Synthesis, Characterization, and *In Vitro* Release of Ibuprofen from Poly(MMA-HEMA) Copolymeric Core–Shell Hydrogel Microspheres for Biomedical Applications

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ABSTRACT: This article describes the development of a new crosslinked poly(methyl methacrylate-2-hydroxyethyl methacrylate) copolymeric core–shell hydrogel microsphere incorporated with ibuprofen for potential applications in bone implants. Initially poly(methyl methacrylate) (PMMA) core microspheres were prepared by free-radical initiation technique. On these core microspheres, 2-hydroxyethyl methacrylate (HEMA) was polymerized by swelling PMMA microspheres with the HEMA monomer by using ascorbic acid and ammonium persulfate. Crosslinking monomers such as ethylene glycol dimethacrylate (EGDMA) has also been included along with HEMA for polymerization. By this technique, it was possible to obtain core–shell-type microspheres. The core is a hard PMMA microsphere having a hydrophilic poly(HEMA) shell coat on it. These microspheres are highly hydrophilic as compared to PMMA microspheres. The size of the hydrogel microspheres almost doubled when swollen in benzyl alcohol. These microspheres were characterized by various techniques such as optical microscopy, scanning electron microscopy, Fourier-transformed infrared spectroscopy, thermogravimetric analysis, and differential scanning calorimetry. The particle size of both microspheres was analyzed by using Malvern Master Sizer/E particle size analyzer. The *in vitro* release of ibuprofen from both microspheres showed near zero-order patterns. © 2002 John Wiley & Sons, Inc. J Appl Polym Sci 83: 3045–3054, 2002; DOI 10.1002/app.10310

Key words: PMMA; HEMA; EGDMA; core–shell hydrogel microspheres; ibuprofen

INTRODUCTION

During the last decade, the development of polymeric drug carriers has grown as an important field of pharmaceutical and medical research. Several materials for the preparation of microspheres and nanospheres to which the drugs are bound by adsorption and/or encapsulation were introduced.[1–3] An efficient and versatile drug carrier system has to fulfill the following requirements: (i) particle size in the submicron range; (ii) the possibility of surface modifications; (iii) high drug-loading capacity; (iv) colloidal stability of the latex in biological media; and (v) the lack of toxic side effects induced by the carrier or additives.[4] Hydrogel is a broad class of hydrophilic polymeric materials that swell extensively, but do not dissolve in water. Hydrogels are three-dimensional polymeric networks held together by crosslinks of covalent bonds and weak cohesive forces in the form of either hydrogen or ionic bonds. Polymeric hydrogel microspheres have re-

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cently attracted attention because of their permanent spherical shape.[5–9] Many researchers found hydrogel microspheres can be used as carrier matrices in a wide variety of mucosal, biological, and biomedical applications such as ophthalmology,[10] drug delivery,[11] orthopedics,[12] and medical devices.[13] The ability of natural tissue to grow into hydrogel matrices makes them very attractive for biomedical uses.[14,15]

The concept of self-anchoring swelling-type orthopedic implants was originally introduced by Greenberg et al.[16] in 1978 with the aim of developing implants with superior fixation characteristics over conventional orthopedic and dental implants. These novel implants would, in principle, dilate in a controlled manner by adsorption of body fluids and achieve fixation by an expansion-fit mechanism. Swelling-type bone implants have several intrinsic merits. When the swelling of the implant is constrained by the surrounding bone, it produces compressive pressure on the bone implant interface. This interfacial pressure, in turn, produces frictional resistance between the bone and the implant and creates tensile hoop stresses in the bone. These tensile hoop stresses have the potential to mitigate stress-shielding effects and induce bone densification in the neighborhood of the implant through a remodeling process. A preliminary set of surgical implantation experiments carried out in canine femur has showed that controlled swelling of the implant can lead to bone deposition along the bone–implant interface. Recently, Kalidini and Ahmad showed the implant–bone interface induced by swelling-type implant and bone system.[17–20]

Many researchers reported that the different kinds of crosslinked poly(2-hydroxyethyl methacrylate) [poly(HEMA)] and poly(methyl methacrylate) (PMMA) beads are used as bone implants.[21–24] Recently, Bulmus and coworkers reported the preparation of methyl methacrylate (MMA) and 2-hydroxyethyl methacrylate (HEMA) by dispersion polymerization in aqueous medium.[25] The main advantage of core–shell-type microspheres is that both the hydrophilic and the hydrophobic drugs can be incorporated. In our earlier article, we reported the preparation of micron-size PMMA functional microspheres by solvent evaporation technique and demonstrated the incorporation of various functional (carboxyl and amino) groups and antibiotic, anti-inflammatory drugs in the PMMA functional microspheres and utilized these microspheres in diverse hard-tissue repair and regeneration.[26,27] In this present investigation, an attempt was made to prepare MMA- and HEMA-based copolymeric core–shell hydrogel microspheres with narrow size distribution of particles for bone and dental-filling applications. Ibuprofen, a nonsteroidal anti-inflammatory drug, was incorporated in the copolymeric hydrogel microspheres, and the *in vitro* release profiles are studied.

EXPERIMENTAL

Materials

MMA (Aldrich, USA) was purified by distillation under reduced pressure, poly(vinyl alcohol) (PVA; MW, 72,000; degree of hydrolysis, 98%; Koch Light Laboratory, England), and poly(vinyl pyrollidone) (PVP; K-30, Sisco Research Laboratory, India). HEMA (Aldrich) was distilled under vacuum pressure (0.3 mm mercury) at 65°C. Benzoyl peroxide was purchased from Fluka, Switzerland and ethylene glycol dimethacrylate (EGDMA) was procured from Polysciences, USA. Ascorbic acid and polyethylene glycol of various molecular weights of 400, 600, 1000, 1500, and 4000 (S.D. Fine Chemicals, India) were used as obtained. Ibuprofen drug (medical grade) was a gift from Tablets India, India. Other chemicals used were of analytical grade (S.D. Fine Chemicals, India).

Methods

Preparation of PMMA Core Microspheres

PMMA core microspheres were prepared by suspension polymerization technique. A mixture of 100 mL viscous solution containing PVA (1.25 g), PVP (0.25 g), and polyethylene glycol (PEG; 1.5 g) was taken in the reactor vessel and heated at 70°C for 30 min with continuous stirring. A mixture containing 15 mL of monomer (MMA), initiator (benzyl peroxide, 10% of MMA monomer), and crosslinking agent (EGDMA, 10% of MMA) was then added to the reactor under nitrogen atmosphere. The reaction was allowed to proceed for 3 h at 75°C. After polymerization, it was allowed to cool to room temperature and the settled microspheres were washed with distilled water three times and finally dried at 75°C for 12 h in an oven. The same procedure was followed for the preparation of various sizes of microspheres by using different molecular weights of PEGs and various concentrations of PEG 1000.

Preparation of Poly(MMA-HEMA) Copolymeric Core–Shell Hydrogel Microspheres

One gram of core PMMA microspheres were allowed to swell in 1 mL HEMA monomer and copolymerization was carried out at room temperature for 15 min with EGDMA (10% of HEMA) as crosslinking agent. Ascorbic acid and ammonium persulfate (0.3 g each) were used as initiators. After completion of the reaction, the microspheres were washed with methanol and water two times and the spheres were dried at room temperature overnight.

Swellabillities of Microspheres

By Volume Ratio Method

To exhibit swellabilities of the microspheres, swelling ratios of microspheres were obtained as follows: the apparent volume of the dry microspheres (0.5 g) was measured within a cylindrical glass tube (10 mL), which was covered to avoid liquid evaporation. The cylinder was vibrated to promote settling. Water or benzyl alcohol was added into the tube, and the microspheres were allowed to swell at 37°C for 620 h (i.e., the predetermined equilibrium swelling time) with continuous shaking, and the volume of swollen microspheres was measured. The percentage change in volume (%V) of the swollen microspheres was calculated as follows:

$$\%V = \frac{V_s - V_d}{V_d} \times 100$$

where V_s is the volume of swollen microspheres (ml) and V_d is the volume of dry microspheres (ml).

By Weight Ratio

The apparent weight of dry microspheres (0.5 g) was measured within a cylindrical glass tube (10 mL), which was covered to avoid liquid evaporation. Water or benzyl alcohol was added into the tube, and the microspheres were allowed to swell at 37°C for 96 h (i.e., the predetermined equilibrium swelling time) with continuous shaking and they were removed at equal intervals from the swelling media during the first 10 h of experiment, blotted to dryness with filter paper, rapidly weighed, and reimmersed into the swelling media. After 10 h, the microspheres were patted dry and weighed at less frequent time intervals until the weights of the swollen microspheres were constant. The degree of swelling was determined as follows:

$$\text{Swelling ratio } (\%) = \frac{W_s - W_d}{W_d} \times 100$$

where W_s is the weight of swollen microspheres (g) and W_d is the weight of dry microspheres (g).

Loading of Ibuprofen into PMMA and Poly(MMA-HEMA) Copolymeric Core–Shell Hydrogel Microspheres

Loading of ibuprofen into microspheres was done in benzyl alcohol at room temperature for 48 h. A measure of 50 mg ibuprofen was dissolved in 5 mL benzyl alcohol and mixed thoroughly by using a vortex mixer for 10 min. An amount of 50 mg PMMA and poly(MMA-HEMA) copolymeric core–shell hydrogel microspheres were weighed exactly and separately suspended in 5 mL benzyl alcohol containing 50 mg ibuprofen (10 mg ml^{-1}). After 48 h, the microspheres were separated by centrifugation. Then the microspheres were quickly washed with distilled water and dried at room temperature for 5 days. The estimation of ibuprofen uptake by the microspheres was carried out through an indirect method, by finding the difference in ibuprofen concentrations in the loading solvent, before and after loading. Percentage loading was calculated using the formula:

$$\text{Percentage loading} = \frac{X - Y}{X} \times 100$$

where X and Y represents the initial and final drug concentration, respectively. The experiment was performed in triplicate.

In Vitro Release of Ibuprofen from PMMA Core and Poly(MMA-HEMA) Copolymeric Core–Shell Hydrogel Microspheres

In vitro release of ibuprofen from PMMA core and poly(MMA-HEMA) core–shell microspheres (50 mg each) was carried out at 37°C in PBS (5 mL) pH 7.4. The released medium was collected at predetermined time intervals and replaced with a fresh buffer of PBS (5 mL) each time. The collected samples were filtered through a 0.45-μm Millipore filter. The amount of ibuprofen released was then measured at 271 nm by using a Shi-

madzu UV-2100S spectrophotometer. These experiments were carried out in triplicate.

Characterization

Microspheres Yield

The dried PMMA core microspheres were weighed in a top-loading electronic balance, and the microspheres yield was calculated by using the following equation:

$$\text{Microspheres yield} = \frac{W_d - W_m}{W_m} \times 100$$

where W_d is the weight of clean and dry polymeric microspheres (g) and W_m is the weight of monomer initially charged in the reactor (g).

Particle Size Analysis

The particle size distribution of the microspheres were determined by using a Malvern Master Sizer/E particle size analyzer, which functions under the principle of laser diffraction. The size distribution curve displays the particle size along the *x*-axis and the percentage along the *y*-axis. From these data, the average mean diameter of the microspheres was determined.

Optical Microscopy

The optical microscope (Reichart 2 Polyvar Mat) was used for determination of shape and swelling properties of PMMA core and poly(MMA-HEMA) core–shell microspheres. The free-flowing dried microspheres and swollen microspheres were sprinkled onto a glass plate and examined with an optical microscope and the image was taken in a camera attached to the microscope.

Scanning Electron Microscopy

The morphological characteristics of PMMA core and poly(MMA-HEMA) core–shell microspheres were studied by using a scanning electron microscope (SEM, Leika Stereo Scan, U.K.). The free-flowing dried microspheres were sprinkled onto aluminum stubs with double-faced adhesive tape on the stub, coated with a thin layer of gold to a depth of about 50 A° under vacuum for 3 min (Polaron SC500 Sputter Coater, Fisons Instruments, U.K.), and examined under an SEM.

FTIR Spectroscopy Studies

The FTIR spectra of the microspheres were recorded by using an FTIR spectrometer (Nicolet 20DXB model spectrometer, Madison, WI). For FTIR spectra, the microspheres and KBr (IR grade) were thoroughly mixed. The mixture was pressed to form a pellet, and the spectrum was recorded over the wave number 4000–400 cm^{-1}.

Thermal Analysis

Thermogravimetric analysis (TGA) of the microspheres was performed at a heating rate of 5°C per min in the range of 35 to 600°C under high-purity nitrogen atmosphere (DuPont 2000, USA). The differential scanning calorimetric (DSC) analysis of the microspheres was performed at a heating rate of 5°C/min in the range of 35–200°C under high-purity nitrogen atmosphere (DuPont 2000). The DSC traces were recorded for finding the transitional changes in the polymeric spheres.

RESULTS AND DISCUSSION

Poly(MMA) core microspheres were prepared by free-radical initiation technique as described in the experimental section. On these core microspheres, HEMA was polymerized by swelling PMMA microspheres with the HEMA monomer by using ammonium persulfate and ascorbic acid. Crosslinking monomers such as EGDMA was also included along with HEMA for polymerization. By this technique, it was possible to obtain core–shell-type microspheres. The core is hard PMMA microspheres and the shell is a hydrophilic poly(HEMA) coat on the PMMA microsphere. In these core–shell microspheres, an anti-inflammatory drug such as ibuprofen was loaded by swelling with benzyl alcohol. PMMA microspheres with 20% PEG 1000 gave satisfactory results in terms of particle size and surface texture of microspheres when compared to other concentrations of PEG 1000. The yield of core microspheres was calculated and found to be 92%.

Particle Size Analysis

The particle size distribution curve of PMMA core microspheres (with 20% of PEG 1000) and poly(MMA-HEMA) copolymeric core–shell hydrogel microspheres are shown in Figure 1(a,b). It is evident from the distribution curve that the mi-

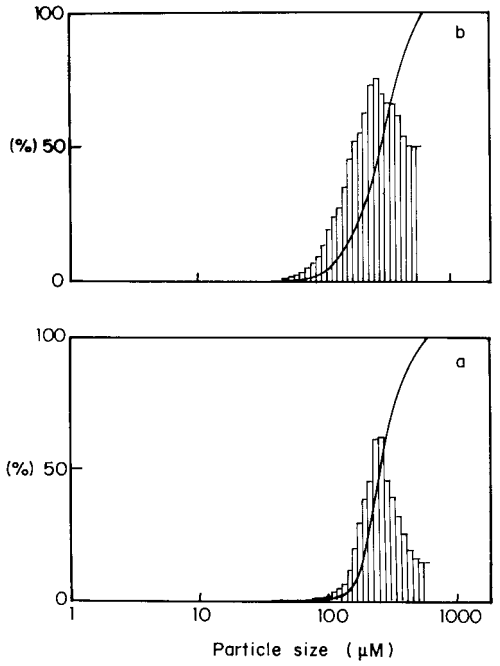

Figure 1 Particle size distribution curve of (a) PMMA core microspheres and (b) poly(MMA-HEMA) core–shell hydrogel microspheres.

crospheres are narrowly distributed. As shown in Figure 1(a), 65% of the microspheres fall in the size range of 200–300 μ with the volume average diameter of 250 μ. Figure 1(b) shows the particle size distribution of core–shell microspheres. It can be observed from the particle size distribution curve that 80% of the microspheres fall in the size range of 250–350 μ with the volume average diameter of 300 μ. Tables I and II show the particle size distribution of PMMA core microspheres by using various molecular weights of PEG and various weight percentages of PEG 1000, respectively.

Table I Average Particle Size of PMMA Core Microspheres with Different Molecular Weights of PEG

Molecular Weights of PEG	Average Particle Size (μm)
200	150 ± 4
400	185 ± 7
600	215 ± 3
1000	250 ± 5
1500	350 ± 4
4000	370 ± 6

Table II Average Particle Size of PMMA Core Microspheres with Various Concentrations of PEG 1000

Concentrations of PEG 1000 (%)	Average Particle Size (μm)
5	380 ± 6
10	360 ± 5
20	250 ± 7
30	230 ± 4
40	210 ± 5

Optical Microscopy

Figure 2(a,b) shows the representative optical micrographs of dried and swollen PMMA core microspheres. The optical micrographs of dried and swollen poly(MMA-HEMA) copolymeric core–shell microspheres are shown in Figure 2(c,d), respectively. It can be observed from these figures that the microspheres are spherical in shape and uniform and are well dispersed. These copolymeric core–shell microspheres were highly swollen in benzyl alcohol, when compared to PMMA core microspheres. The surface morphology of copolymeric core–shell microspheres was different from PMMA core microspheres as expected. Poly(HEMA) shell was seen coated on the PMMA core.

Scanning Electron Microscopy

The representative SEMs of PMMA core and poly(MMA-HEMA) copolymeric core–shell microspheres are shown in Figure 3(a,b), respectively. These figures show the rough surface in the core–shell microspheres due to HEMA coating. The core–shell microspheres indicated high porosity (hydrophilic) as compared to PMMA (hydrophobic) microspheres. The spherical nature of PMMA core and its core–shell microspheres and their uniformity were shown by the SEM studies. By taking advantage of the higher porosity and hydrophilic nature of core–shell microspheres, it is possible to incorporate higher amounts of both hydrophilic and hydrophobic drugs and also growth factors into the microspheres.

FTIR Spectroscopy

The FTIR spectra indicated the details of functional groups present in the PMMA core and poly(MMA-HEMA) copolymeric core–shell hydrogel microspheres. Figure 4(a,b) shows the FTIR

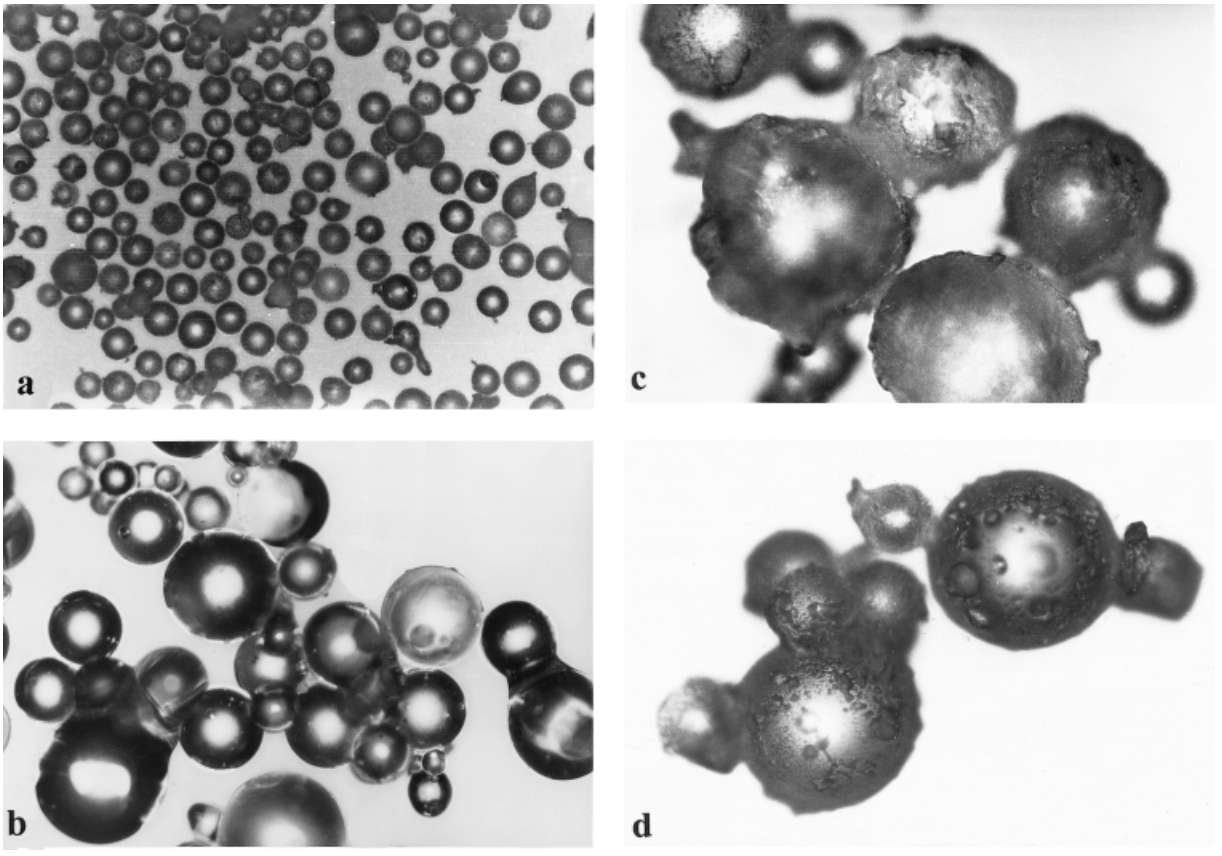

Figure 2 Representative optical micrographs of (a) PMMA core microspheres before swelling; (b) PMMA core microspheres after swelling; (c) poly(MMA-HEMA) copolymeric core–shell hydrogel microspheres before swelling; and (d) poly(MMA-HEMA) core–shell hydrogel microspheres after swelling (swelling medium: benzyl alcohol.).

spectra of PMMA core and poly(MMA-HEMA) copolymeric core–shell microspheres. PMMA spectrum contains strong adsorption at 2950 and 1730 cm^{-1} that corresponds to aliphatic C—H and carbonyl C═O stretches, respectively. Several medium to strong bands in the 1610–1300 cm^{-1} region were due to CH_3 and CH_2 deformations, and a strong band at 1260 cm^{-1} was due to mixing between CH_3 rock and C—C stretching vibrations.[28,29] Two strong bands at 1077 and 1000 cm^{-1} were due to C—O—C asymmetric and symmetric vibrations, respectively. The infrared spectrum of core–shell microspheres contained strong absorption at 3435 cm^{-1} (this peak did not appear in the PMMA core microspheres spectrum) and 2952 cm^{-1} that corresponded to O—H and C—H stretching vibrations, respectively. A sharp intense band was found at 1731 cm^{-1}, corresponding to the C═O stretching vibration. In addition, medium to strong bands observed in the 1610–1300 cm^{-1} region are due to C—O—C stretching vibrations. The IR spectroscopic data clearly indicated the presence of poly(HEMA) shell coat on the PMMA core microspheres.

Thermogravimetric Analysis

To unequivocally attribute changes in polymer thermal properties to effects of alkali halides, it was first necessary to characterize the polymers by using the same analysis techniques that would be used to study polymer matrix. Because the PMMA and poly(MMA-HEMA) copolymeric core–shell hydrogel microspheres used in this study were synthesized by free-radical polymerization, some polymer chain ends were caused by radical combination and radical disproportion, respectively. During TG analysis, both microspheres exhibited decompositions with no observable residue. As shown in Figure 5(a), sample weight loss

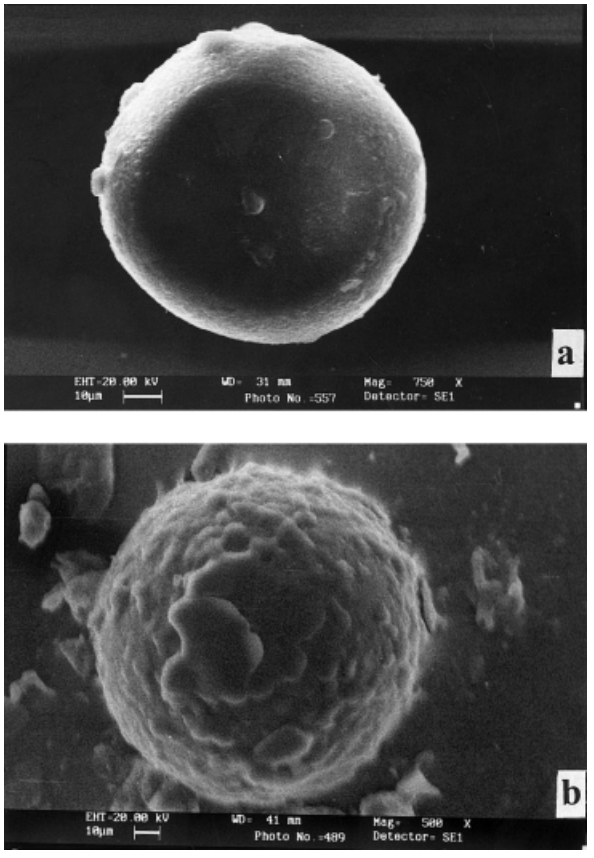

Figure 3 A representative scanning electron micrograph of dried microspheres: (a) PMMA core microspheres; and (b) poly(MMA-HEMA) core–shell hydrogel microspheres.

during the thermal degradation of PMMA core microspheres occurred in three distinct steps. The first step, attributed to unzipping after initial cleavage of head-to-head linkages, reaches a maximum weight loss rate at 187°C and resulted in ~ 5% total weight loss. The second step, attributed to initial β-scission at vinylidene chain ends followed by unzipping, reached a maximum weight loss rate at 300°C and was characterized by a 20% sample weight loss. The third degradation step, due to unzipping after random chain cleavage, reached a maximum weight loss, resulting in the decomposition of the remaining polymer. The weight loss curve for the thermal degradation of poly(MMA-HEMA) core–shell microspheres [Fig. 5(b)] consisted of four stages. The relative magnitude and the widths of copolymeric derivative weight peaks detected at 198 and 305°C were similar to those for the two PMMA weight-loss steps that occurred at comparable temperatures. The first two weight loss steps of copolymeric microspheres were likely caused by the same process attributed to the first two PMMA core microspheres weight loss steps. Unlike PMMA, the weight loss curve for the copolymer indicated that at least two thermal degradation processes occurred between 350 and 450°C during poly(HEMA) thermal degradation and exhibited that more than one variable product was produced in this temperature range.

Differential Scanning Calorimetric Analysis

DSC was used for measuring the glass transition temperature of the synthesized PMMA and poly(MMA-HEMA) core–shell microspheres. Figure 6(a,b) shows the normalized DSC traces of PMMA and core–shell microspheres. The traces indicated that the glass transition temperatures occurred at 155 and 240°C, respectively, for the

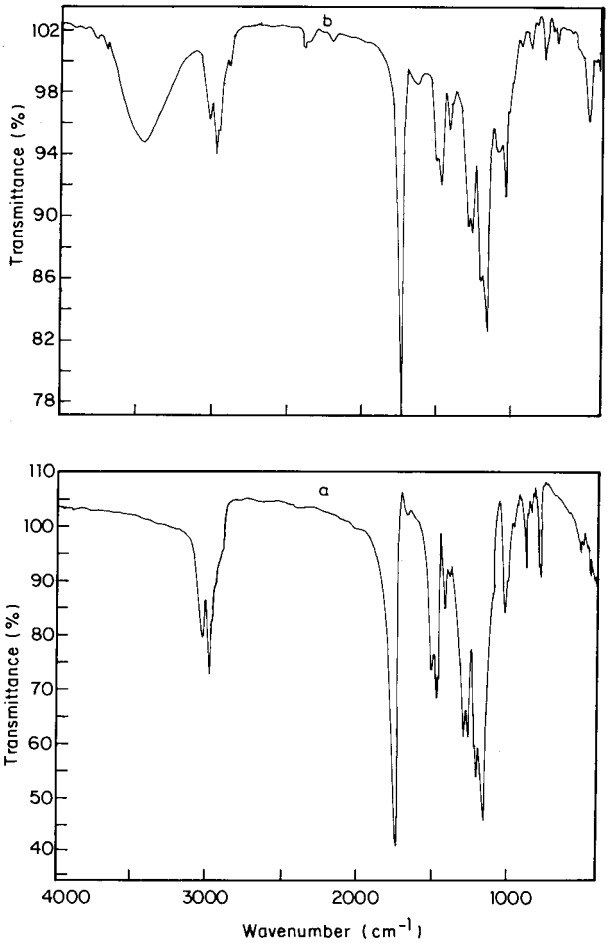

Figure 4 FTIR spectra of (a) PMMA core microspheres and (b) poly(MMA-HEMA) core–shell hydrogel microspheres.

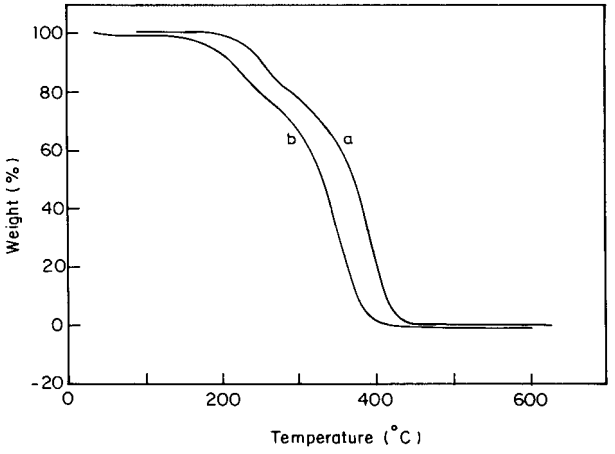

Figure 5 TGA traces of (a) PMMA core microspheres and (b) poly(MMA-HEMA) core–shell hydrogel microspheres.

synthesized PMMA and copolymeric hydrogel polymeric microspheres.

Swelling Studies of PMMA Core and Poly(MMA-HEMA) Copolymeric Core–Shell Hydrogel Microspheres

Porosity and surface area of the polymeric microspheres are the most important functional characteristics in many applications. PMMA spheres suspended in benzyl alcohol are found to swell more than two times that of their dry radius and were observed to undergo an equilibrium phase transition from liquid to crystalline structure with increasing concentration. Homogeneous

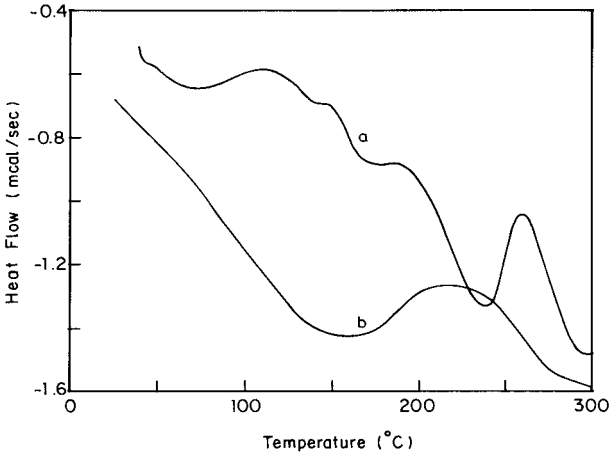

Figure 6 DSC traces of (a) PMMA core microspheres and (b) poly(MMA-HEMA) core–shell hydrogel microspheres.

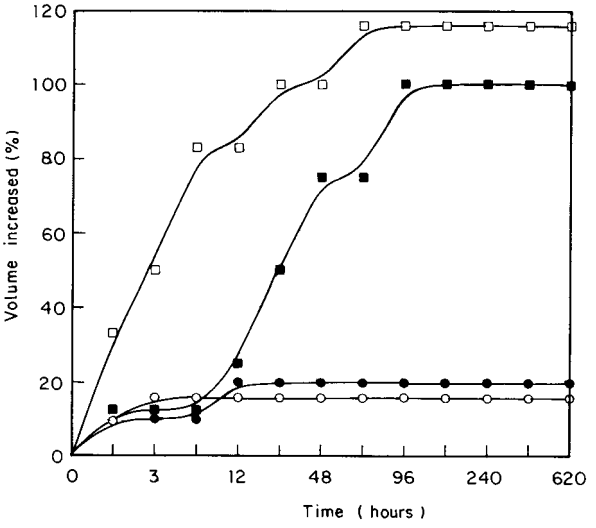

Figure 7 Swelling behavior of PMMA core microspheres (○, water; ■, benzyl alcohol) and poly(MMA-HEMA) copolymeric core–shell hydrogel microspheres (●, water; □, benzyl alcohol) by volume fraction.

PMMA core microspheres were swollen in water to a maximum of about 10% at equilibrium for 3 h, whereas in benzyl alcohol, the core PMMA microspheres swelled to a maximum of about 95% at equilibrium for 96 h. In the case of poly(MMA-HEMA) copolymeric core–shell microspheres, the equilibrium swelling values changed from 20% in water to 118% in benzyl alcohol at 72 h.

Figure 7 illustrates the swelling properties of PMMA core and poly(MMA-HEMA) core–shell microspheres by weight ratio method. These curves clearly show the significant effect of increasing the swelling levels of both the synthesized PMMA and the poly(MMA-HEMA) copolymeric core–shell microspheres in water and benzyl alcohol medium. The copolymers exhibit similar time scales in approaching equilibrium. Generally, half of the saturated weight gain was achieved in the first 24 h after immersion, and the saturation weight gain was reached in about 96 h for both microspheres in benzyl alcohol. After the 96 h, swelling was very slow and practically stopped after about 160 h. The equilibrium swelling values were changed by 2% for PMMA microspheres in water medium, whereas in benzyl alcohol, the equilibrium swelling value of PMMA was about 45%. In the case of core–shell microspheres, the equilibrium swelling values changed by 35% for water medium and 80% for benzyl alcohol. The swelling was also confirmed from the optical microscopic studies.

Table III Percentage Loading and *In Vitro* Release of Ibuprofen from PMMA Core and Poly(MMA-HEMA) Copolymeric Core–Shell Hydrogel Microspheres: Results Expressed as Mean ± SD (n = 3)

	Amount of Ibuprofen in Loading in Benzyl Alcohol (mg)		% Loading of Ibuprofen	*In Vitro* Release of Ibuprofen (days)
	Initial	Final		
PMMA core microspheres	50	32.2 ± 0.81	35.6 ± 1.62	11
Poly(MMA-HEMA) copolymeric core–shell hydrogel microspheres	50	25.66 ± 1.16	48.7 ± 2.33	16

Percentage Loading of Ibuprofen into PMMA Core and Poly(MMA-HEMA) Copolymeric Core–Shell Hydrogel Microspheres

PMMA core and poly(MMA-HEMA) copolymeric core–shell hydrogel microspheres were loaded with 17.8 and 24.34 mg of ibuprofen, respectively, by immersing the microspheres in 5 mL benzyl alcohol at 10 mg ml^{-1} concentration for 48 h. The percentage loading of ibuprofen in the microspheres was calculated by using the formula given in experimental section. The percentage loading of ibuprofen was found to be 35.6 ± 1.62 and 48.7 ± 0.94% for PMMA core and poly(MMA-HEMA) core–shell hydrogel microspheres, respectively (Table III).

From these results, it can be observed that poly(MMA-HEMA) core–shell hydrogel microspheres have taken up higher amounts of ibuprofen as expected than PMMA core microspheres. It can be explained that the higher loading efficiency of poly(MMA-HEMA) microspheres in benzyl alcohol can be attributed to the higher swelling (hydrophilic) and porous nature of these microspheres, which might have allowed a slightly higher amount of drug into the microspheres.

In Vitro Release of Ibuprofen from PMMA Core Microspheres and Poly(MMA-HEMA) Copolymeric Core–Shell Microspheres in Phosphate Buffer

Figure 8 shows the *in vitro* release profiles of ibuprofen from PMMA and poly(MMA-HEMA) core–shell microspheres in phosphate buffer (pH 7.4). PMMA microspheres released 60.8% of ibuprofen by 11 days, whereas poly(MMA-HEMA) core–shell microspheres released 87.3% of the drug by 16 days. Both the microspheres released the loaded ibuprofen in a near zero-order fashion. These results clearly indicated that the poly(MMA-HEMA) core–shell microspheres released the encapsulated drug in a controlled manner for a prolonged period of time than the PMMA microspheres. The formation of the HEMA coat over the PMMA core microspheres by polymerization technique could have been controlled on the release of the encapsulated ibuprofen in phosphate buffer. The above prepared PMMA core and poly(MMA-HEMA) core–shell microspheres with the incorporated ibuprofen will have a great potential for bone regeneration and repair.

CONCLUSION

A novel method of poly(MMA-HEMA) copolymeric core–shell hydrogel microspheres was success-

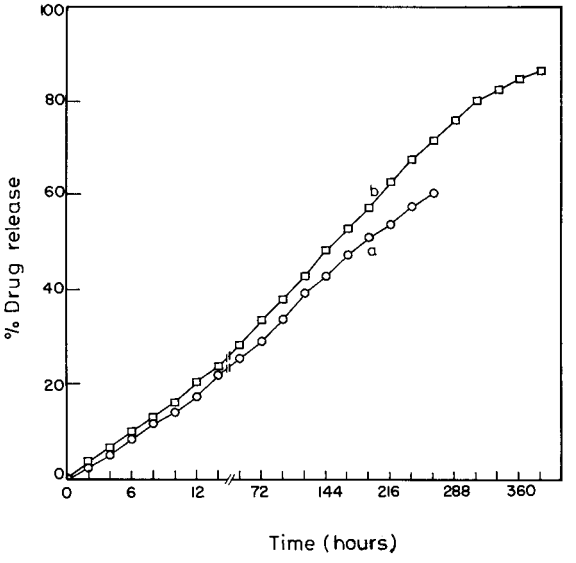

Figure 8 *In vitro* release curve of ibuprofen from (a) PMMA core microspheres and (b) poly(MMA-HEMA) core–shell hydrogel microspheres.

fully prepared for potential applications in orthopedics and dentistry. It is evident from FTIR data that the poly(HEMA) was coated on the PMMA core microspheres. A particle-size analyzer determined the particle size of both microspheres. Thermal studies clearly indicated the hydrophilic nature of core–shell microspheres and the hydrophobic nature of PMMA core microspheres. SEMs and optical micrographs clearly indicated that the poly(HEMA) was coated on the PMMA core microspheres. The swelling experimental data shows that the core–shell microspheres were more swollen than the PMMA core microspheres. *In vitro* release of ibuprofen from poly(MMA-HEMA) core–shell hydrogel microspheres released the loaded drug in a controlled manner for prolonged periods of time than the PMMA microspheres.

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