Preparation and Characterization of Novel Semi-Interpenetrating 2-Hydroxyethyl Methacrylate-*g*-chitosan Copolymeric Microspheres for Sustained Release of Indomethacin

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ABSTRACT: A novel semi-interpenetrating (semi-IPN) graft copolymer of 2-hydroxyethyl methacrylate (HEMA) with chitosan (CS) has been prepared in the form of microspheres, using water-in-oil (W/O) emulsion technique. Microspheres were characterized by Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and X-ray diffractometry (X-RD) to confirm the crosslinking and polymorphism of indomethacin (IDM). The X-RD and DSC techniques indicated a molecular-level dispersion of IDM in the IPN matrix. Scanning electron micrographs (SEM) taken at the cross section of the microspheres have shown rough surfaces around the microspheres. The sustained release characteristics of the matrices for IDM, an anti-inflammatory drug, were investigated in pH 7.4 media. Particle size and size distribution of the microspheres were studied by laser light diffraction particle size analyzer. The drug was released in a sustained manner for up to 12 h. © 2006 Wiley Periodicals, Inc. J Appl Polym Sci 106: 3778–3785, 2006

Key words: chitosan; 2-hydroxyethyl methacrylate; semi-IPN; microspheres; indomethacin; sustained release

INTRODUCTION

Among the many polymeric systems investigated for sustained release (CR) applications, the prime attention has been focused on natural, synthetic as well as combination of both types of polymers.[1–4] Natural polymers are more preferred because of their biocompatibility and biodegradability, but there are some synthetic polymers that exhibit biocompatibility under physiological conditions. However, a combination of judicially selected natural and synthetic polymers is more useful in enhancing the release of short half-lived drugs under extreme physiological conditions. To achieve this, properties of natural[5–7] or synthetic[8,9] polymers can be modified by graft copolymerization, blending, etc. Grafting of vinyl monomers onto natural polymers such as cellulose has been widely attempted. In continuation of our ongoing studies, the present study deals with the development of semi-interpenetrating (semi-IPN) network polymer prepared by grafting hydroxyethyl methacrylate (HEMA) onto chitosan (CS). Microspheres were developed from these polymers to study the CR of indomethacin (IDM), an anti-inflammatory drug.

Chitosan (CS), obtained from the deacetylation of chitin, is one of the most facile polymers, whose structure can be modified chemically.[10,11] It is more widely used in biomedical applications than chitin itself because it degrades in an aqueous environment because of the presence of hydroxyl and amino groups, which can be readily modified.[12,13] The key characteristics of CS in such applications are its biocompatibility, nonantigenicity, nontoxicity (its degradation products are the well-known natural metabolites), ability to improve wound healing and blood clotting as well as its ability to absorb liquids, form protective films and coatings, etc.[14] Poly(hydroxyethyl methacrylate) (PHEMA) has good biocompatibility and mechanical strength required for biomedical applications. PHEMA is a hydrogel that swells, but is insoluble in water and hence, it possesses the ability to retain water within its structure.[15,16] PHEMA is one of the most frequently used polymers in CR applications because of its good performance

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in addition to its biocompatibility and hydrolysis under physiological conditions.[17,18] PHEMA hydrogels have been the better candidates for implantable applications, including bio-hybrid artificial organs,[19] since they can be lightly crosslinked and can be produced by bulk polymerization, making them transparent and homogeneous with a porous structure having pore sizes in the nanometer[20] dimensions, and thus, these polymers are suited for applications, for which the combination of optical clarity and limited diffusional characteristics is required.[21,22]

Among the class of nonsteroidal anti-inflammatory drugs (NSAIDs) that are widely used as analgesics in the treatment of local and systemic inflammatory pathologies, IDM has been the extensively used, which upon administration will produce the side ulcerogenic effect in the gastrointestinal tract (GIT). Its limited efficacy coupled with a strong predisposition to cause the GIT-associated adverse effects and nephrotoxicity via conventional routes prompted the use of biocompatible polymers to develop CR formulations. IDM is effective in the management of rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, and acute gout.[23] The optimization of systemic profile of IDM by its sustained input of the drug via transdermal route was able to reduce the GIT irritation, but producing the central nervous system (CNS) related side effects.[24] In the present study, IDM was chosen as a model drug, which was loaded before crosslinking of the polymer. Advantages of such formulations over the conventional dosage forms have been reported earlier,[25,26] because these will help to minimize the serious gastric irritation side effects that are common of the conventional dosage NSAID formulations. The high incidence and severity of side effects, which are dose-related and associated with long-term administration, have limited its use.[27] This has led to search for new delivery systems that will overcome the side effects by controlling its release.[28]

Several formulations of IDM-loaded microspheres have been developed earlier[29] by different microencapsulation techniques using a variety of polymers. The effectiveness of nanoencapsulation in reducing the side effects of pristine IDM have been described earlier.[30–32] In this study, semi-IPNs of HEMA-*g*-CS graft copolymers have been prepared and characterized by Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), X-ray diffractometry (X-RD), and scanning electron micrography (SEM) techniques. Microspheres have been prepared by oil-in-water emulsion method with *in situ* loading of IDM before adding glutaraldehyde (GA) as a crosslinking agent. Different formulations were prepared by varying the amount of crosslinking agent and drug content to achieve the CR patterns for IDM.

EXPERIMENTAL

Materials and methods

High-molecular-weight chitosan (CS; MW = 800,000), 2-hydroxyethyl methacrylate (HEMA) and Tween-80 were purchased from Sigma Aldrich (Milwaukee, WI). Potassium persulfate, GA, and light liquid paraffin oil were purchased from S.D. Fine Chemicals, Mumbai, India. IDM drug was purchased from Himedia Chemicals, Mumbai, India.

Preparation of CS-HEMA semi-IPNs

Varying amounts of CS were weighed and dissolved in 2% acetic acid solution under constant stirring overnight. To this solution, required amounts of HEMA and potassium persulfate were added and stirred well. The reaction mixture was polymerized under inert nitrogen atmosphere for 6 h at 70°C. The polymerized product was cooled and the solid polymer was extracted by precipitating the reaction product in acetone. The precipitated polymer was dried under vacuum for 24 h. Then, 0.5 g of the dried polymer was weighed and dissolved in 2% acetic acid solution. To this, a required amount of IDM was added and stirred to obtain a homogeneous solution.

The drug powder was filtered through 0.2 mm aperture sieve and mixed into the final polymerized mixture. The drug-loaded polymer mixture was emulsified by liquid paraffin (100 mL) with 1% (w/v) Tween-80 taken in a 500-mL beaker and agitated at 400 rpm with a three-blade propeller stirrer (diameter = 5 cm), linked to a stirring motor (Eurostar; IKA Labortechnik, Germany). The complex comprising of CS and PHEMA was prepared by polymerizing HEMA in the presence of CS. This complex was crosslinked with GA, which can crosslink —OH and —NH_2 groups of CS instead of —OH groups of HEMA, resulting in the formation of a semi-IPN structure.

The microspheres were prepared by water-in-oil emulsion technique.[33] To this mixture, different amounts of GA and 1 mL of 0.1*M* HCl were added. Microspheres formed were collected in a Buchner funnel, washed with 50 mL of ether, dried at room temperature for 24 h, and stored in a desiccator before further experimentation. Totally, eight formulations were prepared by varying the amount of GA, HEMA, and IDM as well as pure CS microspheres with 5 mL GA and 10 wt % IDM.

Fourier transform infrared spectroscopy

FTIR spectra were recorded using a Nicolet spectrophotometer (Model Impact 410, USA) to confirm the presence of crosslinking in CS-HEMA matrix.

TABLE I
Results of % Encapsulation Efficiency and Mean Particle Size of Different Formulations

Formulation no.	% HEMA in microspheres	% Indomethacin loaded	Crosslinking agent (GA, in mL)	% Encapsulation efficiency	Mean particle size ± SD (μm)
1	–	10	5	55.0 ± 2.5	75 ± 5
2	10	10	5	59.9 ± 1.6	101 ± 5
3	20	10	5	65.9 ± 2.4	146 ± 5
4	30	10	5	72.7 ± 1.8	185 ± 5
5	20	5	5	68.1 ± 1.4	110 ± 5
6	20	20	5	82.7 ± 1.9	153 ± 7
7	20	10	2.5	72.2 ± 1.8	113 ± 6
8	20	10	7.5	50.5 ± 1.4	88 ± 4

SD = standard deviation calculated at 95% confidence limit.

Semi-IPN microspheres were finely ground with KBr to prepare pellets using a hydraulic pressure of 400 kg to scan the spectra between 400 and 4000 cm^{-1}.

Differential scanning calorimetry

DSC curves of the plain CS, placebo CS-HEMA microspheres, plain IDM, and IDM-loaded microspheres were recorded using a Rheometric Scientific differential scanning calorimeter (Model-DSC SP, London, UK). The analysis was performed by heating the samples at the rate of 10°C/min in an inert atmosphere.

X-ray diffraction studies

X-RD patterns of the placebo beads, plain IDM, plain CS-HEMA microspheres, and IDM-loaded microspheres were recorded using a Rigaku Geigerflex diffractometer equipped with Ni-filtered CuK[acute]α radiation (λ = 1.5418 Å). Dried microspheres of uniform size were mounted on a sample holder and X-RD patterns were recorded in the range of 0°–50° at the speed of 5°/min.

Scanning electron microscopy

Cross-sectional SEM image of the IDM-loaded microspheres were recorded using a Leica 400, Cambridge, UK, scanning electron microscope at 35× magnification. A working distance of 39 mm was maintained and the acceleration voltage used was 25 kV with the secondary electron image (SEI) as a detector. Samples were coated with gold to neutralize the charging effects.

Particle size analysis

Particle size of the microspheres was measured by using particle size analyzer (Mastersizer 2000, Malvern Instruments, UK). About 100 mg of the microspheres were transferred to a dry sample holder and stirred vigorously to avoid agglomeration of the microspheres during data acquisition. For size measurement of different formulations/batches, the sample holder was cleaned by vacuum. Particle size of microspheres was also measured using optical microscopy.

Estimation of drug loading and encapsulation efficiency

Specific amounts of dry microspheres were vigorously stirred in a beaker containing 10 mL of dichloromethane to extract IDM from the semi-IPN particles. About 10 mL of 7.4 pH phosphate buffer containing 0.02% Tween-80 solution was added to the above solution, and dichloromethane was evaporated with a gentle heating and continuous shaking. The aqueous solution was filtered and assayed by UV spectrophotometer (model Anthelie, Secomam, Dumont, France) at the fixed λ_{max} value of 320 nm. The encapsulation efficiency is given by two digits with SD, which was measured by diffusion method, i.e., the microspheres were dispersed in a buffer solution and made to swell. The release of drug into the buffer solution was measured spectrophotometrically. The results of % IDM loading and encapsulation efficiency were calculated using eqs. (1) and (2), respectively. These results are compiled in Table I.

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

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

In-vitro release

In vitro release studies have been carried out by performing the dissolution experiments using a tablet dissolution tester (LabIndia, Mumbai, India) equipped with eight baskets. Dissolution rates were measured at

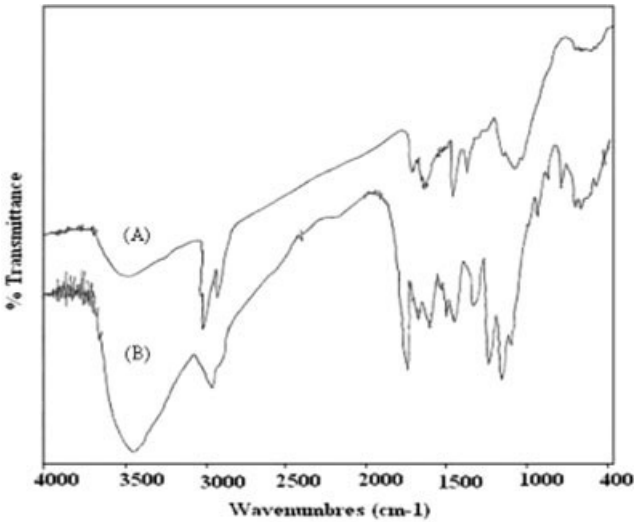

Figure 1 FTIR spectra of (A) crosslinked CS-HEMA microspheres and (B) uncrosslinked CS-HEMA microspheres.

37°C under 100 rpm speed. Drug release from the microspheres was studied in an intestinal (7.4 pH phosphate buffer) fluid. At regular intervals of time, sample aliquots were withdrawn and analyzed by UV spectrophotometer (Model Anthelie) at the fixed λ_{max} value of 320 nm.

RESULTS AND DISCUSSION

Fourier transform infrared spectroscopy

Figure 1 compares FTIR spectra of (A) CS-HEMA crosslinked with GA and (B) uncrosslinked CS-HEMA microspheres. In case of uncrosslinked CS-HEMA, there is a broad peak at 3450 cm^{-1}, which is due to the presence of hydroxyl and amine group of CS. An increase in peak intensity at 1022 cm^{-1} is due to an increase in the extent of crosslinking due to the formation of acetal ring and ether linkage, resulting from the reaction between amine groups of chitosan and aldehydic groups of GA [Fig. 1(B)]. The peak at 1133 cm^{-1} is attributed to C—O stretching mode in HEMA, while the peak at 819 cm^{-1} is due to O—H out-of-plane motion of the carboxylic group in HEMA.

Differential scanning calorimetry

DSC thermograms of pure IDM, plain CS, IDM-loaded CS-HEMA, and plain CS-HEMA microspheres are displayed in Figure 2. IDM shows a sharp peak at 160°C because of polymorphism and melting, but in case of IDM-loaded microspheres, no characteristic peak was observed at 160°C [Fig. 2(C)], suggesting that IDM is molecularly dispersed in the IPN matrix. A peak at 250°C corresponding to HEMA was observed in the DSC thermograms viz., Figures 2(C) and 2(D), which is absent in pure CS [Fig. 2(A)].

X-ray diffraction

X-RD analysis provides a clue about the crystallinity of the drug in the microspheres. X-RD patterns recorded for IDM, IDM-loaded microspheres, and placebo microspheres are presented in Figure 3. For IDM, the major peaks are observed at a 2θ of 17°, 20°, 22°, 24°, 26°, and 29°, suggesting its crystalline nature [Fig. 3(A)]. Figure 3(C) represents the plain HEMA-*g*-CS micropsheres, which are amorphous in nature, as confirmed by X-RD. Figure 3(B) represents the X-RD spectra of IDM-loaded HEMA-*g*-CS micropsheres, which shows the amorphous nature even after loading IDM, suggesting that the crystalline nature of IDM might have been reduced. Further, IDM particles are molecularly dispersed in the microspheres, since no indication about its crystalline nature was observed in the drug-loaded microspheres.

Scanning electron microscopy

Figure 4 shows the cross-sectional SEM micrograph of IDM-loaded CS-HEMA microspheres. Cross sec-

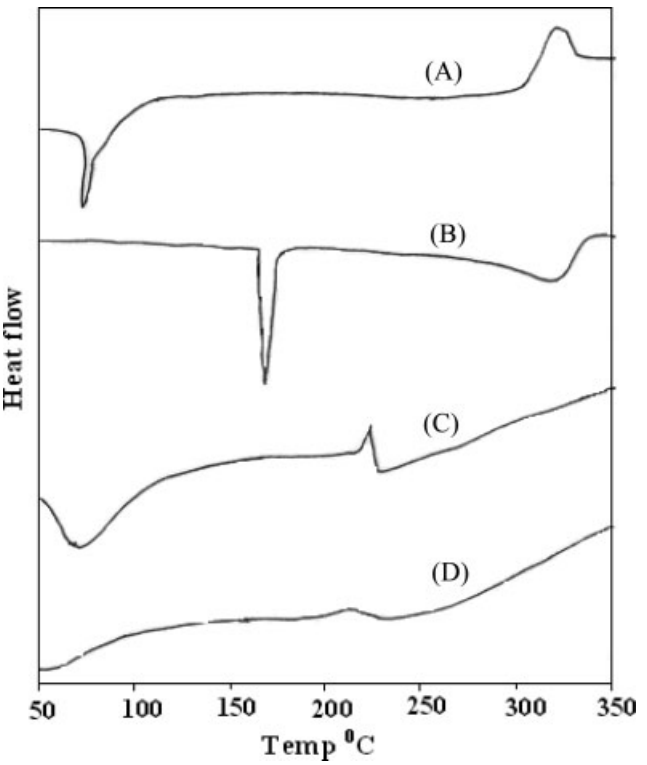

Figure 2 DSC thermograms of (A) pure CS, (B) plain indomethacin, (C) IDM-loaded CS-HEMA microspheres, and (D) plain CS-HEMA microspheres.

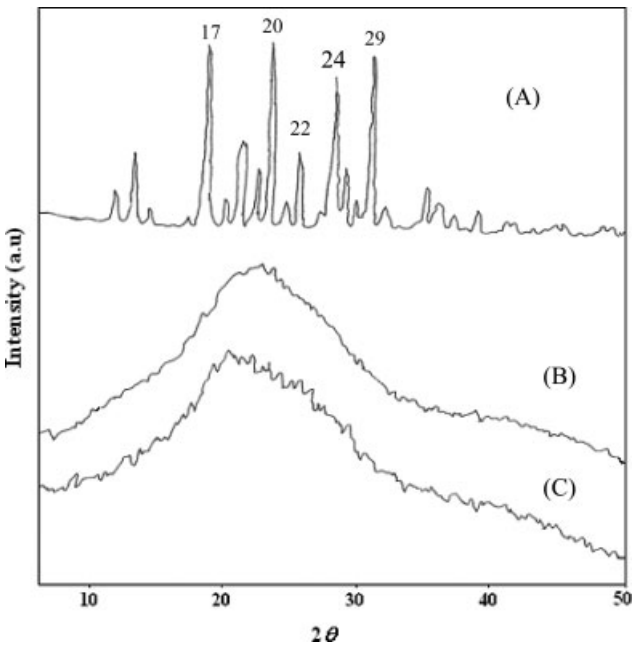

Figure 3 X-RD spectra of (A) plain Indomethacin, (B) IDM-loaded CS-HEMA microspheres, and (C) plain CS-HEMA microspheres.

tion of the CS-HEMA microspheres show corrugated structures that are common with the graft copolymers.

Particle size

Particle size and size distributions have been analyzed by laser light diffraction technique (Mastersizer-2000). Results of volume mean diameter of the microspheres produced by taking three different amounts of crosslinking agent are included in Table I. These results suggest that as the extent of crosslinking increases, the volume mean diameter decreased. On a population basis, particle size distribution is unimodal. Microspheres used in preparing the drug-loaded formulations were selected from a uniform size distribution range as displayed in Figure 5. A narrow size distribution of microparticles was observed with particles ranging from 80 to 500 μm, but majority of particles are in the size range between 180 and 200 μm.

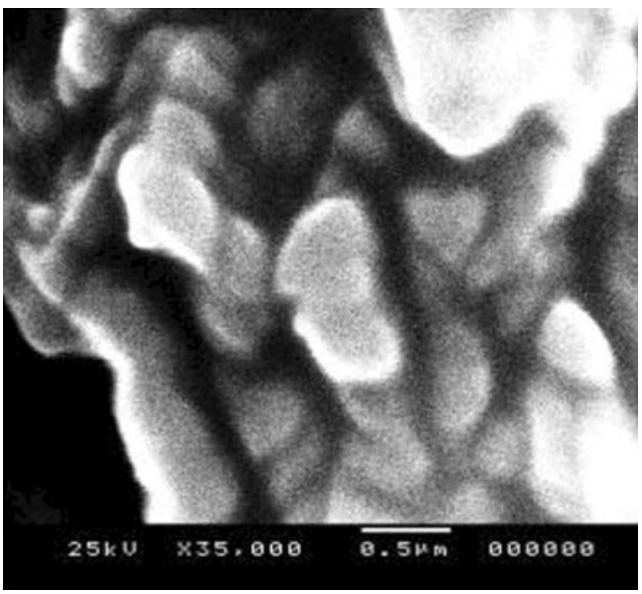

Figure 4 Cross-sectional scanning electron micrograph of drug-loaded CS-HEMA microsphere.

Microscopic study

Particle size was also measured alternatively by optical microscopy. These results along with % encapsulation efficiency, % drug-loading, and mean particle size for different formulations are presented in Table I. The size of particles depends on the amount of

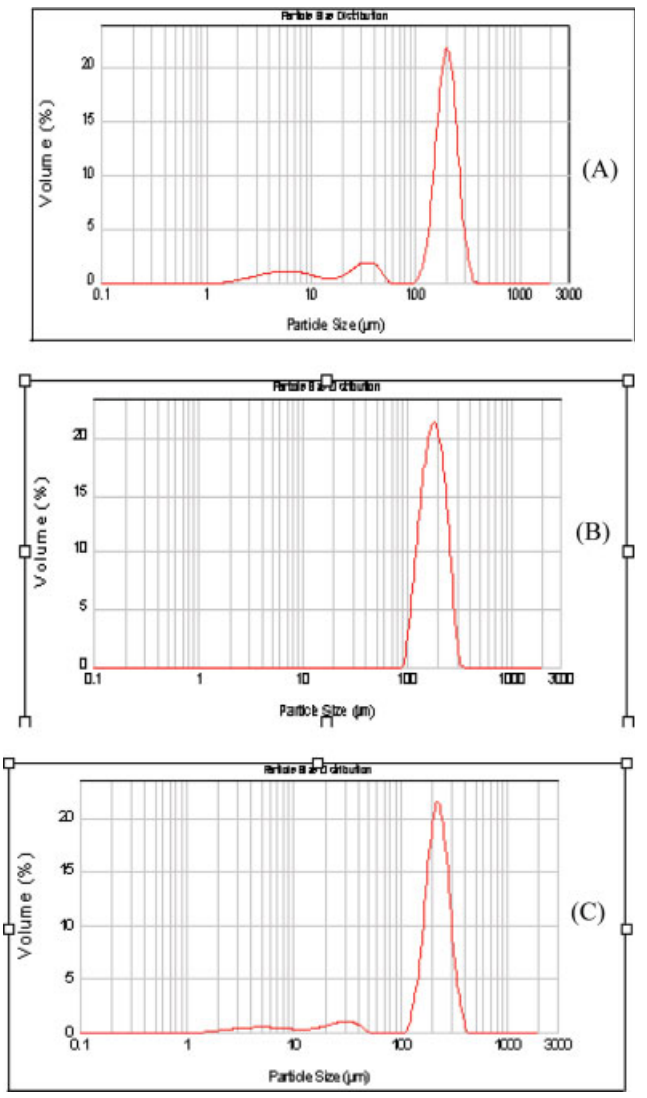

Figure 5 Particle size distribution curve for CS-HEMA microspheres with different amount of crosslinking agent: (A) 7.5 mL, (B) 5 mL, and (C) 2.5 mL. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

drug present, % HEMA content, and extent of GA employed. Particles are generally spherical in shape with sizes ranging from 75 to 185 μm. Particle size of the pristine CS is smaller than those of the CS-HEMA microspheres. By increasing the HEMA content of the microspheres, size of the microspheres increased from 101 to 185 μm for 10% IDM-loaded microspheres. This can be explained on the basis of hydrodynamic viscosity concept, i.e., as the amount of HEMA in the microspheres increases, interfacial viscosity of the polymer droplets in the emulsion also increases, because HEMA has more water-uptake capacity than CS, which will hinder the breaking of the dispersed phase into smaller size particles during emulsification. As the CS content increases, the size of microspheres decreased because of the availability of more free sites for crosslinking. On the other hand, with increasing amount of HEMA, the number of free sites available for crosslinking is less so that size of the microspheres will also increase with increasing HEMA content of the microspheres; for instance, as the amount of HEMA increases from10% to 30%, the particle size has increased from 101 to 185 μm.

For all the formulations, with increasing amount of drug in the microspheres, particle size also increased. For formulations containing 20% HEMA and microspheres loaded with different amounts of drug, particle size has increased from 110 to 153 μm; a similar trend was also observed for all other formulations (Table I). This is attributed to the fact that drug molecules might have occupied the free volume spaces within the IPN matrix, thereby hindering the inward shrinkage of the polymer matrix.[34] The 10% IDM-loaded and 30% HEMA-containing microspheres exhibited the maximum particle size of 185 μm. However, the extent of crosslinking has shown an effect on the particle size (see data in Table I). For microspheres containing 20 wt % HEMA and 10 wt % IDM, with increasing amount of GA from 2.5 to 7.5 mL particle size decreased from 113 to 88 μm. This is attributed to the fact that with increasing amount of GA in the semi-IPN matrix, the shrinkage of particles has taken place, thereby reducing their size.[34,35]

Encapsulation efficiency

Three different concentrations of IDM, i.e., 5, 10, and 20 wt %, were loaded during crosslinking of the microspheres. Results of % encapsulation efficiency included in Table I show increasing trends with increasing drug loading. Encapsulation efficiency of 55% was observed for the pristine CS microspheres, but for the remaining formulations, it ranged from 59% to 82%. Such smaller values are due to less soluble drug in the polymer solution, thus making less amount of IDM to be incorporated into the microspheres. Notice that % encapsulation efficiency increased with increasing amount of HEMA in the semi-IPN matrix. For microspheres containing 10, 20, and 30 wt % HEMA and 10 wt % IDM, encapsulation efficiencies were 59.9%, 65.9%, and 72.7%, respectively. For 20% HEMA in the semi-IPN matrix, the results of size and encapsulation efficiency decreased with increasing amount of crosslinking agent (Table I). For microspheres crosslinked with 2.5, 5, and 7.5 mL of GA, encapsulation efficiencies are 72.2%, 65.9%, and 50.5%, respectively. Such a decreasing trend is due to increase in crosslink density, because the microspheres become rigid, thereby reducing the free volume spaces within the polymer matrix, and hence, a reduction in encapsulation efficiency.

TABLE II
Release Kinetics Parameters of Different Formulations

Formulation no.	k	n	Correlation coefficient, r
1	0.104	0.369	0.993
2	0.108	0.358	0.957
3	0.099	0.363	0.994
4	0.035	0.529	0.994
5	0.136	0.325	0.965
6	0.100	0.343	0.993
7	0.110	0.330	0.956
8	0.103	0.373	0.967

Drug release kinetics

Drug release kinetics was analyzed by plotting cumulative release data versus time by fitting to the empirical equation[35]:

$$\left(\frac{M_t}{M_\infty}\right) = kt^n \tag{3}$$

Here, M_t/M_∞ represents fractional drug release at time t, k is a constant characteristic of the drug–polymer system, and n is an empirical parameter characterizing the release mechanism. Using the least squares procedure, we have estimated the values of n and k for all the eight formulations developed; these values are given in Table II. If $n = 0.5$, drug diffuses and releases out of the polymer matrix following a Fickian diffusion or Case I. If $n > 0.5$, anomalous or non-Fickian transport occurs. If $n = 1$, non-Fickian or Case II release kinetics is prevalent. The intermediary values of n ranging between 0.5 and 1 indicate the anomalous transport.[36]

In the present research, values of k and n showed a dependence on the extent of crosslinking, % drug loading, and HEMA content of the semi-IPN matrix.

Values of n for microspheres prepared by using varying amounts of HEMA (10, 20, and 30 wt %) keeping IDM (10 wt %) and GA (5 mL) constant have ranged from 0.352 to 0.529, producing a slight deviation from the Fickian transport. The different amount of IDM-loaded microspheres have shown the n values ranging from 0.325 to 0.529, indicating a shift from the erosion type release to swelling-sustained non-Fickian transport. Correlation coefficients, r, obtained while fitting the release data fall in the range of 0.953–0.993, but non-Fickian trends are due to a reduction in the regions of low microviscosity and closure of microcavities in the swollen state of the semi-IPN matrix. Similar findings have been observed elsewhere[37] wherein the effect of different polymer ratios on the dissolution kinetics was investigated. The n values for formulations containing different amounts of HEMA, IDM and GA are <0.5 and 0.529. The values of $n < 0.5$ indicate a non-Fickian type diffusion, i.e., slight deviation from the Fickian trend.

Effect of HEMA content

The effect of HEMA content was studied at a constant loading of 10 wt % IDM. It was found that CS produced almost 100% cumulative drug release in about 10 h, whereas CS-HEMA microspheres produced up to 90% cumulative release in 12 h. Release of CS-HEMA microspheres prepared with different amounts of HEMA is displayed in Figure 6(A). This could be due to the fact that during dissolution, microspheres have systematically swollen with an increasing amount of HEMA, due to the formation of loosely crosslinked network chains of HEMA. Thus, a relaxation-type response of the polymeric chains might be possible due to stresses induced by the surrounding solvent medium during the dissolution, resulting in an increase of chain dimension (radius of gyration) of the polymer; this will increase the molecular volume of the hydrated polymer due to increased swelling of HEMA component of the semi-IPN, reducing the free volume space of the matrix. The nature of release profiles remains almost identical in all the formulations containing different amounts of GA, indicating that swelling of HEMA establishes a linear relationship with their release profiles.

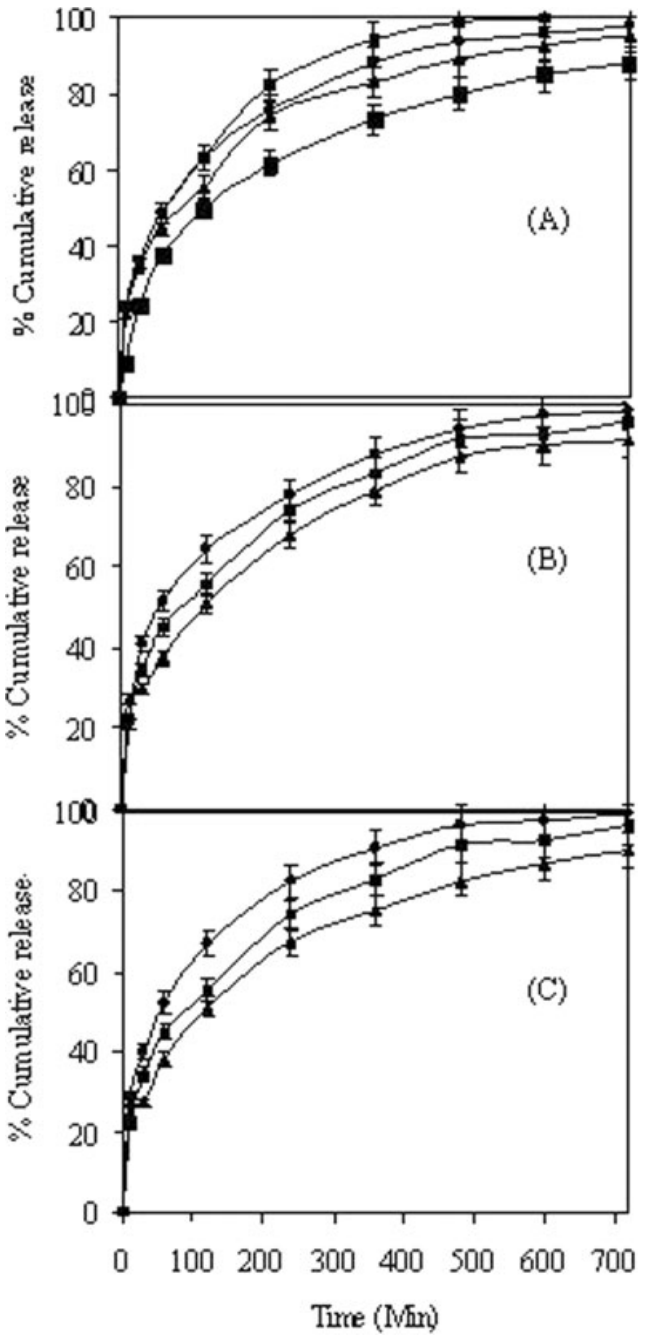

Figure 6 % Cumulative release of IDM through CS-HEMA microspheres containing (A) different amounts of HEMA: (■) pure CS, (■) 10%, (▲) 20%, and (●) 30%; (B) different amounts of IDM: (●) 20%, (■) 10%, and (▲) 5%; and (C) different amounts of GA: (●) 2.5 mL, (■) 5 mL, and (▲) 7.5 mL.

Effect of drug loading

Figure 6(B) shows the release profiles of IDM-loaded microspheres of CS-HEMA at different amounts of drug loadings. The formulations exhibited lower encapsulation efficiency in the range 55–82 due to lesser solubility of IDM in the polymer solution, since it is insoluble in water. Release data showed that formulations containing highest amount of IDM (20 wt %) displayed the highest (99%) release than those containing small amount of IDM. On the other hand, those formulations containing lower amount of IDM have released only 90% of IDM. Thus, CR was observed for formulation containing lower

amount of IDM, since its release from the microspheres was sustained by the diffusion mechanism.[38] With increasing concentration of IDM in the microspheres, volume swelling of the semi-IPN matrix decreased due to the hydration effect, but increased hydrophobicity lowered the drug diffusion rate. Thus, release rates are slower at the lower amount of IDM due to the availability of more free void spaces through which lesser number of drug molecules will transport. For all the IDM-loaded formulations, the complete release of IDM was not observed even after 600 min, but almost complete release occurred at 720 min.

Effect of crosslinking agent

The % cumulative release data versus time plots for varying amounts of GA (i.e., 2.5, 5.0, and 7.5 mL) at the fixed amount of IDM (20 wt %) are displayed in Figure 6(C). The % cumulative release is quite higher when a small amount of GA (i.e., 2.5 mL) was used, whereas release was lower at higher amount of GA (i.e., 7.5 mL) in the semi-IPN matrix. Therefore, cumulative release is smaller at lower amount of GA, because at the higher concentration of GA, polymeric chains will be more rigid due to the contraction of microvoids as observed before.[39] This will decrease the swelling as well as % cumulative release of IDM through the microspheres. As expected, drug release becomes slower at the higher amount of GA, but it will be fast at the lower amount of GA.

CONCLUSIONS

CS-HEMA semi-IPN network polymers have been prepared by polymerizing HEMA in the presence of CS using potassium persulfate as an initiator. CS-HEMA semi-IPN was crosslinked with GA to prepare microspheres that could be loaded with IDM by the water-in-oil emulsion method. Drug-loaded microspheres were subjected to *in vitro* release studies in pH 7.4 medium to understand their CR characteristics. The half-life of pristine IDM, 1.2–2 h, was found to be extended up to 12 h after encapsulation into the semi-IPN matrix when the release studies were performed in pH 7.4 media. Results of this study indicated that microspheres developed here are successful in achieving the sustained release of IDM.

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