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Dynamic Release of Riboflavin from Ethyl Cellulose Coated Barium Alginate Beads for Gastrointestinal Drug Delivery: An *in vitro* Study

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The present work describes the dynamic release of model drug riboflavin form uncoated and ethyl cellulose coated barium alginate beads in the media of continuous varying pH at the physiological temperature 37°C. The drug release behavior has been studied in the simulating gastric fluid (SGF, pH 1.2) for 0–2 h and then in the simulating intestinal fluid (SIF pH 6.8) for 2–48 h. In addition to the traditional dissolution test (TDT, the dynamic release has also been studied by a newly developed method, called 'flow through diffusion cell' (FTDC). The release profiles, obtained by using these two methods have been found to differ appreciably from each other. Moreover, the nature of the solid mass surrounding the beads in the FTDC method also influences the release behavior of beads. The uncoated beads demonstrated faster drug release of drug in the medium of lower pH (i.e., 1.2) as compared to that in the medium of pH 6.8 and the release process was found to be diffusion controlled.

Keywords 'flow through diffusion cell', microencapsulation, barium alginate, gastrointestinal tract

Introduction

Because of the immunostimulative properties of alginates, the chemical and physical properties of alginate gels have been studied in relation to the development of implants and controlled drug delivery systems (1). Sodium alginate is water soluble salt of alginic acid, a naturally occurring non-toxic polysaccharide found in all species of brown algae. In the recent past it has been frequently used for the entrapment of peptide drugs (2), macromolecules (3), vascular endothelial growth factor (4), murine insulinoma βTC 3 cells (5) and enzymes (6) etc. It contains two uronic acids; β-D-mannuronic acid (M) and α-L-guluronic acid (G), and is composed of homopolymeric blocks MM or GG, and blocks with an alternating sequence, the MG blocks (7). It undergoes ionotropic gelation when divalent cations (usually, Ca^{2+} and Ba^{2+}) interact ionically with blocks of guluronic acid residues, resulting in the formation of three-dimensional network which is usually described by the 'egg-box' model (8).

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In our previous work (9), we synthesized calcium alginate and barium alginate beads and studied their swellability and degradability in simulating gastric and intestinal fluids so as to explore the possibilities of using them for oral drug delivery at the colon. It was observed that the beads crosslinked with barium ions possessed greater stability as compared to the calcium alginate beads, thus showing greater potential for being used in gastrointestinal drug delivery.

Although tremendous work has been done in the field of site specific drug delivery it appears that in nearly all the *in vitro* studies, the experimental conditions do not match with the *in vivo* gastrointestinal conditions. For example, in stomach water the content is high and pH is quite low (i.e., between (1) and (2)) while in the large intestine the water content is small, agitation intensity is quite low and dosage form is surrounded by a semi-solid mass (the undigested food particles). But these conditions are usually not maintained in *in vitro* studies. So attempts should be made to minimize the difference between the *in vitro* experimental conditions and *in vivo* GI conditions. In other words, the *in vitro* studies should be carried out in such a way that results thus obtained can form a concrete basis for using the proposed delivery systems in *in vivo* conditions.

In the present study, we have developed a novel approach, called 'flow through diffusion cell' (FTDC) to study the release of a low molecular weight drug, riboflavin from barium alginate beads. The results have also been compared with those obtained with 'traditional dissolution test' (TDT) which is carried out under sink conditions.

The model drug riboflavin, a dimethyl iso-alloxazine attached to d-ribitol, is a part of riboflavin nucleotides, which take part in enzymatic reactions. Infants with hemolytic hyper bilirubinaemia subjected to phototherapy are likely to be riboflavin deficient (10). The red blood cell is one of the active sites for the conversion of pyridoxal phosphate through the action of riboflavin. In riboflavin deficiency, this conversion is low.

Experimental

Materials

Sodium alginate (SA, average molecular mass 60000, M/G ratio 1.75 $\pm$ 0.12, medium viscosity 200 cP for 1% aqueous solution at 20°C) was obtained from Research Lab (Mumbai, India). The crosslinker barium chloride, ethyl cellulose, acetone and model drug riboflavin (molar mass 376.36, purity 99.1%) were obtained from S.D. Fine–Chem. Ltd. (Mumbai, India). Soribtan tristerate (ss-30) and liquid paraffin were purchased from Research Lab (Mumbai, India).The double distilled water was used throughout the investigations.

Preparation of Riboflavin Loaded Barium Alginate Beads

A pre-calculated quantity of drug riboflavin was added to a 4% (w/v) aqueous solution of sodium alginate and mixed thoroughly to ensure homogenous mixing of the drug. The solution was then added dropwise into a 250 mL $BaCl_2$ solution (4% w/v) using a 20 mL hypodermic syringe through a needle #21 under constant stirring at room temperature. The droplets were cured with a gelation medium for 10 min and then taken out, followed by washing with distilled water. The well shaped spherical beads, so produced (Figure 1) were allowed to dry at 30°C till they attained constant weight.

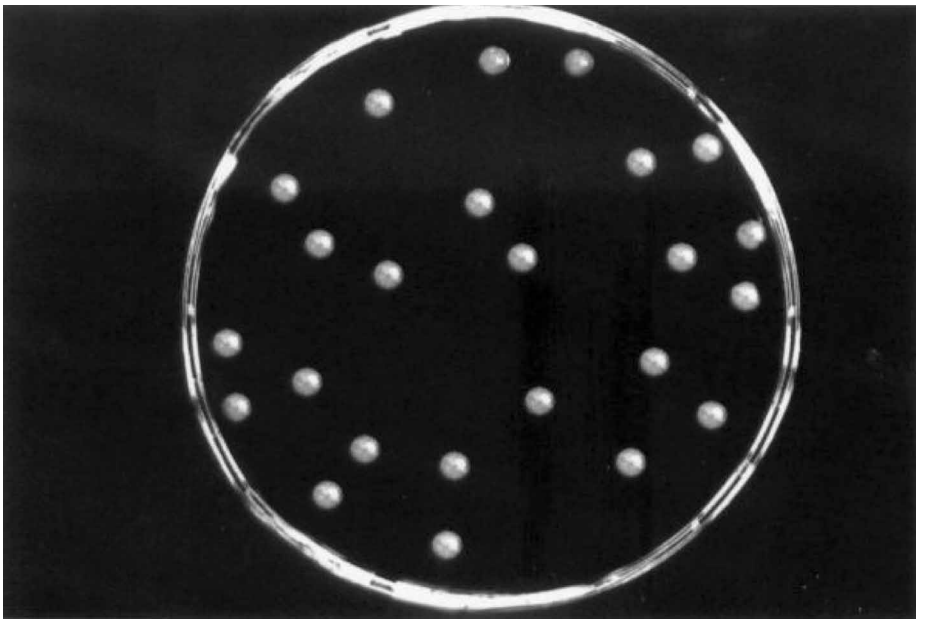

Figure 1. Photograph of spherical barium alginate beads.

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

Coating of Beads

The beads were coated with ethyl cellulose by the method described elsewhere (11). In brief, a definite amount of ethyl cellulose was dissolved in 5 mL of acetone and to this approximately 200 mg of drug-loaded beads were added and mixed thoroughly for 5 min to disperse them uniformly. The suspension was added dropwise to 200 ml of liquid paraffin containing ss-30 at 2% (w/v). The resulting mixture was stirred at 60°C for 30 min. Then, the mixture was filtered through a sieve and the beads were washed with n-Hexane, warmed at 55°C, and finally dried at room temperature.

The coated and uncoated beads are designated as CBA $(X)_y$ and UBA $(X)_y$ where x and y are percent concentrations of the crosslinker solution and actual amount of drug (in mg) retained per gram of beads, respectively. For example, UBA $(4)_{13}$ represents uncoated barium alginate beads prepared in 4% $BaCl_2$ solution and actual loading of drug is 13 mg per gram of polymer.

Drug Release Studies

The traditional dissolution test (TDT) was carried out by putting a definite amount of drug loaded beads in the 25 mL of simulating intestinal fluid (i.e., phosphate buffer medium of pH 6.8) 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 (12). After each measurement, the buffer was replaced by the fresh one. The release study in simulating gastric fluid (SGF, pH 1.2) was carried out by putting the beads in 900 mL of a 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.

As stated earlier, the above TDT was modified to get a more realistic prediction of release behavior of dosage form in the human GI tract. For this, a new approach, called 'flow through diffusion cell' was followed which has been depicted in the Figure 2.

A cylindrical cell with a cone shaped bottom (in accordance with the dissolution test method-3 of JP) was filled with swollen crosslinked polyacrylamide hydrogel particles (initially sieved to 600 μm) as a filler. The test medium (HCl of pH 1.2 as JP 1st fluid and phosphate buffer of pH 6.8 as JP 2nd fluid) is dropped from the upper side of the cell at a constant flow-rate and the outflow from the bottom of the cell is collected in fractions at different time-intervals. Since the dropped medium drains through the swollen gel particles into the bottom and volume of the medium in the diffusion cell remains consistently small, this mimics the low water content and presence of undigested food particles in the large intestine. To the best of our knowledge, such a type of study has been carried out for the first time with alginate beads. All the experiments were carried out in triplicate and the average values have been reported in the data points.

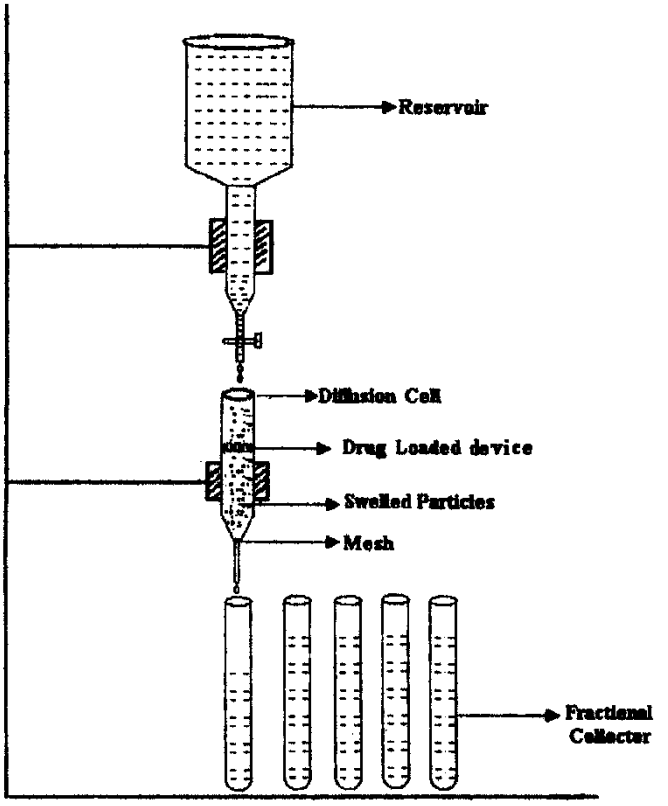

Figure 2. Schematic diagram of flow through the diffusion cell (FTDC) method.

Results and Discussion

Entrapment Efficiency of Barium Alginate Beads

In order to determine the percentage of drug entrapped within the polymer matrix, beads were made by dropping an aqueous solution containing 4% sodium alginate and 0.12% model drug riboflavin into a $BaCl_2$ solution of varying concentrations in the range of 3 to 6 percent (w/v). The amount of drug retained as percent of total drug taken against the concentration of $BaCl_2$ solutions are presented in Figure 3. As can be seen, up to nearly 55 of riboflavin could be retained in the beads using a 4% $BaCl_2$ solution.

Now, lower entrapment efficiency of beads while using $BaCl_2$ solutions with concentrations below 4% may be attributed to the fact that these concentrations of Ba^{2+} ions may not be sufficient to form compact beads. In other words, due to a lower degree of crosslinking, more drug diffuses out of the beads during the curing time (which was 10 min) and subsequent washings. This can also be supported by the fact that in the sodium alginate used for the study, the poly (guluronic acid) content is relatively small (i.e., $M/G = 1.75$ as per manufacturer's specifications) and this G content is responsible for the formation of 'egg-box' structure, which provides stability to the beads. Therefore, a $BaCl_2$ concentration below 4%, may not be enough for the formation of stable and compact beads. Figure 3 reveals one more interesting fact. The beads formed by using crosslinker solutions of more than 4% concentrations also show less percent entrapment of the drug. This can be explained by the fact that when the concentration of Ba^{2+} ions is sufficiently high (i.e., 5 and 6%), the carboxylate groups of the guluronate blocks bind very strongly with the barium ions, thus resulting in the formation of compact network, which subsequently reduces the space occupied by alginate and therefore decreases the volume of the beads (13). This finally causes an appreciable amount of drug solution to diffuse out of the shrinking beads. Therefore, we can conclude that in the present study 4% $BaCl_2$ solution may provide an optimum entrapment efficiency of the beads. Therefore, we carried out all the studies using beads formed by crosslinking with a 4% barium chloride solution.

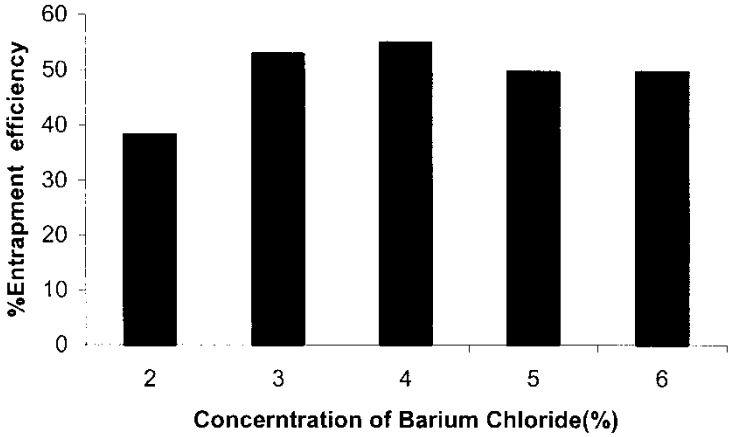

Figure 3. Riboflavin loading efficiency as a function of $BaCl_2$ concentrations.

Effect of pH on the Dynamic Release

It has been reported by previous authors that at low pH, alginate beads do not significantly swell or release their contents (14). It is thus expected that if they are taken orally, they should release the encapsulated drug in minimum quantity in the acidic environment of the stomach and deliver most of the entrapped drug in the large intestinal fluid where pH lies between 6 and 7. In order to investigate this aspect, the dynamic release of the model drug was studied by a traditional dissolution test in the medium of pH 1.2 (artificial gastric juice) and in the medium of pH 6.8 (artificial intestinal fluid) to mimic the digestive tract environment. The results, as depicted in the Figure 4 were opposite to the predictions. As can be seen, the beads exhibited a greater release in the SGF (i.e., medium of pH 1.2) while the drug released at various time intervals in the SIF (pH 6.8) was less. The observed findings may be explained on the basis of reduced crosslinking in the barium alginate beads and small size of the entrapped drug (hydrodynamic radius 5A°). When the beads are put in the acidic medium, the negatively charged $-COO^-$groups present along the guluronic residues get protonated to yield uncharged carboxylic groups. This results in reduction in the electrostatic attraction, which existed among $-COO^-$ groups and cross-linker Ba^{2+} ions within the 'egg box' junctions. This ultimately causes a decrease in the degree of crosslinking and the mesh size within the beads increases. In addition to this, the alginates undergo proton-catalyzed hydrolysis to yield low molecular weight alginic acid (15), which also contributes towards decreased crosslinking within the beads. There is one more reason for faster release in acidic medium. At low pH, the $-COO^-$groups get protonated to $-COOH$ groups and hence, the free Ba^{++} ions within the beads may undergo a little ion-exchange process with external H^+ ions that are in large concentration. Due to this ion exchange process, the large-sized barium ions within the beads are replaced by small sized H^+ ions, thus producing a rather 'loose structure' with bigger voids. This may cause a faster release of entrapped drug molecules in the simulating gastric fluid. However, for the beads in the simulating intestinal fluid of pH 6.8, the situation is somewhat different. The $-COO^-$ groups present in the guluronic residues are bound strongly to the Ba^{2+} ions thus forming a crosslinked network. As the size of the barium

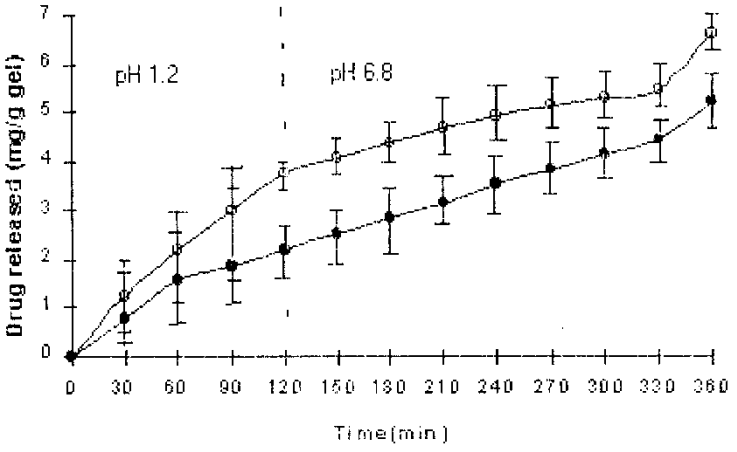

Figure 4. Dynamic release of riboflavin from the uncoated barium alginate beads UBA $(4)_{13}$ in the medium of pH 1.2 (○) and pH 6.8 (●) at the physiological temperature 37°C. (Data points show average value ±s.d. for three experiments.)

ions is sufficiently large (i.e., 1.74 Å), it is supposed to fill a large space between the alginate molecules, thus producing a tight arrangement with smaller voids. Therefore, exchange of larger barium ions in the beads with Na^+ ions of phosphate buffer is hindered or becomes extremely slow, thus permitting a less amount of drug to come out of the beads. The release exponent 'n' was calculated from the double logrithmic form of equation $M_t/M_\infty = kt^n$ where M_t and M_∞ are the drug released at time 't' and at equilibrium, respectively. The values of 'n' for the release of riboflavin in the medium of pH 1.2 and 6.8 were found to be 0.33 and 0.45, respectively. The values, thus obtained are indicative of diffusion controlled release mechanism from the alginate matrix. This was also confirmed by the almost linear plots obtained between fractional release and time$^{1/2}$ (data not shown). Similar results have also been reported for the release of low molecular weight drug Brilliant Blue form the alginate matrix (16).

Release in the Media of Continuous Varying pH

From the above discussion, it is clear that barium alginate beads are unable to retain the entrapped low molecular weight solute within the matrix in the medium of lower pH (SGF, pH 1.2). In fact, they have demonstrated a faster release of entrapped drug in the acidic pH as compared to the medium of pH 6.8.

When a dosage form is administered orally, first it goes to stomach and after residing there for some time, it passes on to the small intestine and then finally to the colon. Thus, while carrying out *in vitro* study, the same dosage form should be allowed to release the drug in SGF, as well as in SIF. Hence, it should be put in the media of varying pH so that it can mimic the transition of dosage form from mouth to colon.

Now, in order to have some idea about the average transit time of an oral dosage form in the GI tract, we followed the results obtained by a group of pharmaceutical scientists (17) who, after carrying out gamma scientigraphic studies on guar gum tablets using ^{99m}Tc-DTPA as tracer in human volunteers, reported a mean gastric emptying time of 1.08 ± 0.11 h and the mean colonic arrival time of 2.83 ± 0.33 h. It means that the small intestinal transit time is likely to be 1.75 ± 0.25 h, thus suggesting that the formulation should enter the colon between 1.75 and 3.75 h after its oral administration. Relying on this data, we opted to expose the barium alginate beads UBA $(4)_{13}$ to the simulating gastric fluid of pH 1.2 (JP 1st fluid, SGF) for a period of 2 h, and then for the rest of the time to the medium of pH 6.8 (JP 2nd fluid, SIF), thus mimicking the transition of beads from mouth to colon along the GI tract. The results have been depicted in Figure 5. It is clear that the amount of drug released from the beads in the first 2 h in the 1st fluid (i.e., pH 1.2) is nearly 3.98 ± 0.12 mg per g gel, while in the next 8 h, when beads are transferred to the medium of pH 6.8, the drug released is 6.82 ± 0.14 mg gel. It means that out of the total drug released over a duration of 10 h, nearly $37.1 \pm 2.2\%$ release occurs in the first 2 h in the medium of pH 1.2, thus suggesting that an appreciable amount of drug shall be released in the first 2 h in the acidic environment of the stomach if the beads are taken orally. This finding is contradictory to the basic requirement of a colon-targeted oral delivery system according to which a minimum release should occur in the gastric fluid during the stay of the oral dosage form. So it can be concluded that uncoated barium alginate beads, although quite stable in the media of varying pH, proved to be a failure in protecting the entrapped low molecular weight drug in the acidic environment of stomach.

A close look at Figure 5 reveals one more interesting fact. After 2 h, when the beads are transferred into the simulating intestinal fluid of pH6.8, there occurs a 'burst release'

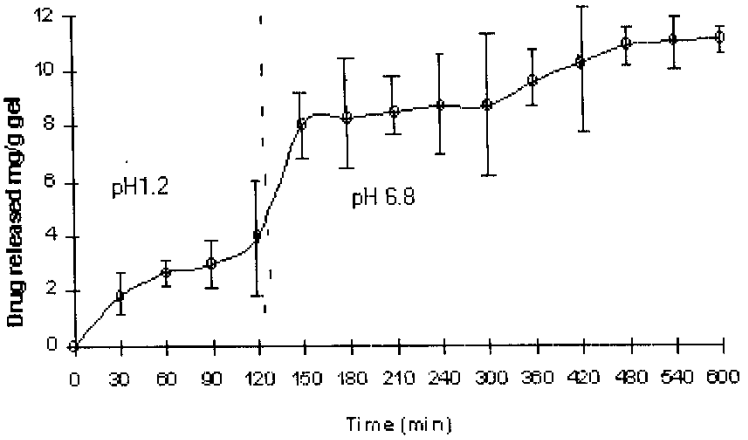

Figure 5. Composite depiction of release of riboflavin from the uncoated beads UBA $(4)_{13}$ in the changing pH environment. In the medium of pH 1.2 (SGF) for 0–2 h and then in a phosphate buffer of pH 6.8 (SIF) for 2–48 h (data shown for 10 h only). (Data points show average value $\pm$ s.d. for 3 experiments.)

from the beads in next 30 min. This can be well attributed to the acid-catalyzed hydrolysis of barium alginate.When the beads are put initially into SGF of pH 1.2 for a period of 2 h, the alginate undergoes acid-catalyzed hydrolysis to yield low molecular weight alginic acid. Later on, on transferring the beads into the medium of pH 6.8, the alginic acid produced previously may now tend to dissolve, thus resulting in a sudden burst of entrapped drug. This result is in agreement with our previous study (9) in which acid treated alginate beads demonstrated a drastic water uptake when put in the simulating intestinal fluid. In the present study, although the beads remained quite stable for more than 48 h but they released nearly all the entrapped drug in 16 h only, the amount of drug released being 12.21 $\pm$ 0.18 mg per g beads. Now, as the colonic transit time of an oral dosage form is between 20 to 30 h, the dosage form must release the entrapped drug over this duration. However, the beads seem to be unable to prolong the drug release over the required time period.

Hence, it can be concluded from the above discussion that barium alginate beads cannot protect the entrapped low molecular weight drug in the simulating gastric fluid of pH 1.2 because they release an appreciable amount of drug in the first 2 h in acidic pH 1.2. Moreover, they cannot prolong the drug release for a longer period in the simulating intestinal fluid of pH 6.8. Therefore, in order to use these beads as an oral drug delivery system, it becomes necessary to coat the beads with some suitable film forming material, which can provide maximum protection to the entrapped drug in acidic medium and also prolong the drug release process in the simulating intestinal fluid.

Release from Ethyl Cellulose Coated Beads in Media of Varying pH

In the pharmaceutical field, ethyl cellulose is a polymer used to prepare sustained release medications as well as a coating material (18). Although ethyl cellulose is considered insoluble, it can take up water (19). This can be explained on the basis of the hydrogen bonds forming capability of the polymer with water. There is polarity difference between the oxygen atom and the ethyl group in the ethoxy group. The presence of

hydroxyl groups, depending on the degree of substitution can also contribute to the interaction of the polymer with water.

From the discussion in the previous section, it has been crystal clear that although barium alginate beads are quite stable, they release an appreciable quantity of the encapsulated drug in first 2 h in the acidic environment (i.e., SGF, pH 1.2) and hence, prove to be unable to protect the entrapped drug in the gastric fluid as was predicted in the beginning of the study. Moreover, they exhibit a faster release, extended over a time period of nearly 16 h, in SIF and hence, fail to prolong the drug release for a much longer period to match the colonic transit time of oral dosage.

Therefore, in order to minimize the release of encapsulated drug in simulating gastric fluid (SGF, pH 1.2), and prolong the duration of drug release in the medium of colonic pH, the beads were coated with 6% (w/v) solution of ethyl cellulose (see Experimental section) and their release behavior was studied in the media of varying pH by putting them in SGF for 2 h and then transferring into SIF for rest of the period (as described in the previous section). The release profiles, obtained with ethyl cellulose coated beads have been depicted in Figure 6. As the purpose of coating of beads is to retard the diffusion of drug in the first 2 h in the simulating gastric fluid of pH 1.2, the data shown in the Figure 6 can be compared with the release data obtained with uncoated beads in the Figure 5. A comparison of the two profiles reveals that ethyl cellulose coated beads release nearly 1.21 ± 0.12 mg drug per g beads in first two hours in simulating gastric fluid while uncoated beads release 3.98 ± 0.16 mg drug under a similar environment. In this way, due to the coating of beads there is approximate $68 \pm 3\%$ decrease in the amount of drug released in the first 2 h. Moreover, it is also clear that the coated beads demonstrate a slower release as compared to the uncoated beads and they also prolong the drug release process as indicated by the fact that they release nearly 12.16 ± 0.21 mg of drug per g beads in a total duration of nearly 36 h (data shown for 20 h only). In this way, due to the coating of beads by ethyl cellulose, a comparatively little quantity of drug is released in the acidic medium and total release is prolonged over a much longer time period which is almost the same as the colonic transit time of an oral dosage form in the GI tract.

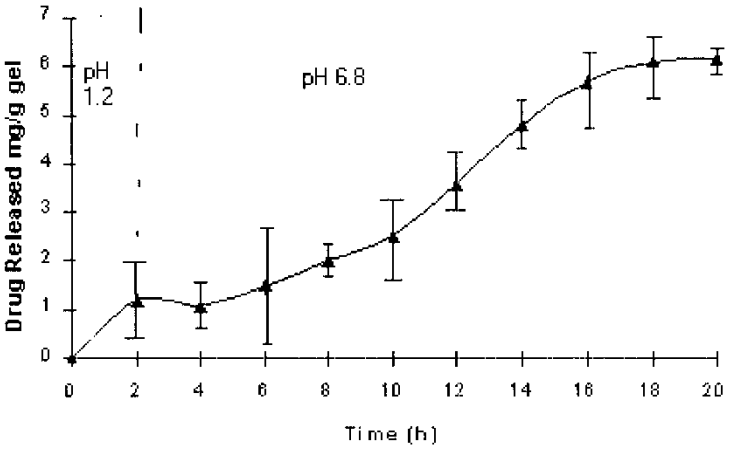

Figure 6. Cumulative release profiles of riboflavin from the barium alginate beads CBA $(4)_{13}$ coated with ethyl cellulose solution of 6% (▲) in the medium of pH 1.2 (0–2 h) and pH 6.8 (2–48 h) (data shown for 20 h only). (Data points show average value $\pm$ s.d. for 3 experiments.)

Release in the Media of Varying pH by FTDC Method

The above drug release studies, carried out by traditional dissolution tests, cannot act as a basis for predicting the behavior of alginate beads in the gastrointestinal tract because the above studies have been carried out under sink conditions (when the beads sink in the release medium) while the conditions in human GI tract are totally different. When a dosage form is taken orally after the meals, it moves down the GI tract along with semi-solid food particles (20). Therefore, the dosage form contacts with water through the wet semi-solid mass and this condition is quite different from those maintained in the above dissolution tests where the dosage form sinks in the release medium. Moreover, in a large intestine water content and agitation, intensity is low. In order to incorporate these *in vivo* GI conditions, we carried out drug release studies using a FTDC method, and data obtained, was compared with that obtained by the TDT method. However, in both the approaches, the initial release for 2 h in simulating gastric fluid was studied under sink conditions because in the stomach water content is high. For this, the beads were placed in 900 mL of simulating gastric fluid (SGF, pH 1.2) for 2 h and then, for the FTDC method, the same beads were buried in the swollen polyacrylamide gel particles as described in the section 'Materials And Method' (also see Figure 2). Figure 7 displays a comparative depiction of release profiles demonstrated by the bead samples CBA $(4)_{13}$ in the media of varying pH (0–2 h in pH 1.2 and, 2–48 h in pH 6.8) by the 'traditional dissolution test' (TDT) and 'flow through diffusion cell' (FTDC) method with swollen crosslinked polyacrylamide gel particles (crosslinking ratio 0.023, particle size 600 μm) used as fillers. The results, as depicted in Figure 7, indicate that the beads demonstrate different profiles by the above two approaches. The amount of drug released at different time intervals is more in the FTDC method, while a slower diffusion is observed in TDT. At first, the results appear to be quite surprising because in TDT, the beads sink in the release medium and hence, are in direct contact with it, which should have resulted in a faster release. But the results obtained are just the opposite. The faster release of drug, observed in the FTDC method, may be explained as follows.

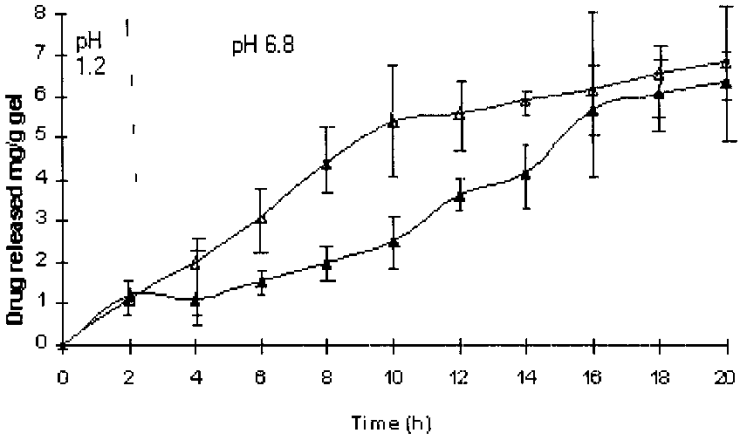

Figure 7. Cumulative release profiles of riboflavin from the 6% ethyl cellulose coated alginate beads CBA $(4)_{13}$ in the medium of pH 1.2 (0–2 h) and pH 6.8 (2–48 h) by TDT (▲) and FTDC method (△) with swollen gel particles as fillers (data shown for 20 h only). (Data points show average value ± s.d. for 3 experiments.)

The diffusion of drug from a polymer matrix depends upon a number of factors like the concentration gradient developing within the device, mesh size of the polymer network, and partition coefficient of the drug between the gel phase and release medium, etc. However, the concentration gradient developed at the bead-solution interface seems to be a governing factor in the present case. In TDT, the beads were put in 25 mL of a buffer solution and the release medium was replaced after definite intervals (which was 2 h in the present study) by fresh buffer solutions. It means that for a period of 2 h, the drug, coming out of the beads, remains in the surrounding fluid. This may probably retard the diffusion process in two ways. First, since the drug coming out of the beads remains in the medium and hence, there are chances of its sorption back into the beads. Secondly, the presence of the drug in close vicinity of the beads may also result in lowering of the concentration gradient at the gel-solution interface. Therefore, it appears that diffusion of the drug in TDT is relatively slower. On the other hand, in the FTDC method, drug coming out of the beads goes down along with the buffer medium, which is continuously dripping down at a constant flow rate. So, the drug molecules that have just diffused out from the beads will not stay in the close vicinity of the beads, but they will go down and will be collected in a fractional collector at the bottom. This immediate removal of drug from the surrounding of the beads develops a sharp concentration gradient at the gel-solution interface, thus making the release faster. Moreover, the immediate removal of drug from the close vicinity of the beads also minimizes the chances of sorption of drug back into the polymer matrix. Thus, a faster diffusion is observed in the FTDC method as compared to the traditional dissolution test. The above discussion can be summarized by stating that in FTDC, the continuous flow of the release medium is mainly responsible for the high concerntration gradient developed at the gel–solution interface, thus resulting in faster release.

Effect of Nature of Filler Particles on Drug Release Profile

As observed in the previous section, the two profiles obtained by TDT and FTDC methods differ appreciably from each other. The beads exhibited a greater release when studied by the FTDC method with crosslinked polyacrylamide swollen particles used as fillers. The size and nature (hydrophobic or hydrophillic) of filler particles may also affect the release profile in the FTDC method. To investigate this aspect, in addition to gel particles, glass beads of diameter 0.48 ± 0.01 cm were also used as filler particles and the results have been depicted in Figure 8. It is clear that alginate beads, surrounded by glass beads, show a greater release as compared to beads buried in the crosslinked gel particles. In the presence of the glass beads, the amount of drug released in 20 h is nearly 11.22 ± 0.31 mg per g gel, while in the same duration, the beads surrounded by gel particles exhibit nearly 6.62 ± 0.28 mg per g beads. This can be explained on the basis of the big size and great hydrophobic character of the glass beads. For a given volume of the diffusion cell, the glass beads occupy less space as compared to the micrometer sized gel particles, which produce rather compact packing. In other words, the buffer medium flowing down the diffusion cell filled with glass beads have a greater area of contact with the alginate beads. In addition to this, the hydrophobic or water repelling tendency of the glass beads also provides a greater opportunity to the dripping medium to interact with the drug-loaded beads. Moreover, as compared to the crosslinked swollen gel particles, the big sized glass beads provide wider water channels through which the buffer solution can contact with beads and the drug can diffuse down in the fractional collector put at the bottom of the diffusion cell. Here, it is worth mentioning that for

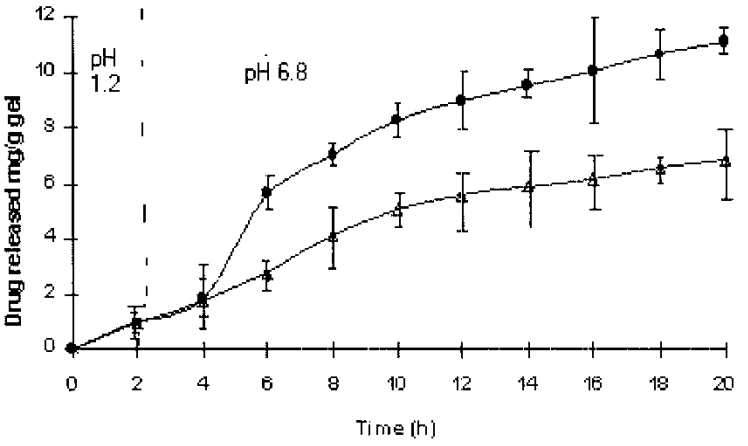

Figure 8. Dynamic release of riboflavin as a function of time from 6% ethyl cellulose coated barium alginate beads CBA $(4)_{13}$ in the medium of pH 1.2 (0–2 h) and pH 6.8 (2–48 h) as studied by the FTDC method with glass beads (•) and gel particles (△) used as fillers (data shown for 20 h only). (Data points show average value ± s.d. for 3 experiments.)

the first 2 h the release data is almost the same because during the first 2 h the release has been studied under sink conditions in the medium of pH 1.2 (to mimic stomach conditions) and then the same beads have been transferred into diffusion cell filled with gel particles, as well as glass beads. Thus, we see that nature of the filler particles play a significant role in governing the release behavior of barium alginate beads. Finally, it should be mentioned here that the purpose of using glass beads as fillers in the diffusion cell is just only to reflect the hydrophobic nature of the filler particles.

Conclusions

The release of model drug riboflavin has been studied from ethyl cellulose coated and uncoated barium alginate beads in the artificial gastric fluid (SGF, pH 1.2) and intestinal fluid (SIF, pH 6.8) at the physiological temperature 37°C. The uncoated beads demonstrated faster release in the medium of pH 1.2 and therefore, the beads were coated with ethyl cellulose to suppress the diffusion of drug in the acidic pH and to prolong the release process. The results obtained with the 'traditional dissolution tests' were compared with those obtained from the FTDC method. It was observed that drug released at different time intervals was less in 'traditional dissolution test' while a faster release was observed in the FTDC method. Moreover, the drug release from the beads in the presence of glass beads was found to be more as compared to the beads surrounded by swollen gel particles. The beads crosslinked in 4% barium chloride solution showed maximum drug entrapment efficiency.

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