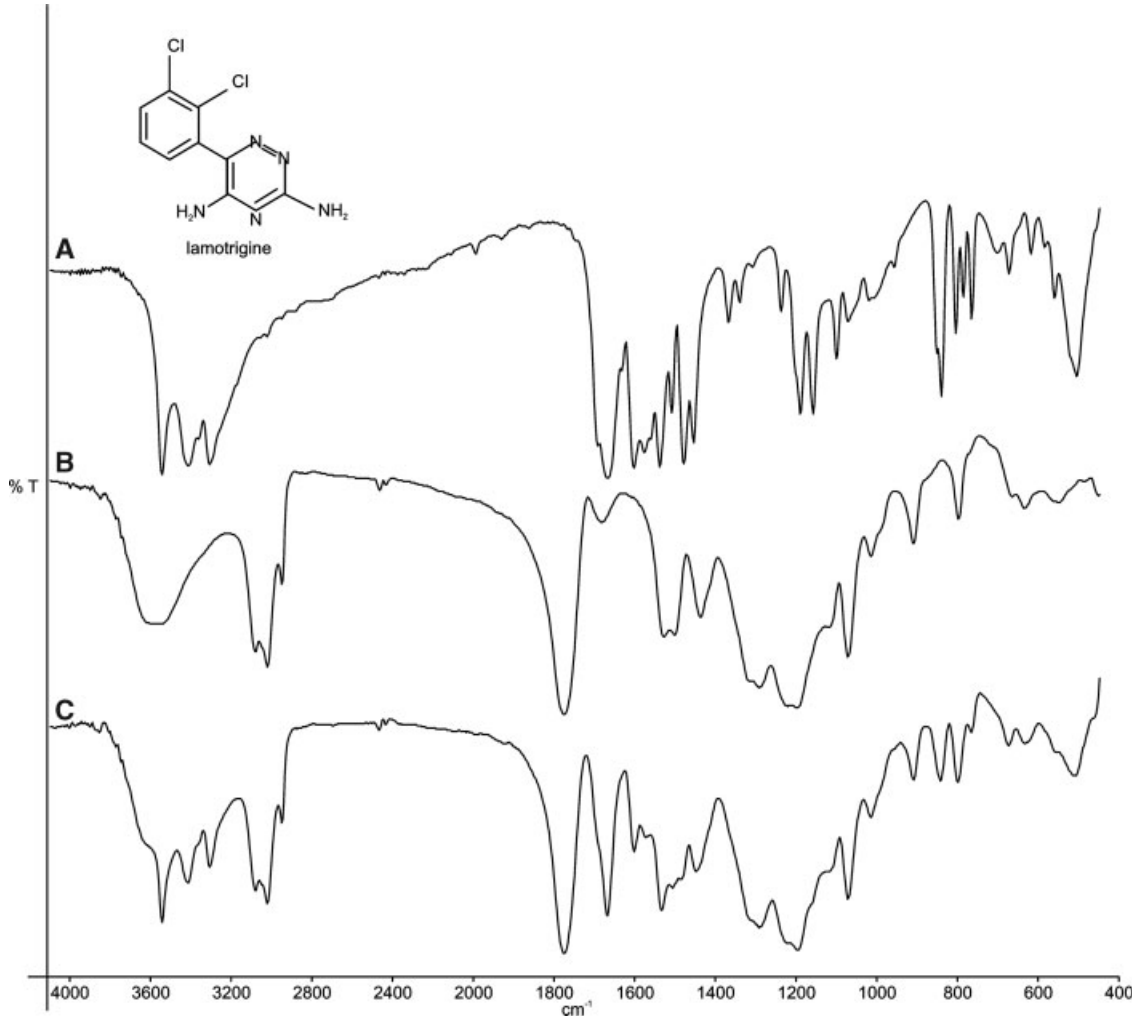

Figure 1 IR spectra of (A) lamotrigine, (B) copolymeric nanoparticles (90 : 10 EMA : HEMA), and (C) drug-loaded copolymeric nanoparticles.

examine the size and morphology of the copolymeric nanoparticles. Figure 3 shows a TEM photograph of drug-loaded EMA–HEMA (90 : 10) copolymeric nanoparticles [Fig. 3(A)] and placebo nanoparticles [Fig. 3(B)]. Particles were observed to be smaller than 25 nm in diameter with spherical morphologies and monodispersed natures. The shrinkage in particle size observed in the drug-loaded nanoparticles compared to the copolymeric nanoparticles may have been due to the density difference between the copolymer and drug-loaded particles. Peak molecular weights and molecular weight distributions determined by gel permeation chromatography (Fig. S.2) were found to be 1.4×10^5 and 1.07, respectively, which confirmed the monodispersed nature of the particles.

%EE of lamotrigine in the nanoparticles

%EE of lamotrigine in the copolymeric nanoparticles was determined with UV–vis spectroscopy and is shown in Figure 4. %EE was found to vary from 26 to 62% when 1% lamotrigine was added during the polymerization of different copolymer compositions. The UV spectrum of lamotrigine showed a maximum absorbance around 306 nm [Fig. 4(A)] in absolute alcohol, and that of the copolymeric nanoparticles was at 235 nm [Fig. 4(B)]. The UV spectra of the lamotrigine-loaded copolymeric nanoparticles showed two distinct peaks at 306 and 235 nm [Fig. 4(C)]. From the calibration plot at 306 nm, %EE of lamotrigine in nanoparticles was calculated. The maximum entrapment of lamotrigine was observed for the 70 : 30 EMA–HEMA composition. Table I shows %EE of lamotrigine-loaded nanoparticles of different compositions. The variation in encapsulation efficiency and the rate of drug release from copolymeric particles was attributed to the variation in the microstructure of the copolymers, which has been correlated to HEMA content.[21,24] In this study, the percentage encapsulation efficiency was observed to increase up to 30% of HEMA content, and there-

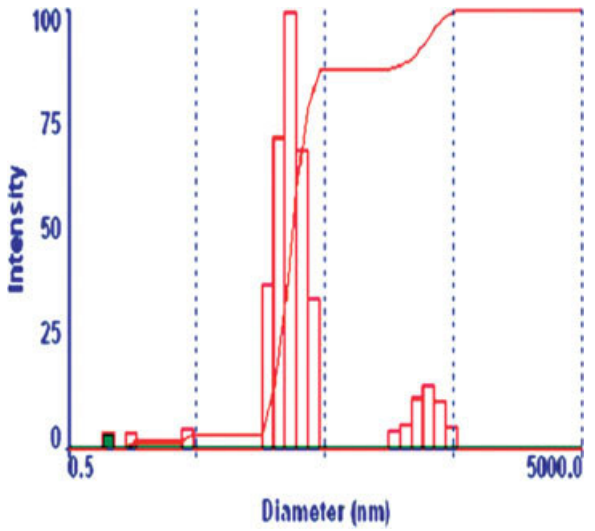

Figure 2 Representative particle size histogram for the 90 : 10 EMA : HEMA drug-loaded nanolatex. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

after, it decreased. The observed initial burst release was attributed to the increased relaxation of the polymer chains with increasing HEMA content, which was followed by a slow release of the drug due to the surface erosion of the matrix. The percentage cumulative release was also lower at 30% HEMA content, which was attributed to the variation in the swelling behavior of the copolymers.

Swelling study

The results obtained in the equilibrium swelling studies performed by an equilibrium weight gain method at gastric pH conditions for the copolymeric nanoparticles are presented in Table I. Q was found to be dependent on the copolymer composition. The maximum Q observed for a 50 : 50 EMA–HEMA copolymer composition was 41.5% and was gradually reduced to 10.4% with increasing concentration of EMA in the copolymer. The reduction in Q was due to the increase in the hydrophobic character of the copolymer. To predict and compare the release behavior of the drug from the polymeric system, it was necessary to fit the data into the release kinetic equation:

$$\frac{M_t}{M_\infty} = kt^n \tag{2}$$

where M_t is the swelling of the nanoparticles with respect to time t and M_∞ is the swelling of the nanoparticles at equilibrium. From the plot of log M_t/M_∞ versus log t, the diffusional exponent (n) was calculated and found to be in the range 0.28–0.45, which indicated more Fickian behavior.

In vitro release

The release of lamotrigine from copolymeric nanoparticles in 0.1M HCl, as given in Figure 5, showed a two-phase release profile. The first phase showed an initial high rate of release for a maximum period of 50 min. This was followed by a slow release phase. The total percentage cumulative release up to a maximum of 45% for the batches with 50 : 50 EMA–HEMA and a minimum of 23% for the 90 : 10 EMA–HEMA composition for a period of 15 h showed a sign of controlled and prolonged release of lamotrigine. The initial fast release of the drug was the outcome of a burst release due to the fast dissolution and quick diffusion of drug particles migrating to the

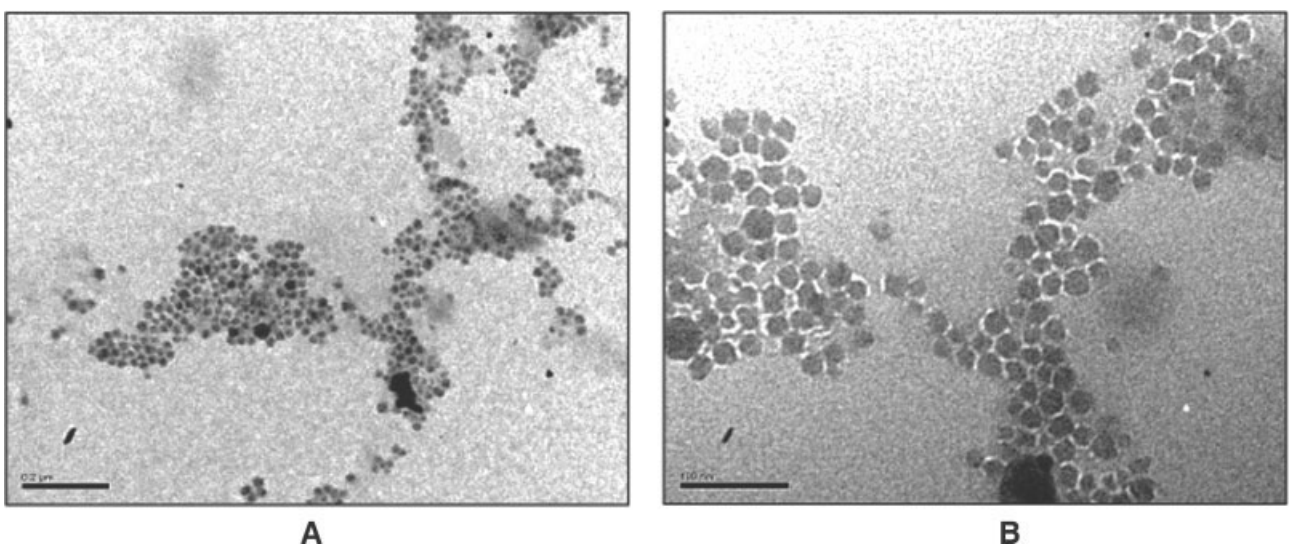

Figure 3 TEM analysis of the 90 : 10 EMA : HEMA nanolatex (A) with drug and (B) without drug.

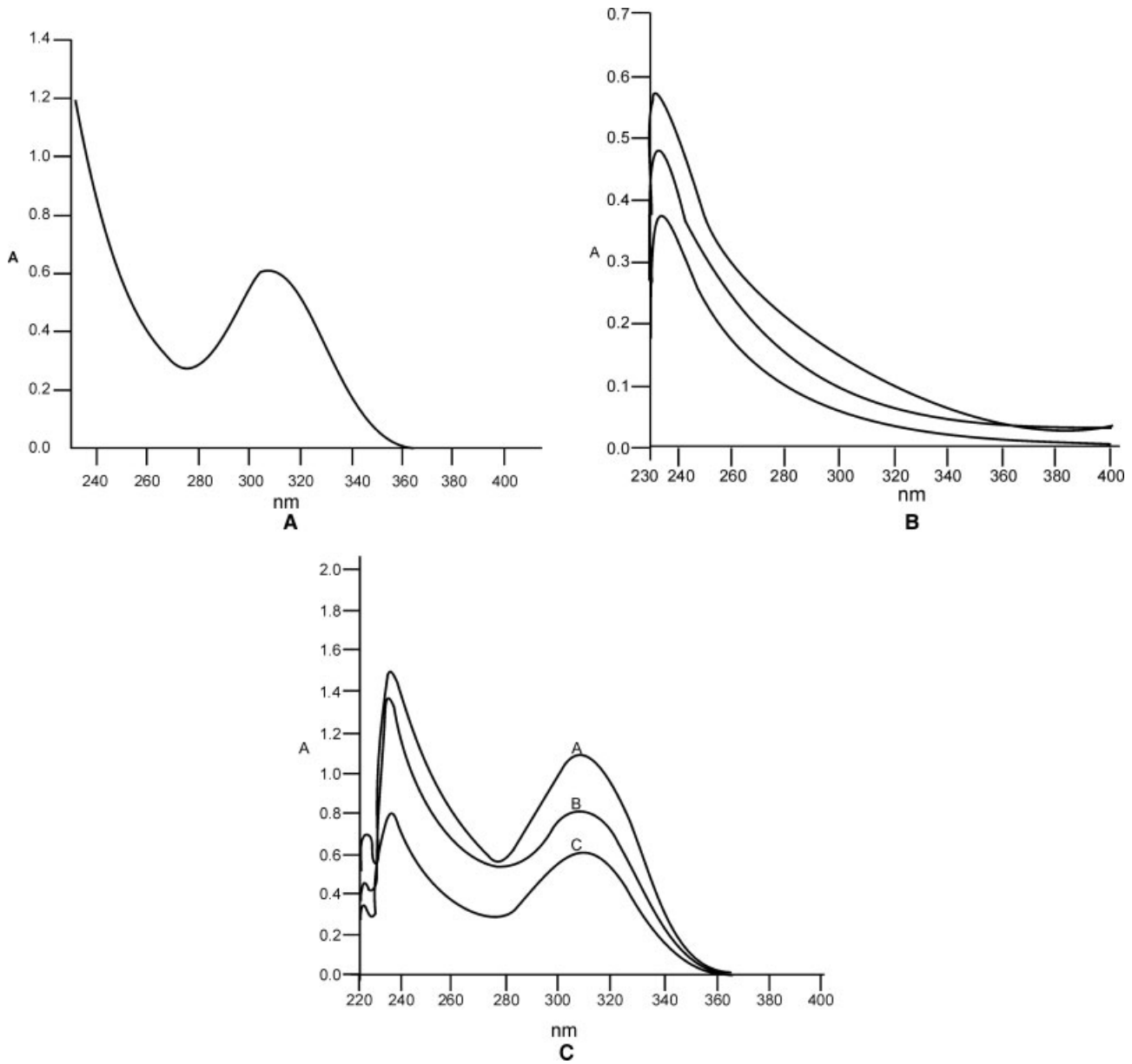

Figure 4 UV spectra of (A) lamotrigine, (B) copolymeric nanoparticles, and (C) drug-loaded copolymer nanoparticles.

periphery during the formation of the particles by co-acervation or by *in situ* polymerization. The extent of drug accumulation at the boundary depends on many parameters, such as the differential solubility of the drug and the polymer in the common solvent in the case of co-acervation, whereas it may be the difference in the rate of precipitation of the drug and the rate of polymerization of the monomer during an *in situ* polymerization process. In addition, a drug like lamotrigine, with a low partition coefficient at acidic pH, diffuses faster in a hydrophilic polymer matrix than in a hydrophobic polymer matrix. A similar observation was made in this case, where copolymers with higher hydrophobic character showed lower burst ($\sim$ 15%) than those with low hydrophobicity.

The kinetics of the first phase release were obtained by plotting of the cumulative percentage drug release versus time for zero-order kinetics, log of the percentage release versus t for first-order kinetics, percentage release versus the square root of time ($t^{1/2}$) for the Higuchi model, and fractional release M_t/M_∞ versus t for the Peppas model. Table II gives the calculated kinetic constants and correlation coefficients (r^2's) for these methods and models. The kinetic constant of release (k) was found to be independent of the composition of the copolymer. This may have been due to the fact that the maximum release during this phase was due to the fast dissolution of the drug molecules adsorbed at the surface, and the diffusion process had little to do in this phase. Interestingly, all of the copolymers

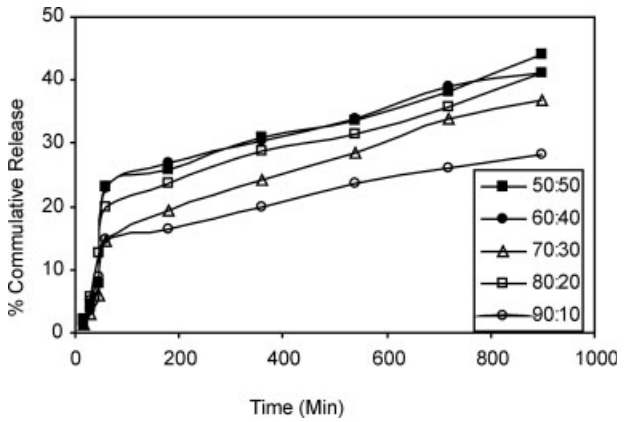

Figure 5 Percentage cumulative release pattern of lamotrigine through copolymeric nanoparticles: (○) 90 : 10, (□) 80 : 20, (△) 70 : 30, (●) 60 : 40, and (■) 50 : 50 EMA:HEMA.

showed r^2 values nearer to unity with the Peppas model, which indicated the role of polymer relaxation in the nanoparticle surface in the dislodging of the drug molecule and release, as discussed by Peppas.[25]

The second phase of the release profile was almost linear in all the batches. The mechanism of release in this phase from a matrix is generally by the diffusion of the drug through the matrix or by polymer erosion/degradation in the release media.[26] The kinetics of drug release in a matrix by diffusion was explained the first time by Higuchi,[27,28] and the mathematical model proposed relates the cumulative percentage drug release as proportional to $t^{1/2}$. The kinetics of the second-phase release profile studied showed r^2 values relatively nearer to unity with respect to the zero-order kinetic model. This pattern of release is generally due to polymer degradation in the matrix, particularly by surface erosion. However, it was quite difficult to confirm the mechanism with the existing experimental observations because the combination of several other processes, including high swelling behavior, could also show zero-order-like kinetics.

Stability studies

The stability studies were carried out according to USP/ICH guidlines.[29,30] The study was carried out for 3 months of storage time. The lyophilized powder was stored at defined conditions, and retained drug and particle size values were determined at specific time intervals. As shown by the data in Table III, the particle size went on increasing with storage time and HEMA content in the copolymer. However, relatively little difference in particle size was observed at lower temperature storage. Figure 6(A,B) shows the percentage of drug retained with time in the copolymeric nanoparticles at 2–8 and 30 ± 2°C, respectively. A 5–10% loss due to the leaching of the drug took place at lower temperature for various compositions of the EMA–HEMA copolymer after 3 months of storage. At room temperature (30 ± 2°C), the loss due to the leaching of the drug was 5–22% for these copolymer compositions. Polymeric nanoparticles showed better stabilities at lower temperatures.

CONCLUSIONS

The addition of a model drug, lamotrigine, to polymeric nanoparticles synthesized through emulsion polymerization proved to be successful with a 26–62% drug entrapment with respect to the copolymer compositions. The incorporation of lamotrigine did not appear to interfere significantly with the physicochemical properties of the polymer, such as structure, molecular weight, particle size, and morphology. IR analysis confirmed the copolymer formation. UV analysis indicated the molecular-level dispersion of the drug in the polymeric matrix. TEM and DLS

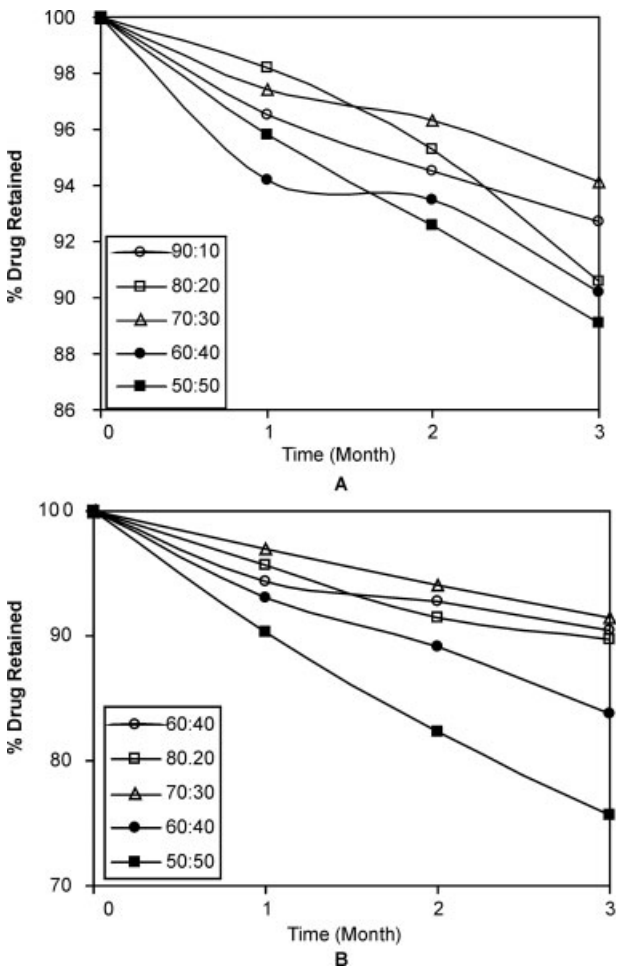

Figure 6 Percentage drug retained at (A) 2–8 and (B) 30°C from the copolymeric nanoparticles with time: (○) 90 : 10, (□) 80 : 20, (△) 70 : 30, (●) 60 : 40, and (■) 50 : 50 EMA : HEMA.

analyses of nanolatex confirmed the formation of well-defined, reasonably well monodispersed particles with spherical morphologies. With increasing HEMA content in the copolymer with time, an increase in particle size and leakage of lamotrigine was observed. The release profile of lamotrigine from the copolymeric nanoparticles showed an initial burst effect followed by a continuous slow release for a period of 15 h, which indicated a sign of CR of lamotrigine from the nanoparticles.

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