Journal of Macromolecular Science, Part A
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597274

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To cite this Article Bajpai, S. K. and Sharma, S.(2006) 'Investigation of pH-Sensitive Swelling and Drug Release Behavior of Barium Alginate/Carboxymethyl Guar Gum Hydrogel Beads', Journal of Macromolecular Science, Part A, 43: 10, 1513 — 1521
To link to this Article: DOI: 10.1080/10601320600896728
URL: http://dx.doi.org/10.1080/10601320600896728

Journal of Macromolecular Science®, Part A: Pure and Applied Chemistry, 43:1513–1521, 2006

ISSN 1060-1325 print/1520-5738 online
DOI: 10.1080/10601320600896728

Investigation of pH-Sensitive Swelling and Drug Release Behavior of Barium Alginate/Carboxymethyl Guar Gum Hydrogel Beads

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The water uptake behavior of barium ions crosslinked sodium alginate/carboxymethyl guar gum bipolymeric beads has been studied in the media of varying pH. The beads swelled to nearly 15 ± 4% in simulating gastric fluid (SGF) of pH 1.2 in 3 h. On transferring the hydrogel into simulated intestinal fluid (SIF) of pH 7.4, the swelling was enhanced to nearly 310 ± 12%. Swelling response to the change in pH was so fast that when the beads were transferred to SIF, their water uptake increased to nearly 8 times in the first hour. When loaded with the model drug vitamin B_{12}, the total release in SGF in 3 h was nearly 20%, while nearly 70% was released in SIF in the next 7 h. The percent entrapment was nearly 50% when the beads were crosslinked with a 5 or 6% (w/v) $BaCl_2$ solution.

Keywords vitamin B_{12}, barium alginate, carboxymethyl guar gum

Introduction

Recently, considerable interest has grown in natural polymers such as starch (1), sodium alginate (2, 3), chitosan (4, 5), guar gum (6), dextran (7), etc., for gastrointestinal drug delivery, probably due to their non-toxic and biocompatible nature. From various approaches employed to synthesize polysaccharide-based hydrogels, microencapsulation is the commonly used technique since this method is very mild and is done at room temperature in aqueous medium by using physiologically acceptable chemicals.

These beads suffer from a major drawback that it is not possible to incorporate desirable properties in them until they are modified chemically (8). For example, calcium alginate beads demonstrate excellent swelling properties in sodium phosphate buffer, but later on, start to disintegrate and dissolve completely. On the other hand, the barium alginate beads are stable for a sufficiently longer time, but do not exhibit much water uptake on swelling. Therefore, drug loaded calcium alginate beads may undergo an appreciable swelling with subsequent release of drug but they may not possess

Received May 2006; Accepted June 2006.
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sufficient stability to match with the gastrointestinal transit time of oral dosage form. On the other hand, the barium alginate beads will possess higher stability due to the compact structure of beads but may not exhibit appreciable water uptake with subsequent release of the encapsulated drug. Hence, in order to use the alginate beads for gastrointestinal delivery of drugs which have an especially large hydrodynamic radius, both the properties are essential, i.e., the beads must exhibit an appreciable water uptake so that large mesh size of swelling beads can cause an appreciable release of loaded drugs and should also be sufficiently stable in the release media.

Therefore, a sincere attempt has been made to introduce such desirable properties in a hydrogel bead system by synthesizing bipolymeric beads, ionically crosslinked with a common crosslinking ion. As a representative system, sodium alginate and carboxymethyl guar gum have been simultaneously crosslinked with Ba^{2+} ions in the aqueous medium to produce bipolymeric hydrogel beads for delivery of vitamin B_{12} model drug, along the GI tract.

Experimental

Materials

Sodium alginate (S.A.; average molecular mass 60,000 M/G ratio 1.75 $\pm$ 0.12 medium viscosity 200 cps for 1% aqueous solution at 20°C) was obtained from Research Lab, Mumbai, India. Barium chloride, used as crosslinker (molecular weight 244.30) was obtained from E. Merck, Mumbai, India. Guar gum (GG viscosity 3500 cps for 1% w/v aqueous solution in distilled water at 20°C) was received from S.D. Fine Chem. Ltd., Mumbai, India. The ampoules of vitamin B_{12} (sold in the market as 'neurobion') used as the model drug had batch no. 60633002. Methanol (mol. wt. 32.03) was purchased from E. Merck, Mumbai, India. The sodium monochloroacetate (mol. wt. 116.48 g/mol $ClCH_2COONa$), used for derivatizing guar gum, was purchased from E. Merck, Mumbai, India. The CO_2 free water, used as the reaction medium, was prepared by double distillation of water containing a small amount of alkaline $KMnO_4$ in pyrex glass assembly.

Preparation of Barium Ions Crosslinked SA–CMGG Beads

Guar gum was derivatized to give carboxymethyl guar gum using the method described elsewhere (4). Sodium alginate and carboxymethyl guar gum were dissolved in distilled water at a concentration of 4% (w/v), unless otherwise noted. The polymer solution was then added dropwise into the gelation medium of 250 ml of $BaCl_2$ solution of definite composition (w/v), using a 10 ml hypodermic syringe at room temperature. The beads, thus formed, were cured in the gelation medium for 20 min and then removed, washed with distilled water, and then allowed to dry at 30°C in a dust free chamber until they attained constant weight. Here it should be noted that the mode of drying affects the stability of beads. The drying of beads at a higher temperature may result in surface cracking which can facilitate the surface erosion upon rehydration. This will ultimately affect the swelling/degradation behavior.

Experimental conditions such as distance between the syringe and gelation medium, number of drops of polymer solution falling into gelation medium per minute and the temperature were maintained uniform throughout the investigations.

The drug-loaded beads were also prepared by the same procedure, with the difference being that a known quantity of B_{12} drug was also added to the aqueous solution of the polymers before the dropwise addition of polymer solution into the gelatin medium for beads formation (Figure 1).

Swelling Behavior of Beads

The beads swelling behavior was investigated in simulated, enzyme-free gastric, as well as intestinal fluids. For this, 50 mg of dry beads were suspended in 100 ml of either pH 1.2 HCl–NaCl buffer (SGF) or pH 7.4 phosphate buffer (SIF) at the physiological temperature 37°C. The 'weight change' was monitored at different time-intervals until the beads showed constant weight or complete dissolution. The fractional weight change was transformed to percentage using the following empirical relationship:

$$\text{Dynamic weight } (\%) = \text{Final weight} - \text{Initial weight}/\text{Initial weight} \times 100$$

The measurements were made in triplicate and the average of the data was used for calculations.

In vitro Drug Release Studies

The traditional dissolution test was carried out by placing **a** definite amount of drug loaded beads in the 25 ml of simulating intestinal fluid (i.e., phosphate buffer medium of pH 7.4) at the physiological temperature 37°C with a constant agitation speed of 50 rpm. The amount of drug released at different time-intervals was determined spectrophotometrically at 437 nm (9).After each measurement, the buffer was replaced by a fresh one. The release study in simulating gastric fluid (SGF, pH 1.2) was carried out by placing the beads in 900 ml of buffer solution. The amount of drug released was computed by comparing the absorbance with the standard curve prepared for the pure drug in the appropriate concentration regions.

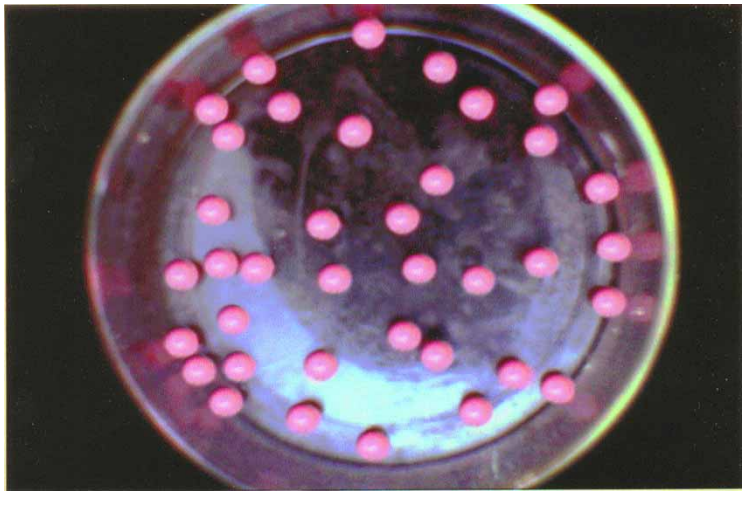

Figure 1. Photograph of drug loaded freshly prepared beads.

Results and Discussion

Entrapment Efficiency of Beads

In order to determine the percentage of drug entrapped within the polymer matrix, the beads were made by dropping an aqueous solution containing 4% sodium alginate and 4% carboxymethyl guar gum and 0.5 mg/ml model drug cyanocobalamine (Vit. B_{12}) into a $BaCl_2$ solution of varying concentrations in the range of 4 to 6% (w/v). The amount of drug retained as a percent of total drug loaded against the concentration of $BaCl_2$ solutions are presented in Figure 2. As can be seen, up to nearly 49.06% of cyanocobalamine is retained in the beads using a 5% $BaCl_2$ solution.

It is clear that a lower concentration of $BaCl_2$ solution (i.e., 4%) may not be sufficient to form compact beads. Therefore, due to a lower degree of crosslinking, more drug diffuses out of beads during the curing process and subsequent washings. This is also supported by the fact that in the sodium alginate used for the study, the poly(guluronic acid) content which is responsible for the bead formation, is relatively small (i.e., $M/G = 1.75$ as per manufacturer's specification).

Proton NMR Spectral Analysis of Beads

The proton NMR spectrum of a polymer sample is depicted in Figure 3(a). A peak value, due to hydrophilic polygalactomannan OH groups, generally lies between δ 5 and δ 4.5 ppm in non–polar solvent. Thus, for hydrogen, two signals at δ 4.800 and δ 4.909 ppm are observed Figure 3(b). The two up field pair of doublets at δ 3.779 and δ 3.830 ppm may be attributed to C-O-C bonding in polynuclear aromatic hydrocarbon. Thus, the two signals for hydrogen, along with C-O-C linkage, indicates the basic structure of pure guar gum.

Due to derivatization of guar gum by sodium monochloroacetate, all H (from OH groups) are replaced by CH_2COONa groups (Figure 3(c)). The peak has been of slightly

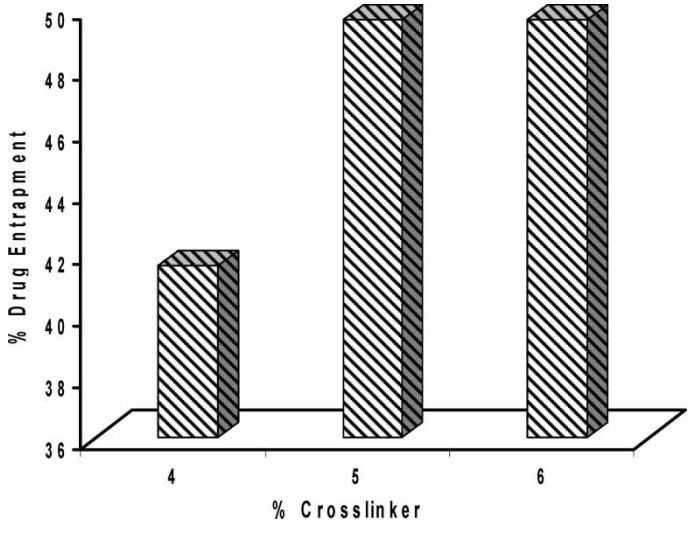

Figure 2. Bar diagram showing cyanocobalamine loading efficiency as a function of Barium Chloride concentrate.

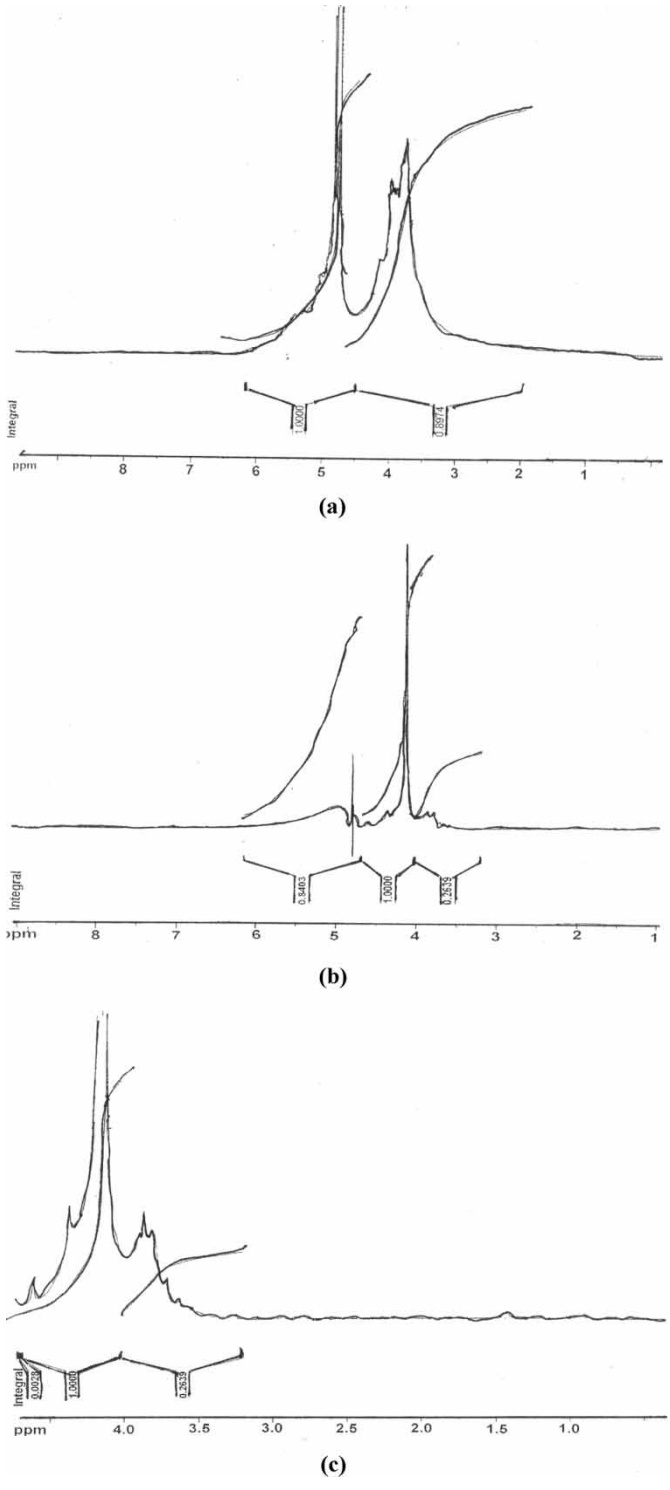

Figure 3. (a) Proton NMR spectral analysis of pure guargum; (b) and (c); proton NMR spectral analysis of derivatized guar gum.

higher frequency as compared to underivatized guar gum. The peak at δ 4.144 ppm is due to sodium salt of carboxymethyl guar gum.

Swelling in Media of Varying pH

A dosage form, when administered orally, goes to the stomach, and after residing there for a definite time-period, it passes on to the small intestine, and then finally to the colon. In the course of this journey along the GI tract, the formulation has to get exposed to a sharp pH change in the range 1–2 (gastric fluid) to 7–8 (intestinal fluid). Therefore, in order to mimic the transition of proposed bipolymeric beads from mouth to colon, they should be exposed to varying pH.

Relying on the data given by a group of pharmaceutical researchers (10) regarding the transit time of a dosage form along the GI tract, the beads were exposed to simulating gastric fluid, pH 1.2 for a period of 3 h and then transferred into the SIF, pH 7.4 for the remaining time. The results of swelling measurements have been depicted in Figure 4. It is clear that the water uptake of the beads is nearly 15 $\pm$ 4% in the SGF in the first 3 h. When they are transferred into a medium of pH 7.4, there is a sudden rise in the water uptake which is indicative of the enhanced swelling of the beads. The beads swell to nearly 178 $\pm$ 9% in the next 8 h. It was found that the beads exhibited equilibrium water uptake of nearly 210 $\pm$ 13% in the total duration of 12 h and then started to dissolve and finally disappeared completely. When the beads are placed in the medium of pH 1.2, they exhibit almost minimum swelling (i.e., nearly 15 $\pm$ 4% water uptake) as expected. However, on transferring them into a phosphate buffer medium of pH 7.4, they begin to absorb water at a faster rate. This can be explained on the basis of the fact that prior to their transfer into a phosphate buffer of pH 7.4, their stay in the medium of pH 1.2 results in acid catalyzed hydrolysis of alginates into low molecular alginic acid

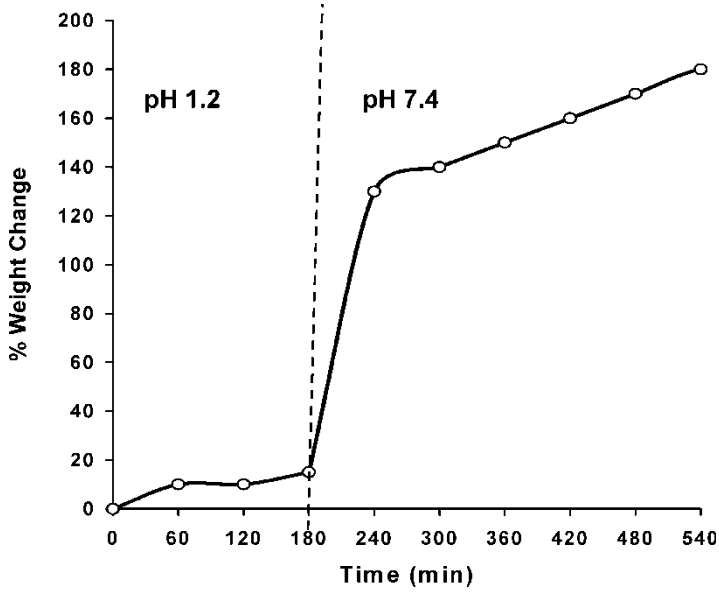

Figure 4. Dynamic uptake of water for the bead sample BIC 4/4/4 in the media of pH 1.2 (○) for 3 h followed by their transfer in the medium of pH 7.4 (○) at 37°C.

(11). At the same time, the protonation of carboxylate groups, attached at polyguluronate blocks of alginate and galactose side chains of guar gum, also results in a decrease in ionic crosslinking of the beads.

When transferred into the phosphate buffer of pH 7.4, the loosely crosslinked hydrogel beads begin to take up water. The ion-exchange (although at a slower rate) between Ba^{2+} ions of the beads (present in polyguluronate and polymannuronate blocks of alginate and between the galactose side chains in guar gum) and Na^{+} ions of phosphate buffer also makes the structure loose, enhancing the uptake of water. Finally, when the beads attain maximum swelling (which is nearly $310 \pm 12\%$) the polymeric segments (low molecular weight segments of alginic acid and linear chain of mannose units of guar gum) become unable to retain the hydrated structure and hence, the beads begin to disintegrate. This finally causes total dissolution of the beads (dissolution data not shown).

In Figure 4, one more interesting fact can be observed. When the beads are transferred into the phosphate buffer of pH 7.4, they exhibit a drastic water uptake in the next 2 h (i.e., in the time interval of 180–300 min). This might be due to formation of low molecular alginic acid chains from acid-catalyzed hydrolysis, which begin to dissolve in the buffer medium of pH 7.4, loosening the bead structure and letting solvent molecules enter the gel phase with a faster rate.

Drug Release by Traditional Dissolution Test

The drug release behavior of the beads in simulating gastric fluid of pH 1.2 and simulating intestinal fluid of pH 7.4, was studied by the traditional dissolution test, as shown in Figure 5. It was found that the beads demonstrate faster release in the medium of pH

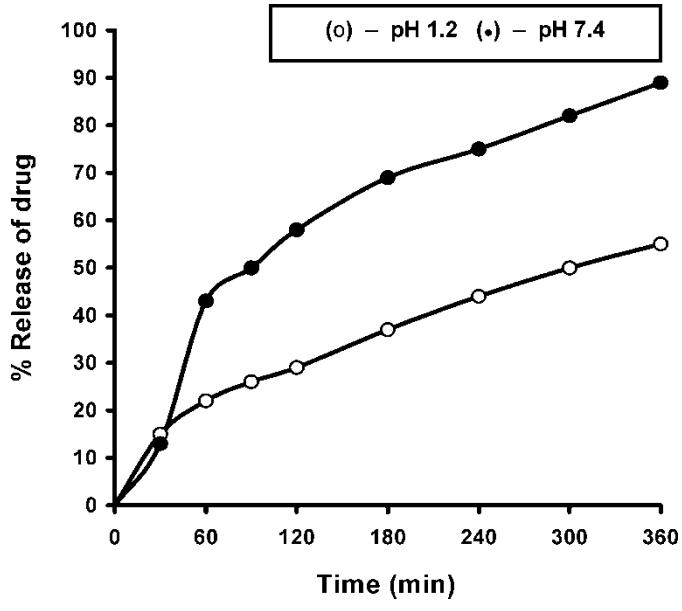

Figure 5. Dynamic release of drug in the medium of pH 1.2 (○) and pH 7.4 (●) as studied by traditional dissolution test at 37°C.

7.4, which may be attributed to the ion-exchange induced swelling of the beads, allowing the drug molecules to escape. Moreover, carboxylic groups present within the hydrogel beads also ionize, thus, resulting in relaxation of the macromolecular chains and causing faster release. On the other hand, the beads demonstrate slower release in the medium of pH 1.2. This is due to the fact that in the acidic pH, the carboxylic group remains almost unionized, minimizing the repulsive forces within the beads. Therefore, chain relaxation does not take place. Moreover, guar gum is also an acid resistant polymer. Finally, the absence of Na^+ ions in the release medium also contributes to lower release as the ion-exchange process is not operative.

Drug Release in Media of Varying pH (TDT)

As stated earlier, the transition of an oral formulation from mouth to colon can be mimicked by exposing the formulation in the media of varying pH. Figure 6 depicts the release of the model drug from the beads in the media of varying pH. It can be seen that nearly 20% drug is released in first 3 h in the simulating gastric fluid of pH 1.2 while nearly 70% drug is released in the next 7 h in the SIF of pH 7.4 at 37°C. The observed minimum release in the medium of pH 1.2 may be attributed to the fact that the beads do not exhibit appreciable swelling in the acidic environment. However, when the beads are transferred into the SIF of pH 7.4, a faster release is observed which may be attributed to the appreciable swelling demonstrated by the beads (as discussed in previous section). Here it is also worth mentioning that in the present discussion natural force/conditions like hydrophillic nature of drug, its partition coefficient between solution and gel phase etc., have not been included in accounting for drug release process. Finally, it can be claimed that the beads, when taken orally, will exhibit

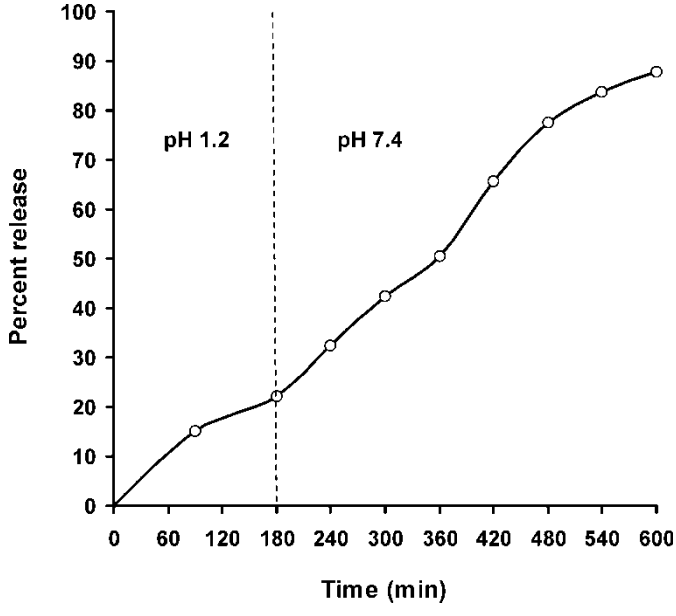

Figure 6. Dynamic release of drug in the media of varying pH as studied by TDT at 37°C.

maximum release in the medium of pH 7.4, while they shall keep the drug almost protected in the gastric fluid by exhibiting minimum swelling with low drug release.

Conclusions

From the above studies, it can be concluded that Ba^{2+} ions crosslinked polymeric beads, composed of sodium alginate and carboxymethyl guar gum, demonstrate appreciable water uptake, fair mechanical strength and higher stability, which are basic requirements for a dosage form to be used for oral drug delivery along the GI tract. The beads exhibited appreciable water uptake and stability in the medium of continuous varying pH, thus, proving their ability to be used for oral along the GI tract. The beads release nearly 20% drug in the SGF in 3 h while 70% drug was released in the next 7 h in the simulating intestinal fluid of pH 7.4 as studied by traditional dissolution test (i.e. TDT).

References

1. Athawale, V.D. and Lele, V. (1998) *Carbohydrate Polymers*, 35: 21–27.
2. Wang, L., Shelton, R.M., Cooper, P.R., Lawson, M., Triffitt, J.T., and Barralet, J.E. (2003) *Biomaterials*, 24: 3475–3481.
3. Bajpai, S.K. and Sharma, S. (2005) *J. Macrom. Sci., Pure and App. Chem.*, 42 (5): 649–661.
4. Ghanem, A. and Skonberg, D. (2002) *J. Appl. Poly. Sci.*, 84: 405–413.
5. Bajpai, S.K. and Tankhiwale, R. (2006) *Reactive and Functional Polymer*, 66 (6): 645–658.
6. Reddy, T. and Tammuhetti, S.J. (2002) *Microencapsulation*, 19 (3): 311–318.
7. Cadee, J.A., de Groot, C.J., Jiskoot, W., Otter, W., den, and Hennink, W.E. (2002) *J. of Cont. Rel.*, 78: 1–13.
8. Knill, C.J., Kennedy, J.F., Mistry, J., Minaftab, M., Smart, G., Groocock, M.R., and Williams, H.J. (2004) *J. Carbohydrates Polym.*, 55: 65–76.
9. Wang, L., Shelton, R.M., Cooper, P.R., Lawson, M., Triffitt, J.T., and Barralet, J.E. (2003) *Biomaterials*, 24: 3475–3481.
10. Krishnaiah, V.S.R., Satyanarayan, S., Rama Prasad, Y.V., and Narasimha, Rao S. (1998) *J. Cont. Release*, 55: 245.
11. Gombotz, W.R. and Wee, S.R. (1998) *Adv. Drug Deliv. Rev.*, 31: 267–285.