Controlled Release of Chlorpheniramine Maleate Through IPN Beads of Sodium Alginate-*g*-Methylmethacrylate

C. Lakshmi Narayana Reddy,[1] B. Yerri Swamy,[1] C. Venkata Prasad,[2] M.C.S. Subha,[1] K. Chowdoji Rao[2]

[1]*Department of Chemistry, Sri Krishnadevaraya University, Anantapur 515 003, Andhra Pradesh, India*
[2]*Department of Polymer Science and Technology, Sri Krishnadevaraya University, Anantapur 515003, Andhra Pradesh, India*

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ABSTRACT: Controlled release of chlorpheniramine maleate drug, through sodium alginate-*g*-methylmethacrylate (NaAlg-*g*-MMA) interpenetrating polymeric network beads, has been investigated. Beads were prepared by precipitating the viscous solution of NaAlg-*g*-MMA in acetone followed by cross-linking with glutaraldehyde. The beads were characterized by Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and scanning electron microscopy (SEM). Different formulations of beads were developed by varying amounts of MMA, cross-linking agent, and drug concentration. DSC thermograms of chlorpheniramine maleate drug-loaded NaAlg-*g*-MMA beads confirmed the molecular level distribution of drug in the polymer matrix. FTIR of beads confirm the grafting and cross-linking, SEM of the beads suggested the formation of spherical particles. Swelling experiments on the beads provided an important information on drug diffusion properties. Release data have been analyzed using an empirical equation to understand the nature of transport of drug containing solution through the polymeric matrices. The controlled release characteristics of the matrices for chlorpheniramine maleate was investigated in pH 7.4 media. Drug was released in a controlled manner upto 12 h. © 2010 Wiley Periodicals, Inc. J Appl Polym Sci 118: 2342–2349, 2010

Key words: sodium alginate; methylmethacrylate; IPN beads; controlled release; polymeric matrices

INTRODUCTION

Polymeric controlled delivery systems have been used in a wide range of the drug industry. The main objective in drug delivery application is to achieve an effective therapeutic administration over an extended period of time. Stimuli sensitive drug delivery has been required depending on the changes in physiological signals in the body. The advantages of using drug delivery system relay on maintaining the right concentration of the drug at the right period, the therapeutic level, and targeting the drug for the site of action, avoiding any side effects.

The most frequently used polymers for the production of particles used in the CR of drugs include acrylic acid derivatives, polyalkylcyanoacrylates, and polyalkylmethacrylates. However, particles prepared from the aforementioned monomers have low drug loading capacities particularly for hydrophilic drugs.[1] To increase the hydrophilicity of particle surface, attempts have been made to employ copolymerization of alkylmethacrylate with various hydrophilic natural polymers[2–4] such as NaAlg, guar gum, and chitosan.

Generally, natural/semi synthetic polymers are preferred as a vehicle for drug delivery as they are biodegradable, nontoxic, as well as biocompatible. Polymeric beads are important in controlled release (CR) applications,[5–8] which have received a greater attention in the recent years as the effective drug delivery devices, in biomedical engineering.[9–11] The widely used natural polymers for CR of drugs are chitosan, sodium alginate (NaAlg), cellulose derivatives, and guar gum due to their biocompatibility, biodegradation, and nontoxicity upon *in vivo* administration.[12,13] Among these, sodium alginate (NaAlg), is a natural polysaccharide composed with 1,4-linked β-D-mannuronic acid (M) and α-L-guluronic acid (G) is derived from brown seaweeds [Fig. 1(a)]. This polysaccharide has been used extensively in food industry as a gelling agent and for encapsulation of living cells.[14–16] Earlier literature cites many applications of NaAlg in agriculture[17–21] after it is cross-linked with glutaraldehyde (GA).

From a search of literature, we find no studies were reported on the use of NaAlg and

Correspondence to: K. C. Rao (chowdojirao@yahoo.com).
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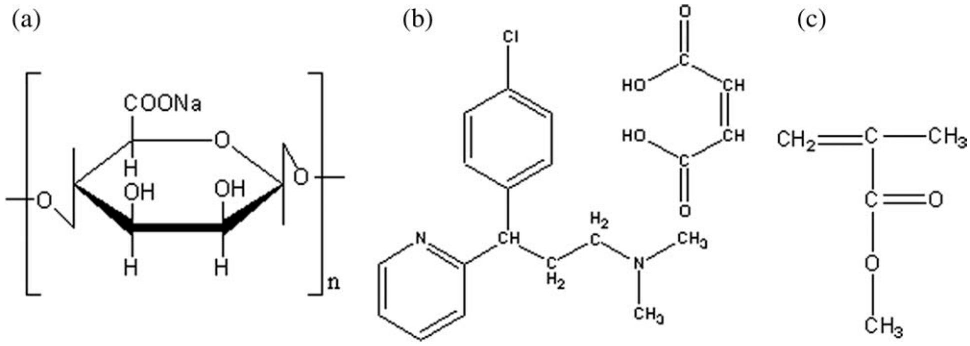

Figure 1 (a) Structure of sodium alginate, (b) structure of chlorpheniramine maleate drug, and (c) structure of methyl methacrylate.

methylmethacrylate for the CR of chlorpheniramine maleate (CPM), an antibiotic drug. This prompted the author to undertake a detailed study on the CR of CPM. Pure CPM is an antibiotic drug [Fig. 1(b)] used extensively in the treatment of various diseases like bacterial infections, allergic diseases, many of other skin diseases, etc.

Various nondegradable polymers, like poly(methylmethacrylate) (PMMA) have been utilized for antibiotic delivery purposes. Antibiotic loaded PMMA, is extremely used as a nondegradable antibiotic delivery system for the treatment of osteomyelitis.[22–25] The antibiotic loaded bone-cement based on PMMA has been used to prevent bone infection in total or joint arthroplasty.[26,27] The nondegradability of PMMA has the inherent limitation that the polymer material remains intact inside the body even after its proposed application. Sodium alginate, which is known for its biodegradability, can be copolymerised with PMMA, and the properties of the graft copolymer can be tuned properly by adjusting concentration of the reactants. Graft copolymerisation is considered to be a promising approach for designing a wide variety of molecular matrices.[28] Recently, it is noticed that the reports on synthesis of chitosan-HEMA graft copolymer and its properties in biological environment[29] have been studied. In this study, sodium alginate has been graft copolymerised with methylmethacrylate (MMA) [Fig. 1(c)] loaded with CPM, and the drug release studies have been carried out.

EXPERIMENTAL

Materials and methods

Sodium alginate (NaAlg) (medium viscosity), MMA, Liquid Paraffin Oil (light), Hydrochloric acid, Potassium per sulfate ($K_2S_2O_8$) and GA (25% aqueous solution) (GA) of all AnalaR grade samples were purchased from S.D.Fine Chemicals, Mumbai, India. Tween-80 was purchased from Sigma Chemicals, Mumbai, India. Chlorpheniramine maleate ($C_{16}H_{19}ClN_2C_4H_4O_4$) was obtained as a gift sample from Waksman Salesman Pharmaceuticals, Anantapur (A.P.), India.

Synthesis of sodium alginate-*g*-methylmethacrylate beads

Sodium alginate-*g*-methylmethacrylate interpenetrating polymeric networks (IPN's), here after designated as NaAlg-*g*-MMA was prepared by mixing NaAlg with MMA, using potassium per sulfate ($K_2S_2O_8$) as an initiator.[19,30] In brief, 3% aqueous solution of NaAlg was prepared by dissolving NaAlg in water overnight, under constant stirring. The solution was degassed by passing nitrogen gas inlet for 30 min. To this solution, different amounts of methylmethacrylate were added stirred thoroughly for 1 h. The initiator solution containing 50 mg of $K_2S_2O_8$ was added to the earlier mentioned mixture and stirred for 2 h at the temperature of 70°C. To this, the required amount of CPM, an antibiotic drug was added and stirred until complete dispersion of the drug in the polymer solution is obtained. A 5 mL of drug-loaded polymer solution was added drop wise in a short time of 50 to 75 s into the acetone solution containing the required amount of cross-linking agent GA and 1 mL of 0.1 HCl using a 25 mL hypodermic syringe having 1-mm diameter under constant stirring condition. The beads formed were removed from acetone at a particular time and were repeatedly washed with distilled water. The beads were prepared by five different ratios of NaAlg-MMA [NaAlg pure (100 : 0), NaAlg-*g*-MMA-2 (60 : 40), NaAlg-*g*-MMA-8 (50 : 50), NaAlg-*g*-MMA-6 (40 : 60) and NaAlg-*g*-MMA-7 (20 : 80)], three different amounts of cross-linker [NaAlg-*g*-MMA-4 (2.5 mL GA), NaAlg-*g*-MMA-2 (5 mL GA), NaAlg-*g*-MMA-5 (7.5 mL GA)] and three different amounts of drug [NaAlg-*g*-MMA-1 (5% CPM), NaAlg-*g*-MMA-2 (10% CPM) and NaAlg-*g*-MMA-3 (15% CPM)].

Fourier transform infrared spectroscopy (FTIR)

FTIR spectra were recorded using a Perkin Elmer spectrophotometer (USA) to confirm the presence of grafting and cross-linking in NaAlg-MMA polymeric matrix. IPN beads were finely ground with KBr to prepare pellets using a hydraulic pressure of 400 kg to scan the spectra between 4000 and 400 $cm^{-1.}$

Differential scanning calorimetry (DSC)

DSC curves of the placebo NaAlg-*g*-MMA beads, unloaded CPM and CPM-loaded beads 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^{-1} in an inert atmosphere.

Scanning electron microscopy (SEM)

SEM image of the CPM-loaded beads were recorded using a Leica 400, Cambridge, UK, scanning electron microscope at 35× magnification. A working distance of 6.9 mm was maintained and the acceleration voltage used was 15 kV with the secondary electron image (SEI) as a detector. Samples were coated with gold to neutralize the charging effects.

Estimation of drug loading and encapsulation efficiency

Specific amount of dry beads were vigorously stirred in a beaker containing 10 mL of dichloromethane to extract the drug from the beads. A 10 mL of 7.4-pH phosphate buffer containing 0.02% Tween-80 was added to the above solution to make the drug soluble and dichloromethane was evaporated with a gentle heating and continuous shaking. The aqueous solution was then filtered and assayed by a UV spectrophotometer (Model LabIndia-UV 3000^{+}, UK) at the fixed λ_{max} value of 253 nm. The results of % CPM loading and encapsulation efficiency were calculated using eqs. (1) and (2). These results are compiled in Table I.

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

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

Swelling studies

Dynamic swelling of the NaAlg-*g*-MMA beads prepared using three different concentration of cross-linker as well as three different drug loadings was studied in water by mass uptake measurements with time. Swelling experiments performed in 7.4 pH buffer solutions produced no significant changes and hence, we studied the swelling of beads in water. To perform swelling experiments, beads were soaked in water; several of them were removed from the swelling bottles at different time intervals and blotted carefully (without pressing hard) to remove the surface-adhered water. The beads were then weighed (w_1) on an electronic microbalance (Mettler, AT 120, Switzerland) accurate to ±0.0001 g. The beads were then dried to a constant weight (w_2) in an oven maintained at 60°C for 5 h. Swelling experiments were repeated thrice for each sample and average values were used in data analysis. The standard deviations (S.D.) in all cases were <5%. The weight % water uptake was calculated as:

$$\%\ \text{Water uptake} = \left(\frac{\text{Weight of swollen beads } (w_1) - \text{Weight of dry beads } (w_2)}{\text{Weight of dry beads } (w_2)}\right) \times 100 \quad (3)$$

In vitro release studies

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 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 LabIndia-UV 3000^{+}, UK) at the fixed λ_{max} value of 253 nm.

RESULTS AND DISCUSSIONS

Fourier transform infrared spectroscopy (FTIR)

Figure 2 displays the FTIR spectra of plain MMA (curve A), plain NaAlg (curve B) and Cross-linked Sodium alginate-*g*-MMA beads (curve C). In case of NaAlg, a characteristic broad peak appearing at 3456 cm^{-1} corresponds to —OH stretching vibrations of NaAlg. A sharp peak around 1650 cm^{-1} corresponds to the carbonyl group of —COONa moiety present in NaAlg. The peak at 1728 cm^{-1} is attributed to carbonyl (C=O) group stretching mode in MMA. During cross-linking, GA might have reacted with —OH

TABLE I
Results % of Encapsulation Efficiency and % Water Uptake of Different Formulations

Formulation codes	% of NaAlg in beads	% of MMA in beads	%(CPM) loaded	Volume of 25% aq. GA added (mL)	% Encapsulation efficiency ± S.D.	% Water uptake
NaAlg-*g*-MMA-1	60	40	5	5	62.6 ± 0.9	482
NaAlg-*g*-MMA-2	60	40	10	5	67.8 ± 1.2	525
NaAlg-*g*-MMA-3	60	40	15	5	78.4 ± 1.1	550
NaAlg-*g*-MMA-4	60	40	10	2.5	77.2 ± 1.2	568
NaAlg-*g*-MMA-5	60	40	10	7.5	62.3 ± 0.5	329
NaAlg-*g*-MMA-6	40	60	10	5	72.8 ± 1.5	436
NaAlg-*g*-MMA-7	20	80	10	5	78.1 ± 0.8	389
NaAlg-*g*-MMA-8	50	50	10	5	71.7 ± 1.0	458
NaAlg pure	100	–	10	5	40.7 ± 1.4	575

NaAlg = sodium alginate, MMA = methylmethacrylate, CPM = chlorpheniramine maleate, GA = glutaraldehyde, S.D. = standard deviation calculated at 95% accurately.

groups of IPN through the formation of ether linkages (Fig. 2). Hence, the appearance of a peak between 1125–1045 cm^{-1} in the spectra of cross-linked beads confirms the formation of more ether linkages. This is further supported by the presence of a sharp high intensity peak due to $-CH_2$ group of alkyl chain as a result of cross-linking. The acetal ring formation is a further test of cross-linking of hydroxyl groups of the polymer with aldehyde of GA, which is shown by the peak range observed between 1125–1045 $cm^{-1.}$ This is due to the aliphatic ethers; the most characteristic absorption is a strong band in the 1150–1085 cm^{-1} region because of asymmetrical C—O—C stretching. This band usually occurs near 1125 cm^{-1} (curve C).

Differential scanning calorimetry (DSC) studies

DSC thermo grams of pure CPM (a), plain NaAlg-*g*-MMA beads (b) and CPM loaded NaAlg-*g*-MMA beads (c) were recorded using Rheometric Scientific differential scanning calorimeter (Model-DSC SP, UK) and are displayed in Figure 3. The analysis was performed by heating the samples at the rate of 10°C min^{-1} under inert atmosphere. The melting peak of CPM drug was observed at 158°C, but in case of drug-loaded and plain NaAlg-*g*-MMA particles, broad peaks were observed in the range of 155–158°C. However, there is no characteristic peak of CPM in the drug-loaded IPN beads, suggesting that drug is molecularly dispersed in the polymer matrix. The observed endothermic peak was close to the reported[31] melting temperature 158°C of CPM.

Scanning electron microscopic (SEM) studies

Figure 4 shows the SEM micrographs (a) and (b) both are of NaAlg-*g*-MMA beads at high (24000) and low (6000) magnifications, respectively. The beads are porous with nearly spherical structure and are proved to be a promising matrix for the controlled delivery of drugs. The observed shape of the bead was like a droplet and with rough and dense surface. The reason for nearly spherical size may be due to high viscosity of the NaAlg-MMA solution. The approximate size of the beads is in the range of 1.0–1.4 mm. From the morphology of beads shown in Figure 4, one can observe rough and folded surfaces of the beads.

Encapsulation efficiency

Three different concentrations of CPM, i.e., 5, 10, and 15 wt % were loaded during the cross-linking

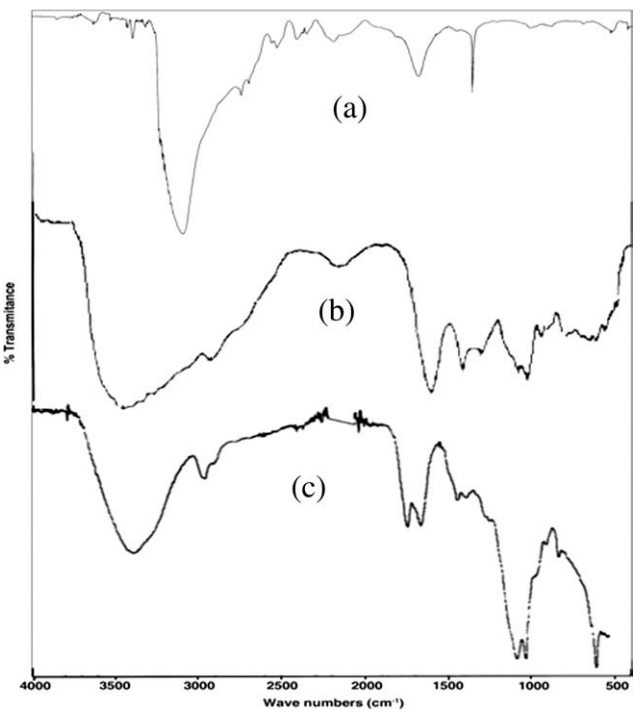

Figure 2 FTIR Spectra of (a) pure methylmethacrylate, (b) pure sodium alginate, and (c) cross-linked sodium alginate-*g*-MMA beads.

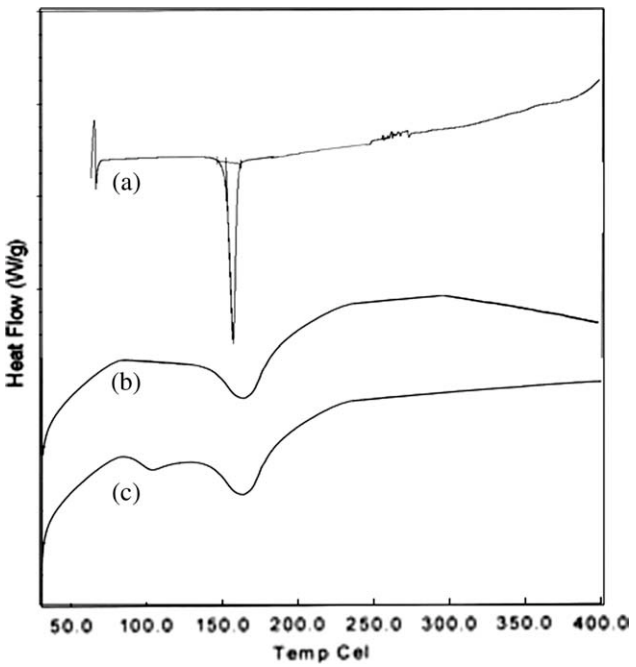

Figure 3 DSC thermo grams of (a) pure CPM drug, (b) plain NaAlg-*g*-MMA beads, and (c) drug-loaded NaAlg-*g*-MMA beads.

reaction of beads. Results of % encapsulation efficiency are included in Table I. From the table, it is noticed that the encapsulation efficiency is increased with increasing drug loading. Encapsulation efficiency of 42.1% was observed for pristine sodium alginate beads, but for the remaining formulations the values ranged from 62.8 to 79.5%. It is also noticed from Table I, that for beads containing 100/0, 60/40, 50/50, 40/60 and 20/80, and 10 wt % CPM with 5 mL of GA, encapsulation efficiencies are 42.1, 69, 72.7, 74.3, and 78.7%, respectively. This indicates that % encapsulation efficiency increased with increasing amount of MMA in the polymeric beads. It is also observed from Table I, that for beads cross-linked with 2.5, 5, and 7.5 mL of GA, encapsulation efficiencies are 78.4, 68.9, and 62.8%, respectively. For the ratios of 60/40 of NaAlg and MMA in the matrix, the results show that as the extent of cross-linking increased, the % of encapsulation efficiency decreased (Table I). Such a decreasing trend is due to an increase in cross-link density, because the beads will become rigid, there by reducing the free volume spaces within the polymer matrix and hence, a reduction in encapsulation efficiency is observed.

Swelling studies

In polymer matrix beads, the extent of cross-linking depends upon the cross-linking agent (GA) used. In this study, different amounts of GA were added as the cross-linking agent to the IPN beads of NaAlg-*g*-MMA containing 10 wt % of CPM and these data are also included in Table I. The equilibrium swelling depends upon the extent of cross-linking. For instance, % equilibrium swelling decreased from 508 to 329 with increasing amount of GA from 2.5 to 7.5 mL. This is due to the increased cross-link density and decreased pore volume of the IPN matrix[32] with increasing amount of GA in the matrix. By increasing the drug loading of the matrix, % water uptake also increased, i.e., as the drug wt % loading increased from 5 to 15%, the % equilibrium swelling were 482, 525, and 550, respectively. Such an increase is due to the total concentration of hydrophilic units present in the network which increases because of the hydrophilic nature of CPM and is responsible for the good swelling capacity of the beads at a fixed concentration of GA and

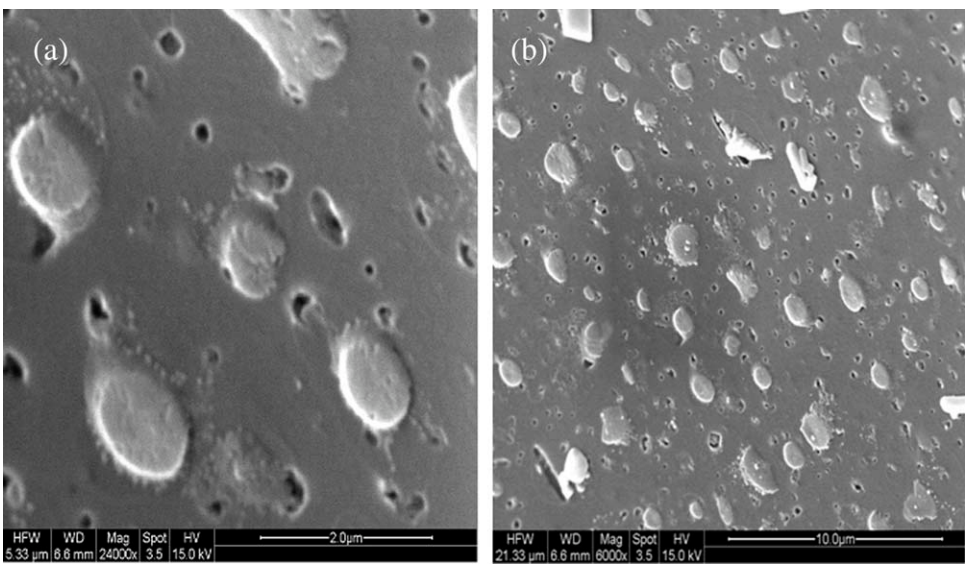

Figure 4 Scanning electron micrographs of NaAlg-*g*-MMA beads at (a) high (24,000) and (b) low (6,000) magnifications.

NaAlg-*g*-MMA copolymer. The % water uptake (or) % dynamic swelling for the formulated IPN matrix containing 100/0, 60/40, 50/50, 40/60, and 20/80 of NaAlg and MMA has decreased with an increasing amount of MMA in IPN matrix and have the values 575, 525, 458, 436, and 389, respectively. This is due to the fact that as the amount of MMA increases in the matrix, hydrophobicity of the matrix could increase slightly due to the presence of methyl groups present in MMA.

Release kinetics parameters of different formulations

Drug release kinetics were analyzed by plotting cumulative release data versus time and by fitting these data to the exponential equation of the type.[33]

$$(M_t/M_\infty) = kt^n \quad (4)$$

Here, M_t/M_∞ represents the 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 nine formulations, and these values are given in Table II. If $n = 0.5$, the drug diffuses and releases from the polymer matrix following a Fickian diffusion. For $n > 0.5$, anomalous or non-Fickian type drug diffusion occurs. If $n = 1$, a completely non-Fickian or Case II release kinetics is operative. The intermediary values ranging between 0.5 and 1.0 are attributed to the anomalous type transport.[33,34]

The values of k and n have shown a dependence on the extent of cross-linking, % drug loading, and MMA content of the matrix. Values of n for beads prepared varying the amount of CPM in the polymer matrices from 5 to 10–15% and keeping GA (5 mL) constant, ranged from 0.65 to 1.15, indicating an anomalous type transport. The CPM-loaded particles have the n values ranging from 0.63 to 1.15 (Table II), indicating the shift from erosion type release to a swelling-controlled, non-Fickian mechanism. This could be possibly due to a reduction in the regions of low microviscosity and closure of microcavities in the swollen state. Similar findings have been observed elsewhere,[35] whereas the effect of different polymer ratios on dissolution kinetics was studied. On the other hand, the values of k are quite smaller for the drug-loaded beads, suggesting lesser interactions compared with beads containing varying amounts of MMA.

TABLE II
Release Kinetics Parameters of k, n and Correlation Coefficient (r) Values for Different Formulations

Formulation codes	k	n	Correlation coefficient, r
NaAlg-*g*-MMA-1	0.0421	0.651	0.9548
NaAlg-*g*-MMA-2	0.0177	0.854	0.9894
NaAlg-*g*-MMA-3	0.0018	1.152	0.8860
NaAlg-*g*-MMA-4	0.0606	0.630	0.9907
NaAlg-*g*-MMA-5	0.0383	0.666	0.9701
NaAlg-*g*-MMA-6	0.0150	0.829	0.9838
NaAlg-*g*-MMA-7	0.0225	0.689	0.9900
NaAlg-*g*-MMA-8	0.0081	0.899	0.8694
NaAlg pure	0.0148	0.736	0.8670

In vitro drug release studies

Effect of cross-linking agent

The % cumulative release data vs. time plots for varying amounts of GA, i.e., 2.5, 5.0, and 7.5 mL at the fixed amount of the drug (5%) are displayed in Figure 5(a). The % cumulative release is quite fast and large at the lower amount of GA (i.e., 2.5 mL), whereas the release is quite slower at higher amount of GA (i.e., 7.5 mL). The cumulative release is somewhat higher when the lower amount of GA was used probably because at higher concentration of GA, polymeric chains become rigid due to the contraction of micro voids, thus decreasing % cumulative release of CPM drug through the polymeric matrices. As expected, the release becomes slower at higher amount of GA, but becomes faster at lower amount of GA. As shown in Figure 5(a).

Effect of percentage of drug loading

Figure 5(b) shows the release profiles of CPM drug-loaded NaAlg-*g*-MMA beads at different amount of drug loadings. Release data showed that formulations containing the highest amount of drug (15%) displayed fast and higher release rates than those formulations containing a small amount of CPM drug. A prolonged release was observed for the formulation containing lower amount of CPM. In other words, with a decreasing amount of drug in the matrix, it is noticed that the release rate becomes quite slower at the lower amount of drug in the matrix, and this is due to the availability of more free void spaces through which lesser number of drug molecules will transport. For all the CPM-loaded formulations, the complete release of CPM was not observed till 600 min, but the release rates showed 100% release around 800 min.

Effect of MMA content

Effect of MMA content was studied at constant loading of 10 wt % CPM. It was found that NaAlg produced almost 100% cumulative drug release in about 12 h, whereas NaAlg-*g*-MMA IPN beads produced upto 80% of cumulative release in 12 h. The release trends of NaAlg-*g*-MMA beads prepared with

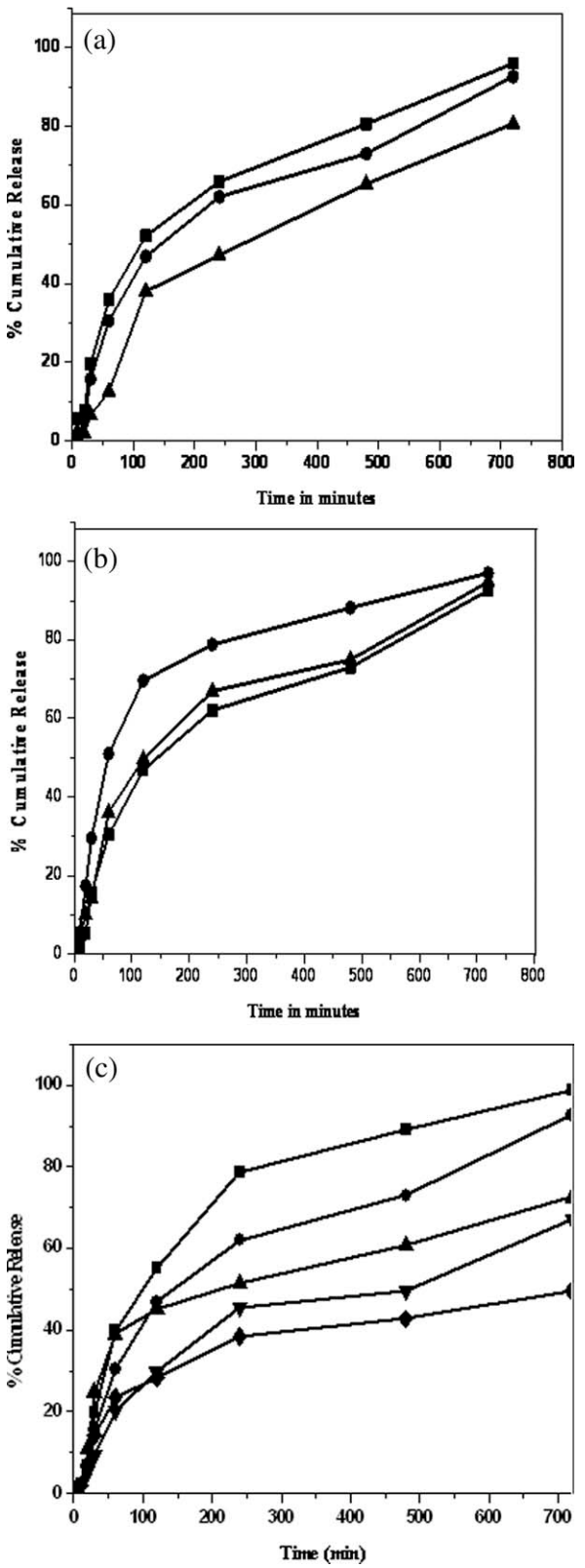

Figure 5 (a) % Cumulative release of CPM at different amounts of GA: (■) 2.5 mL GA, (●) 5.0 mL GA, (▲) 7.5 mL GA, (b) % cumulative release of chlorpheniramine maleate at different amounts of CPM: (■) 5% CPM, (▲) 10% CPM, (●) 15% CPM, and (c) % cumulative release of chlorpheniramine maleate at different ratios of SA and MMA, respectively: (■) 100 : 0, (●) 60 : 40, (▲) 50 : 50, (▼) 40 : 60, and (◆) 80 : 20.

different amounts of MMA are displayed in Figure 5(c). It is noticed that during dissolution experiments, the beads have shown systematic swollen trends with decreasing amounts of MMA, probably due to the formation of loosely cross-linked networks chains of MMA. As the amount of MMA increases, % cumulative release decreased due to lesser swelling of the MMA chains than NaAlg. This could be because as the amount of MMA increases in the IPN matrix, the hydrophobicity of the overall matrix increases due to the presence of methyl groups of MMA, which increases the hydrophobicity of the matrix, thereby decreasing the release rates from CPM thus a regaining type response of polymer chains is possible due to the stresses induced by the surrounding solvent media during the dissolution step, resulting in a decrease of chain dimension (radius of gyration) of the IPN polymer matrix. This will further decrease the molecular volume of the hydrated polymer due to decreased swelling of MMA component of the IPN matrix, there by reducing the free volume spaces of the matrix. It is noticed that the nature of release profile remains almost identical in all the formulations containing different amounts of GA, indicating a linear relationship with the drug release profiles.

CONCLUSIONS

This study explains the CR of CPM through NaAlg-*g*-MMA IPN beads. FTIR spectra, confirms the grafting and cross-linking reaction of NaAlg-*g*-MMA with GA. The SEM studies explained the shape of the beads formed and the surface morphology of the beads. From the DSC thermograms, it is confirmed that the drug is dispersed uniformly at molecular level in the polymer matrix. Swelling studies of the polymer matrix beads have shown that with an increasing amount of MMA in beads, % water uptake has decreased. This effect is correlated with the release rates of drug through the beads containing different amounts of MMA. The CR characteristics of the polymer matrix beads for CPM were investigated in pH 7.4 buffer media. The drug was released in a controlled manner up to 12 h. The results of this study clearly suggest that GA cross-linked NaAlg-*g*-MMA beads are suitable for CR of CPM.

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