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Dynamic Release of Vitamin B_2 from Floating Barium Alginate Beads for Gastric Delivery

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The present study is focused on the development of floating barium alginate beads, which after oral administration, are intended to prolong the gastric residence time and increase the drug bioavailability. Out of three different barium alginate bead samples prepared using $NaHCO_3$ as porogen, the beads prepared with 4 and 5 percent solutions of sodium alginate and with 1.5% content of porogen $NaHCO_3$ remained buoyant for more than 9 h. It took nearly 8–9 h for the beads to release all the entrapped model drug vitamin B_2 in the simulated gastric fluid (SGF, pH 1.2) at 37°C. In addition to the traditional dissolution test, the release study was also carried out by using a recently developed approach called 'Dissolution Test with Refreshing Medium (DTRM)' which reflects the gastric *in vivo* conditions more effectively. Finally, the release data was interpreted by using 'first order' kinetic model.

Keywords: porous beads; vitamin B_2; porogen; gastric delivery

1 Introduction

Although gastrointestinal transit time, to some extent, depends upon the physiology of the patient and condition of the stomach (i.e. whether in a fasted state or feed state) but the average residence time of an oral dosage form in the stomach varies between 1–3 h (1). However, this rapid gastrointestinal transit could result in incomplete release of drug from the device above the absorption zone and thus lead to diminished efficiency of the administered dose (2). Therefore, it becomes necessary to prolong the gastric residence time so that nearly all the drug is released in the stomach or somewhere in the upper small intestine in the desired time period (3, 4). Although various approaches have been made to increase the gastric residence time (5–8), each approach has its own limitations. For example, 'swelling and expanding systems' may show a hazard of permanent retention. Similarly, 'bioadhesive systems' may result in irritation of a mucous layer due to high localized concentration of the drug (9). In addition 'single-unit systems' such as tablets or capsules may exhibit the all-or-none emptying phenomenon (10). Therefore, it appears that the above mentioned problems may be minimized by using porous floating beads to prolong the gastric transit time. Moreover, natural polymers like sodium alginate may best be employed for this purpose because this polysaccharide is biocompatable and undergoes ionotropic gelation under normal conditions.

In the present study, porous barium alginate beads have been synthesized by Ba^{2+} ions induced ionotropic gelation of sodium alginate in the presence of porogen $NaHCO_3$ and release of model drug vitamin B_2 has been studied in the artificial gastric environment at 37°C.

It has been observed that traditional *in vitro* dissolution methods fail to make a fair prediction of the *in vivo* performance of floating dosage forms (11). The reason is that these methods do not mimic the conditions present in the stomach. For example, gastric juice is secreted at the rate of nearly 2 ml/min and emptying of liquid occurs through pylorus openings. In order to incorporate these conditions in the dissolution study, we have also carried out the release study by a newly developed approach, 'Dissolution Test Through Refreshing Medium (DTRM)'.

2 Experimental

2.1 Materials

Sodium Alginate (low viscosity grade; 250 cp in 2% solution at 25°C) and Riboflavin were purchased from HiMedia, Mumbai, India. The crosslinker $BaCl_2$ and porogen $NaHCO_3$ were obtained from Qualigens, Mumbai, India and used as received. The double distilled water was used throughout the investigations.

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2.2 Preparation of Drug–Loaded Barium Alginate Floating Beads

The model drug vitamin B_2 loaded porous barium alginate beads were prepared through ionotropic gelation of sodium alginate in acidified $BaCl_2$ solution. To generate porosity, alginate solution contained a pre-calculated quantity of drug riboflavin, porogen $NaHCO_3$. In brief, definite quantities of sodium alginate and $NaHCO_3$ were dissolved in water and the resulting solution was dropped through a 26 G syringe needle into a 4% $BaCl_2$ solution containing 10% (v/v) acetic acid, with constant stirring at 50 rpm. The beads, thus formed, were cured for 10 min in the gelatin medium, and were finally collected, washed with ethanol and distilled water, and then dried in the dust free chamber at 40°C till they obtained constant weight. In order to test the buoyant behavior of beads, plain beads samples were also prepared by the same method as described above. However, drug was not present in the dope (i.e., sodium alginate solution). In all, three samples of different compositions were prepared as described in the Table 1.

2.3 Drug Entrapment

In order to determine the drug entrapment efficiency of the beads samples, the freshly prepared beads were washed in distilled water of known volumes. After three successive washings, the beads were allowed to be dried and the amount of drug leached out during the washing of beads was determined by measuring the absorbence of the solutions. The percent drug entrapment (DE) may be given as:

$$\%(\mathrm{DE}) = \frac{[\text{Drug loaded per g polymer}] - [\text{Drug leached out per g polymer}]}{[\text{Drug loaded per g polymer}]}$$

2.4 Beads Characteristics

2.4.1 SEM Analysis

For morphological characterization, Scanning Electron Micrographs analysis of nonporous and porous beads was performed on a SEM apparatus (STEREO SCAN, 430, Leica SEM, USA) in the Indian Institute of Technology, Mumbai, India.

Table 1. Composition of various bead samples

Sample code	Sodium alginate (%)	Sodium bicarbonate (%)	Barium chloride (%)
A	4.00	1.50	4.00
B	4.00	2.00	4.00
C	4.00	1.50	5.00

2.5 FTIR Spectra of Beads

The FTIR spectra of plain and drug-loaded beads were recorded in FTIR spectrophotometer (Shimadzu, Japan) at the National Chemical Laboratory, Pune, India.

2.6 Homogenity Test

In order to confirm the formation of homogeneous beads, freshly prepared beads were divided into five parts and their "wet weight to drug weight" ratios were determined. The homogeneous nature is indicated by the horizontal linear plot obtained between the fresh wet/dry weight ratio and number of parts.

This procedure was repeated for all the samples prepared.

2.7 Micrometric Properties

The beads were characterized by their micrometric properties such as apparent density (d_a), true density (d_t), tapped density (d_{tap}) and the compressibility index (CI: a value in the prediction of flowability).

The apparent density (d_a) is given as:

$$d_a = \text{mass of porous beads/volume of beads} \quad (1)$$

Similarly, the true density (d_t) is given:

$$d_t = \text{mass of porous beads/volume of polymer} \quad (2)$$

According to equation (1) and (2), a material is homogeneous if its apparent density is equal to true density. The lower the apparent density, the higher the porosity of beads. The density measurements were carried out using n-heptane as described elsewhere (12).

The tapping method was used to calculate tapped densities and % Cl according to following equations:

$$d_{tap} = \text{mass of beads/volume of beads after tapping} \quad (3)$$

and

$$\%\mathrm{CI} = (1 - v/v_0)100 \quad (4)$$

where v and v_0 are, respectively, the volumes of the beads after and before the standard tapping (13).

The tapping was carried out in a 10 ml measuring cylinder. After observing the initial volume of beads, the tapping was continued on the hard surface at a rate of 100 taps per min until no further change in volume was noted.

Finally, the total percent porosity (%P) and total pore volume (Vp) were calculated using following equations:

$$\%\mathrm{P} = (1 - d_a/d_t) \times 100 \quad (5)$$

and

$$\mathrm{Vp} = (1/d_a - 1/d_t) \times 100 \quad (6)$$

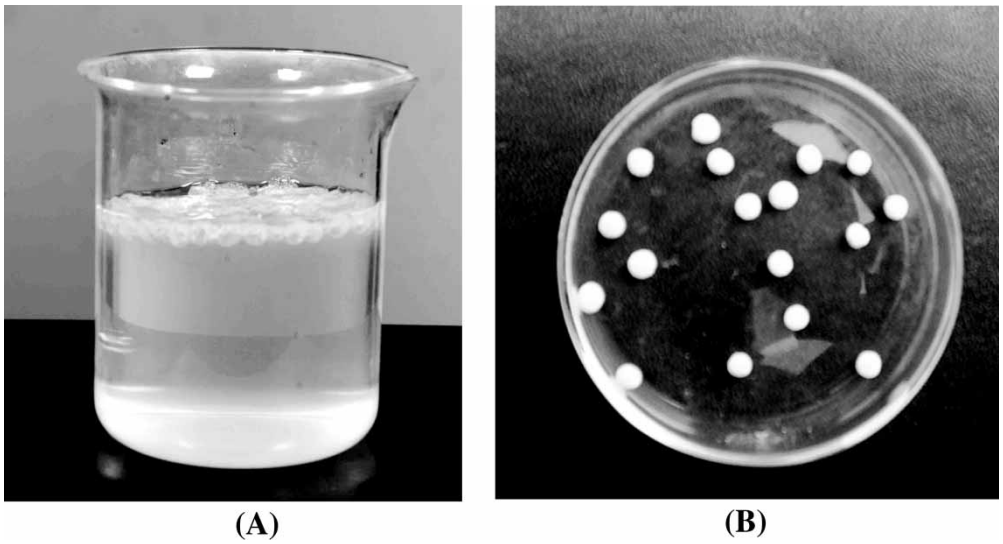

Fig. 1. (A) Photograph of floating beads, (B) Photograph of freshly prepared beads.

2.8 Buoyancy Test

The buoyancy of the beads was studied by using a water bath shaker with a shaking speed of 30 rpm (oscillations per minute) at 37°C, soaking 50 beads in 100 ml of stimulating gastric fluid (pH 1.2, with 0.02% w/v of Tween 80 in order to simulate the surface tension of human gastric juice 35–50 mN/m^2) (14).

Both the number of floating beads (observed visually) and the time for which they remained buoyant in the test solution was determined for an overall duration of 18 h, (Figure 1). Finally, the % buoyancy was calculated as (Soppimath et al., 2001):

$$\%\text{Buoyancy} = Q_f/Q_f + Q_s \times 100 \qquad (7)$$

where Q_f and Q_s are the masses of the floating and settled beads, respectively.

2.9 Drug Release Study by Traditional Dissolution Test (TDT)

Approximately 100 mg of the beads were suspended in 900 ml of simulating fluid of pH 1.2 (US Pharmacopoeia) in Apparatus II at 37°C under sink conditions. Aliquote of 3 ml were withdrawn at different time intervals and amount of B_2 released was determined spectrophotometrically (15). The total volume of release medium was kept constant by the addition of 3 ml of fresh buffer after every withdrawal.

2.9.1 Drug Release Study by DTRM Approach

As mentioned in the 'Introduction' section, the newly developed approach takes into consideration the specific gastric features like refreshing of fluid and emptying of liquid through pylorus openings. The apparatus designed for the DTRM approach consists of a diffusion cell prepared with a separating funnel modified at the base by adding a 'inverted V' shaped glass tube through which SGF of pH 1.2 was allowed to be dropped at the rate of 2 ml/min and collected in the receivers. On the top of this diffusion cell there is a reservoir which contains SGF and the fluid is allowed to be dropped at the same rate i.e. 2 ml per minute into the diffusion cell as shown in Figure 2.

To carry out a dissolution test, a pre-weighed quantity of drug loaded porous beads was placed in 70 ml of SGF in diffusion cell at 37°C. Here it is worth mentioning that this modified method tries to mimic the *in vivo* gastric volume (70 ml), gastric secretion rate (2 ml/min) and emptying of liquid through pylorus opening (11). The fluid dripping from the cell was collected in various receivers at different time-intervals and analyzed for calcium release using

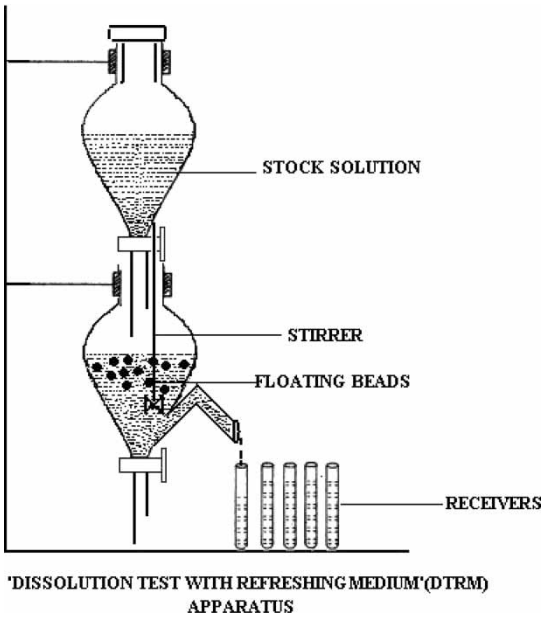

Fig. 2. Diagrammatic scheme for DTRM apparatus.

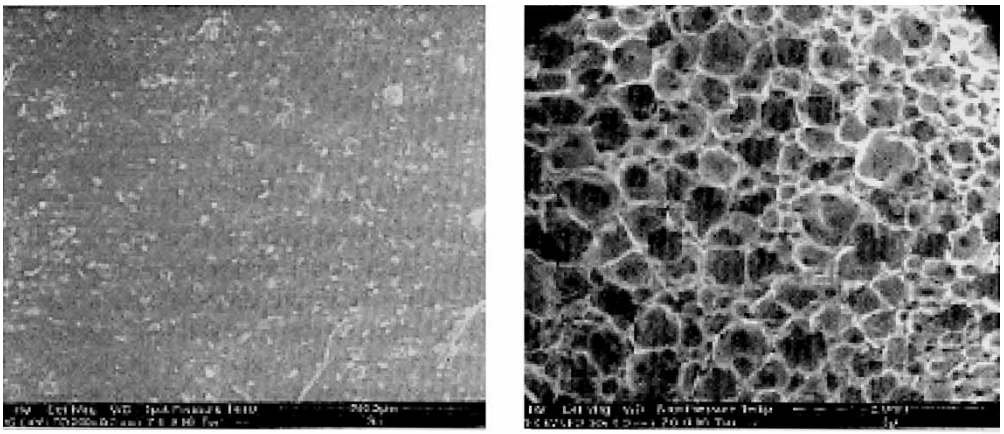

Fig. 3. (A) SEM of nonporous beads, (B) SEM of porous beads.

EDTA method. In order to keep the volume of the SGF constant in the cell, the fresh buffer was also allowed to be dropped from the reservoir at the rate of 2 ml/min into the release medium.

3 Results and Discussion

3.1 SEM Analysis

The morphological features of the nonporous and porous beads have been investigated by recording their SEM images as shown in Figure 3(A) and (B), respectively. A close examination of the photograph of nonporous beads clearly reveals that the beads surface is quite smooth. On the other hand, the porous beads depict a distinct morphology with shell type structures having pores. This entirely different morphology of porous beads may be attributed to the fact that the presence of $NaHCO_3$ generates pores into the polymer by producing CO_2 gas during the gelation process.

3.2 FTIR Spectra of Porous Beads

The broad and diffused bands, seen in the IR spectra of polymers, are indicative of the opacity of the sample which, in turn, is manifestation of high molecular weight of the polymer. A comparison of IR spectra of drug riboflavin, blank and drug-loaded samples (Figure 4) suggest that there is decrease in the intensity in the region 1650–1750 cm^{-1} due to absorption of riboflavin. In other words, the bands due to absorption from drug seem to be merged with the broad peaks of the polymer. This can be attributed to the absorption of riboflavin in the polymer through H-bonded interactions.

3.3 % Drug Entrapment

It has been a well established fact that there is appreciable loss of drug during the washing in the case of porous beads (17). In the present study also, the % drug entrapment for the three samples, namely A, B, and C was found to be nearly 78, 72, and 82 percent, respectively. The minimum entrapment in the sample B could possibly be due to the fact that this sample was prepared by using maximum amount of porogen $NaHCO_3$ (Table 1). In addition, sample C had highest drug entrapment, possibly due to highest amount of crosslinker used (i.e., 5% $BaCl_2$).

3.4 Homogenous Nature of Beads

In order to get the homogeneous beads, it is necessary that the rate of stirring of crosslinking solution and that of falling of drops into the gelation medium must be constant throughout the course of the gelation process. In fact, the constant stirring rate results in the uniform viscosity of the gelation medium and the uniform rate of falling of dope ensures ionotropic gelation of all beads to the nearly same extent.

The results of the homogenity test, as depicted in the Figure 5, clearly indicate that all the samples prepared with

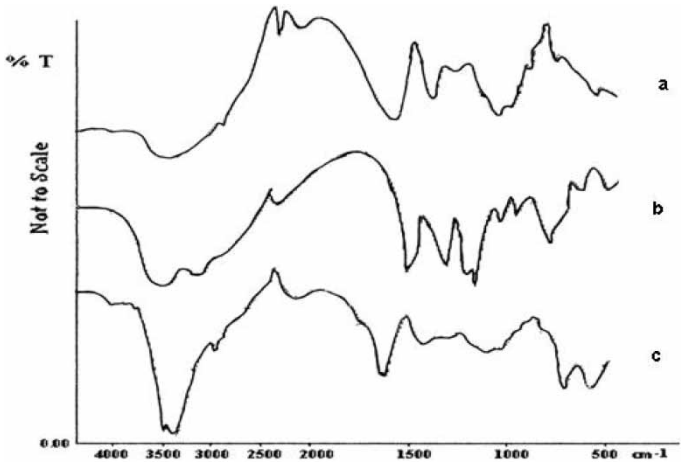

Fig. 4. FTIR spectra of (a) unloaded bead sample, (b) drug, (c) drugloaded bead sample.

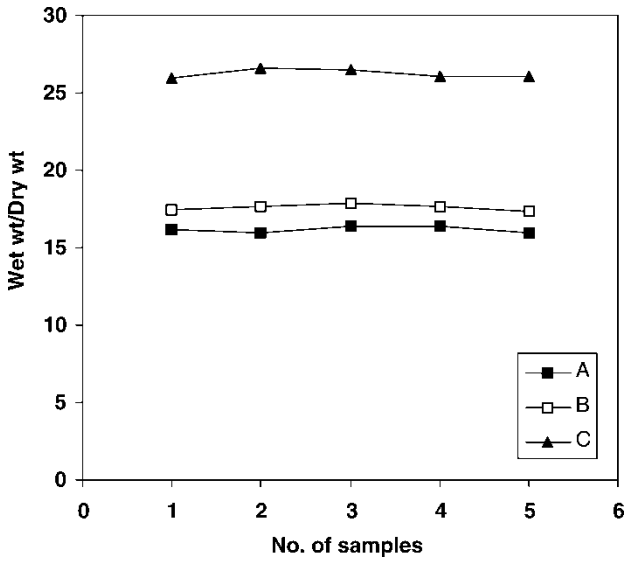

Fig. 5. Homogenity test for various bead samples.

varying compositions (Table 1) exhibit almost linear horizontal plots obtained between 'wet weight/dry weight' and numbers of parts. This indicates that the synthesis conditions for all the samples might have been maintained throughout the course of gelation. It is worth mentioning here that slight deviations from the linearity may be considered within the permissible limits. Moreover, the sodium alginate solution, used in the synthesis of beads, has relatively lower viscosity, which also helps in obtaining homogeneous beads.

3.5 Micrometric Properties of Beads

Table 2 describes various micrometric properties of the three bead samples. The data shown clearly indicate that percent compressibility index (CI) values of the bead samples fall in the range 14.3 to 17.5, thus suggesting good flow characteristics of the beads (16). The values of tapped density and the apparent density lie in the range 0.24 to 0.32 and 0.37 to 0.50 respectively. Obviously these values are quite less than the density of the stimulating gastric fluid (i.e., 1.004 g cm^{-3}) thus indicating that the bead samples will have the propensity to exhibit fair buoyancy *in vivo*.

3.6 Buoyant Behavior of Beads

The results of buoyancy test are depicted in the Figure 6. It is clear that for all the three samples, minimum 80% beads exhibit buoyant behavior and hence, these samples can be considered to have fair floating capacity. A close look at the Figure 6 also reveals that all the three bead samples show a floating lag time of 2–3 h. The sample B shows 80% buoyancy just 2 h after it is put in the simulating fluid. Moreover, nearly 90% beads begin to float after 3 h. However, the bead samples A and C show a comparatively poor buoyancy. The excellent buoyancy, demonstrated by bead sample B, may be attributed to the presence of relatively higher content of porogen $NaHCO_3$ in the dope, thus producing more porous beads during the course of ionotropic gelation. The initial lag time may be explained as below.

The floating behavior of a bead depends upon hydrodynamic balance between the weight and the volume change of the dosage form when it is placed in the floating medium. When the beads are put in the SGF, the beads undergo slight decrease in volume due to shrinking tendency of alginate in acidic pH (17). In addition to this, the beads show almost negligible water uptake because the Ba^{++} ions, due to their larger size, well occupy the 'egg-box' cavities within the polyguluronate blocks and hence barium ions do not undergo ion exchange with external H^+ ions, thus causing almost no weight change. This finally results in increase in the density of the beads and hence they do not float in the initial stage. However, when the beads continue to remain within the stimulating gastric fluid, the plasticization of macromolecular chains and the decrease in electrostatic binding between Ba^{++} ions and protonated -COOH groups result in the generation of the already existing pores within the polymeric beads. This ultimately causes an increase in the beads volume and so the beads begin to float. In this way, after a floating lag time, the beads start to float in the SGF. Finally, we selected bead sample B for the study of drug release behavior in SGF.

3.7 Drug Release Studies

In order to compare the traditional dissolution test with the newly developed DTRM approach for gastric delivery, the

Table 2. Various micrometric properties of bead samples

S. no.	Micrometric parameters	Bead samples		
		A	B	C
1	Volume of pores (cm^3)	0.300	0.200	0.500
2	Volume fraction of polymer	0.625	0.666	0.375
3	Fraction of pores	0.375	0.333	0.625
4	Tapped density (g cm^{-3})	0.250	0.240	0.320
5	Apparent density (g cm^{-3})	0.375	0.500	0.375
6	True density (g cm^{-3})	0.480	0.450	0.800
7	% compressibility index % (C.I.)	16.00	14.30	17.50

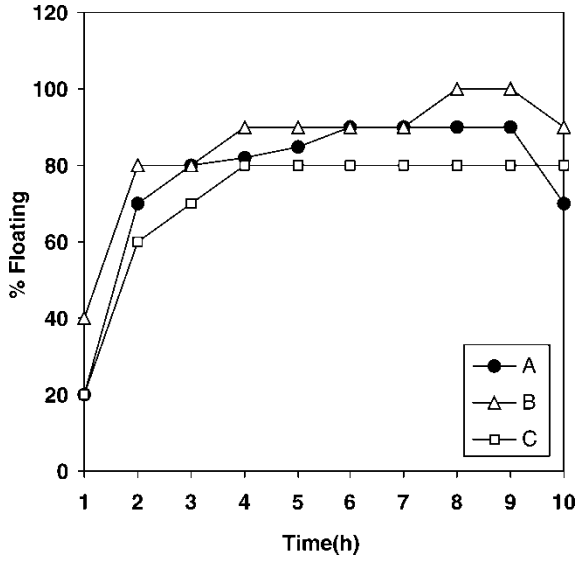

Fig. 6. Number of floating beads vs. time profiles for the bead samples A (•), B (Δ), and C (○) in artificial gastric fluid of pH 1.2 at 37°C. (For composition of A, B, and C, see Table 1).

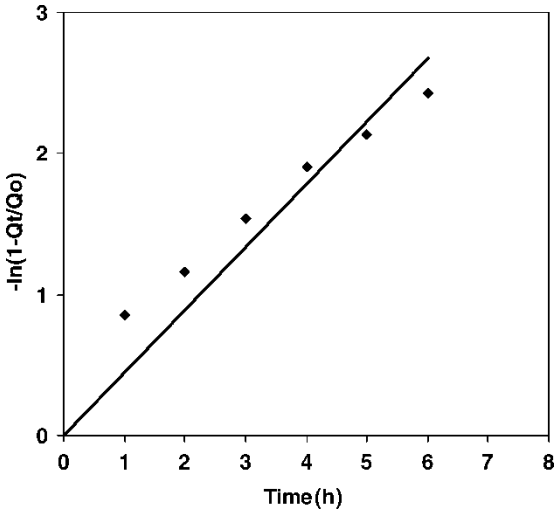

Fig. 8. $-\ln(1 - Qt/Qo)$ vs. t plot for first order kinetics.

dynamic release of vitamin B_2 was studied as a function of time by these two methods. The results, as shown in Figure 7, clearly indicate that the floating beads demonstrate faster release when studied by DTRM approach. This may simply be explained on the basis of the fact that DTRM is a dynamic method in which the release medium is continuously being replaced partially by the fresh buffer. This results in development of sharper concentration gradient at the beads surface–solution interface. On the other hand, in TDT approach the beads remained throughout in the 900 ml of artificial gastric fluid and therefore with the continuous release of drug, the concentration gradient developed at the interface was not so sharp as obtained in the DTRM approach. Here it is being worth mentioned that due to the porous nature of beads the release process was already very fast.

We also attempted to interpret the kinetic data obtained with DTRM approach by first order kinetic model (18). The rearranged kinetic equation for first order release may be given as:

$$-\mathrm{In}\left(1 - \frac{Q_t}{Q_\infty}\right) = kt \tag{8}$$

where Q_t/Q_∞ is the fractional release at time t and k is first order rate constant. In order to test the validity of this equation for observed release data, we plotted a graph between $-\mathrm{In}(1 - Q_t/Q_\infty)$ and t which yielded a straight line, (Figure 8), thus confirming that release of drug from the porous beads follow first order kinetics.

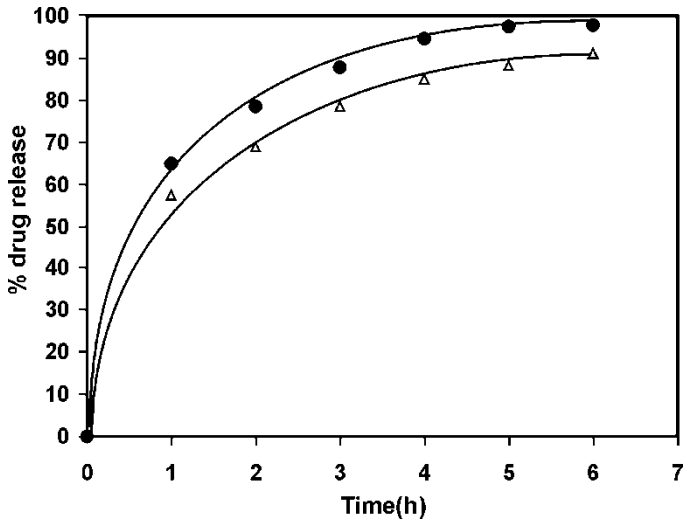

Fig. 7. Comparative depiction of release profiles obtained by DTRM approach (•) and TDT approach (Δ).

4 Conclusions

From the above study, it can be concluded that barium alginate porous beads, prepared by ionotropic gelation of sodium alginate, in the presence of porogen $NaHCO_3$, by acidified $BaCl_2$ solution yields porous beads. The release of model drug B_2 from these porous beads follow first order kinetics and nearly 95% drug is released in7 h in the artificial gastric fluid at 37°C. The drug is released at a faster rate when studied by newly developed approach 'Diffusion Through Refreshing Medium (DTRM)'. The conditions, maintained in this approach, are much closer to the *in vivo* gastric conditions as compared to the traditional dissolution method.

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