Iranian Polymer Journal
16 (8), 2007, 521-527

Available online at: http://journal.ippi.ac.ir

Prolonged Gastric Delivery of Vitamin B2 from a Floating Drug Delivery System: An in Vitro Study

Sunil Kumar Bajpai*, Manjula Bajpai, and Leena Sharma

Polymer Research Laboratory, Department of Chemistry, Government Model Science College, Jabalpur (M.P.)-482001, India

Received 13 January 2007; accepted 30 June 2007

A B S T R A C T

The present study describes the drug release behaviour of vitamin B2 loaded superporous floating hydrogels which was prepared through rapid copolymerization of acrylamide and acrylic acid in the presence of model drug using $NaHCO_3$ as porogen and tetraethylmethylene diamine as catalyst. The gels prepared with 0.12 and 0.58 mM of cross-linker remained buoyant for nearly 96 h, but showed different release behaviours. The cross-linked sample with 0.12 mM released almost 100% drug within two hours in a simulating gastric fluid of pH 1.2, while the sample with 0.58 mM of cross-linker demonstrated a slower release which was extended over a period of 30 h. The mesh sizes of two samples were found to be 23.25Å and 20.11Å as determined from swelling measurements. The asymptotic nature of the release profile indicated a first-order kinetics, which was also confirmed by the regression analysis. The gels offer their strong candidature for prolonged gastric delivery of drugs for the treatment of gastric disorders.

Key Words:

gastric delivery;
first order;
vitamin B2;
Higuchi model.

INTRODUCTION

A problem, frequently encountered with conventional controlled release dosage forms is the inability to increase their residence time in the stomach and proximal portion of small intestine [1]. Retention of an oral formulation in the stomach prolongs the overall gastrointestinal (GI) transit time, thereby, resulting in an improved oral bioavailability of the basic drugs that have poor solubility in higher pH, as well as, the drugs susceptibility to circadian variations [2-4]. Under this condition it becomes necessary to prolong the presence of dosage form in the stomach or somewhere in the upper small intestine until all the drug is released in the desired period of time [5-7].

(*) To whom correspondence to be addressed:
E-mail: mnlbpi@rediffmail.com

The retention of drug delivery system in the stomach prolongs the overall GI transit time, thus resulting in an improved oral bioavailability of drugs. One more reason is to achieve a local therapeutic effect. For example, there is evidence to show that prolonged local concentrations of antibacterial may be of value in achieving eradication of *H. Pylori* from the stomach [3].

In our previous work [8], we prepared macroporous poly (acrylamide-*co*-acrylic acid) gels using $NaHCO_3$ as porogen and investigated their water uptake behaviour. Now, the same hydrogel system has been investigated for its ability to offer prolonged release of model drug vitamin B2 in the artificial gastric fluid of pH 1.2 at 37ºC. We have also tried to regulate the drug release rate by varying degrees of cross-linking of the hydrogels. The novelty of the work lies in the fact that the duration of drug release from the proposed devices in the gastric environment can be easily controlled by varying the degree of cross-linking of the device, without compromising with their floating ability. A small variation in cross-linker concentration can bring out drastic change in release rate of the drugs.

EXPERIMENTAL

Materials

Acrylamide (AAm; BDH; Poole, UK, molecular mass 71) was crystallized twice from methanol (analytical grade) to remove the inhibitor and then dried in vacuum over silica gel for a weak. Acrylic acid (AAc, Merck, Mumbai, India with molecular mass 72) was vacuum distilled at 47ºC/17 mmHg to remove the inhibitor. The catalyst tetraethylene diamine (TEMED), the stabilizer pluronic F-127, and cross-linker *N,N´*-methylene bisacrylamide (MB; Sigma with molecular mass 154) were G.R. grade and used as received. The initiator potassium persulphate (KPS; Merck) was analytical grade and used as received. Model drug, vitamin B2 (molar mass 514.36, purity 99.2%) was obtained from Research Laboratory, Bombay, India. The CO_2-free water used to prepare various solutions was prepared by double distillation of water and containing a little amount of alkaline $KMnO_4$ in Pyrex glass assembly.

Synthesis of Superporous Drug-loaded Poly (AAm-*co*-AAc) Hydrogels

Drug-loaded hydrogels were synthesized by carrying out free-radical aqueous polymerization of AAm and AAc in the presence of CO_2 gas bubbles, generated during the polymerization process due to reaction between citric acid and sodium bicarbonate.

Typically, the following components were added sequentially to the test tube (outer diameter 22 mm, inner diameter of 19 mm and height of 175 mm): 7.03 mM of AAm; 6.93 mM of AAc; 0.12 mM of cross-linker MB; 0.005 g of drug; 0.119 mM of citric acid; 0.074 mM of initiator KPS; 0.012 mM of pluronic F127. The solvent used was de-ionized distilled water unless specified otherwise. The test tube was shaken to mix the solution after each ingredient was added. Now, 200 μL of TEMED was added and the test tube was shaken again. Then, 0.119 mM of $NaHCO_3$ was added and the mixture was immediately stirred vigorously using a spatula for 10 s. The polymerization was accelerated after adding $NaHCO_3$ and was completed within few minutes.

The superporous hydrogel, thus produced, was cured for 30 min and then retrieved from the test tube, cut into discs of thickness 5.0 ± 0.2 mm. The drug-loaded gels were washed in distilled water for five minutes to remove the loosely bound drug on the surface of the hydrogels. However, the gels could not be equilibrated in water to remove the unreacted salts present within the gels, because that would make the entrapped drug to leave the device. Finally, the gels were allowed to dry in a dust-free chamber at 30ºC.

Here it is also worth mentioning that the method of preparing the drug-loaded device is not supposed to be a clean and safe method because after the synthesis of drug-loaded hydrogel it is not possible to remove the unreacted salts and monomers from the gel by equilibrating in distilled water due to the reason mentioned above. However the major advantage with this method is that any desired quantity of drug can be loaded in to the gel as per requirement.

On the other hand, the method of soaking the gel in drug solution is safer and cleaner but the desired quantity of drug cannot be loaded directly as the amount loaded is a function of so many factors such as distribu-

tion coefficient of drug between the solution phase and gel phase, solubility of drug, degree of cross-linking of polymer network, etc. Thus, each method has its own advantages and disadvantage. However the method of equilibration appears to be the best one in cases where the drug loaded device is intended to be used in human body.

We prepared two samples with different amounts of cross-linker MB, namely 0.12 mM and 0.58 mM, whereas all the other quantities were kept the same throughout the tests. The two prepared samples are denoted as HG (0.12) and HG (0.58).

FTIR Spectra

The FTIR spectra of drug, vitamin B2, and plain and drug-loaded polymers were recorded on Shimadzu, 8400 S spectrophotometer.

Determination of Entrapment Efficiency

In order to determine the amount of drug lost during the washing of the freshly prepared drug-loaded gels, various fresh samples were washed with distilled water taken in two installments, each of 250 mL, and the absorbance of each solution was measured at 437 nm. The percentage of entrapment efficiency (PEE) was calculated as:

$$PEE = \frac{\text{Amount of drug initially loaded} - \text{Amount of drug retained in gels}}{\text{Amount of drug initially loaded}} \times 100$$

Stability Test for Drug

The stability of drug riboflavin was carried out by measuring the absorbance of solutions of riboflavin prepared in HCl solution of pH 1.2 (artificial gastric fluid) and phosphate buffer of pH 7.4 (simulating intestinal fluid, SIF) at 37ºC, after the time-interval of every 24 h extended over a period of seven days.

Drug Release Study

Pre-weighed drug-loaded hydrogel was suspended in 900 mL of simulating fluid of pH 1.2 (US Pharmacopoeia) in Apparatus II at 37ºC under sink conditions. Aliquotes of 3 mL were withdrawn at different time intervals and the amount of drug released was determined spectrophotometrically [9]. The total volume of release medium was kept constant by addition of 3 mL of fresh buffer after every withdrawal.

RESULTS AND DISCUSSION

IR Spectral Analysis

The FTIR spectra of (a) riboflavin, (b) drug-loaded polymer and (c) blank sample are shown in Figure 1. A close look at the spectra of blank and drug-loaded polymers reveals the existence of peaks at 3351, 3591, and 2980 cm^{-1} which are due to O-H, N-H, and C-H stretchings of methyl groups, respectively. These peaks confirm the polymer formation. The presence of the drug in the polymer is confirmed by the fact that peaks in the range 3100-3300 cm^{-1} due to C-H stretching of aromatic groups appear in the spectra of both blank and drug-loaded samples. Similarly, the aromatic C-H and out-of-plane peaks appear at 900-700 cm^{-1} and C=C stretching appears at 1590-1600 cm^{-1} in both spectra (a) and (b) of Figure 1 confirming the presence of vitamin B2 in the polymer samples.

Stability of Vitamin B2

The results of stability test, as shown in the Figure 2,

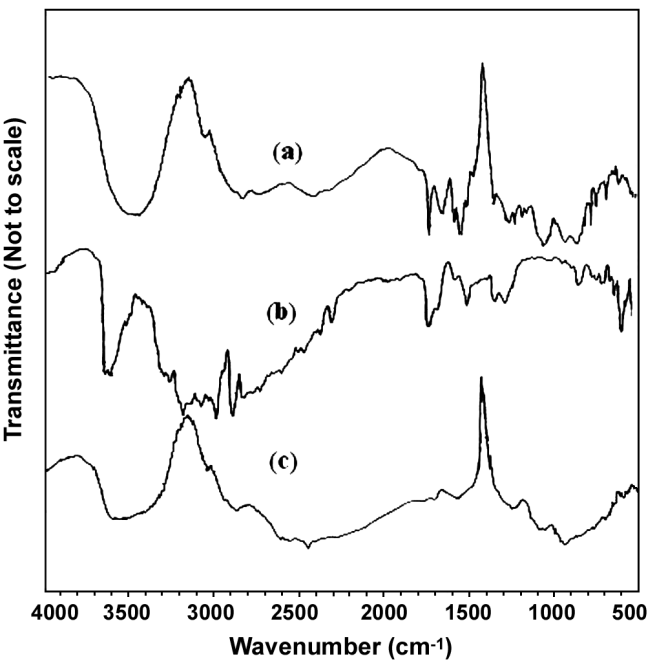

Figure 1. FTIR Spectra of: (a) model drug riboflavin, (b) drug-loaded, and (c) blank samples.

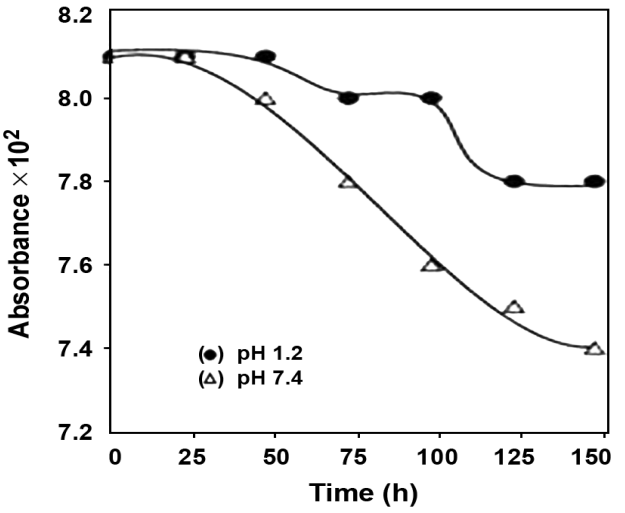

Figure 2. Stability test for model drug riboflavin.

clearly indicate that drug riboflavin is more stable in acidic pH (i.e., in SGF of pH 1.2) as compared to the alkaline pH. The percentages of drug decomposed in six days at the pH 1.2 and 7.4 were found to be 0.48 and 1.20, respectively. Since the floating device released the entrapped drug in the SGF of pH 1.2 for an overall duration of 30 h (as shall be discussed in the forthcoming section), we can very well claim that the stability of drug riboflavin should not have been much affected in this duration.

Entrapment Efficiency

For the two samples synthesized, the percentage of the entrapment efficiencies were found to be nearly 72.5 and 60 thus, suggesting that drug loading into the gels was quite reasonable. This may be attributed to the fact that in both synthesized samples the gelation was almost 100 percent as determined gravimetrically and therefore, the chances of drug loss was less. However, whatever loss has been observed, it might have been due to the presence of loosely bound drug molecules on the surface of the hydrogels and also due to the presence of highly porous network which increases the surface area of the device in contact with the solvent during the washing procedures.

Drug Release Study

Figure 3 depicts the results of drug release study, carried out with the two samples HG(0.12) and HG(0.58) in SGF of pH 1.2 at 37ºC. It is very interesting to see that the sample HG(0.12) demonstrates very fast release and almost 100% drug is released in the first 2 h, while the other sample HG(0.58) which is comparatively more cross-linked, exhibits slow release and it takes nearly 30 h to release nearly all the entrapped drug. Moreover, both of the samples remained buoyant for nearly 96 h.

We have also determined the mesh size of the samples HG(0.12) and HG(0.58) from equilibrium swelling measurements [10]. The mesh sizes of the networks were found to be 23.25 Å and 20.11 Å which also justify the observed release rates, as the gel HG(0.58) with smaller mesh size has exhibited slower release. The observed difference in their release rates may be explained on the basis of the fact that the sample HG(0.58) was relatively more cross-linked and possessed denser network which permitted slower release of the bioactive material. In addition to this, the relaxation of macromolecular chains is also restricted. These two factors ultimately cause slower release of the entrapped drug.

On the other hand the sample HG (0.12) which was relatively less cross-linked permitted faster drug release due to the enhanced chain relaxation process and larger network size. In this way, the two samples, although having similar monomer compositions possess different drug releasing capacities. However, both of the samples remained buoyant nearly 96 h.

Here it is worth mentioning that the movement of pul-

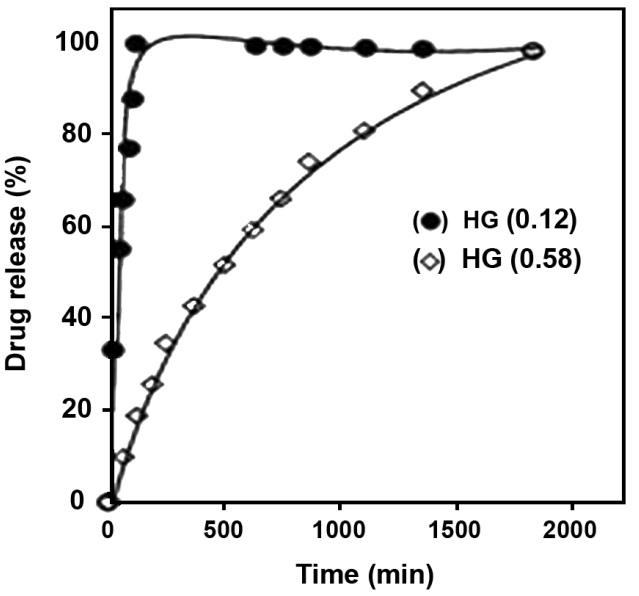

Figure 3. The drug release percentage versus time profiles for the floating devices.

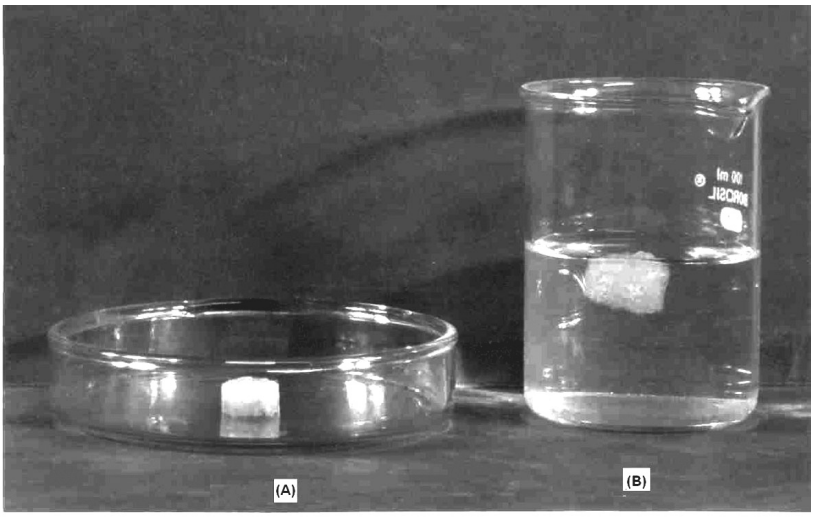

Figure 4. Floating behaviour of the sample HG (0.58).

satile waves in the stomach is ultimately responsible for the passage of oral formulation from the stomach to intestine. However, due to floating behaviour of the device, the gel remains in the gastric fluid and it is expected that it passes into the small intestine only when it sinks down due to over absorption of fluid which finally lets the device sink.

Finally, it can be concluded that in spite of almost the same gastric residence time, both formulations release the drug at different time periods which may be considered as the main feature of the present work.

This suggests that the gastric release rate of an oral dosage form can be very well controlled by varying the degree of cross-linking of the floating drug delivery vehicles. In order to achieve short-term and faster release the sample HG(0.12) seems to be the suitable device while for a long term and slow release in the stomach the sample HG(0.58) can be exploited. The buoyant behaviour of the formulation HG (0.58) has been well depicted in Figure 4. The fair buoyancy justifies its candidature for prolonged gastric delivery.

First Order Kinetic Model

The experimental release data obtained for sample HG(0.58) was fitted in the first order kinetic model [11] and the diffusion controlled Higuchi model [12] as described below.

The release of a bioactive material from a drug-loaded device may be given as:

Drug –loaded device + solvent ⟶ Drug released in medium

If Q_o and Q_t are the amounts of drug initially present and release at time t, respectively, then:

$$\frac{dQ_t}{dt} = k\left[Q_o - Q_t\right]$$

which on integration yields

$$-\ln\left(1 - \frac{Q_t}{Q_o}\right) = kt$$

where, k is the first order rate constant. In order to apply this model to the release data obtained for the sample HG(0.58) the curve was plotted between $-\ln(1- Q_t/Q_o)$ and t as shown in Figure 5. The almost linear plot obtained is indicative of the possibility of the first order release from the device. The regression coefficient R^2 was found to be 0.9846.

Higuchi Model

Finally, the suitability of Higuchi model (Higuchi, 1961) was also tested which describes the release of bioactive material as the square root of time-dependent process based on the Fickian diffusion. The Higuchi equation is:

$$Q_t = K_H\ t^{1/2}$$

Where, Q_t is the amount of drug released at time t and K_H is the Higuchi rate constant. The plot of Q_t versus $t^{1/2}$ which is shown in Figure 6 was found to be almost

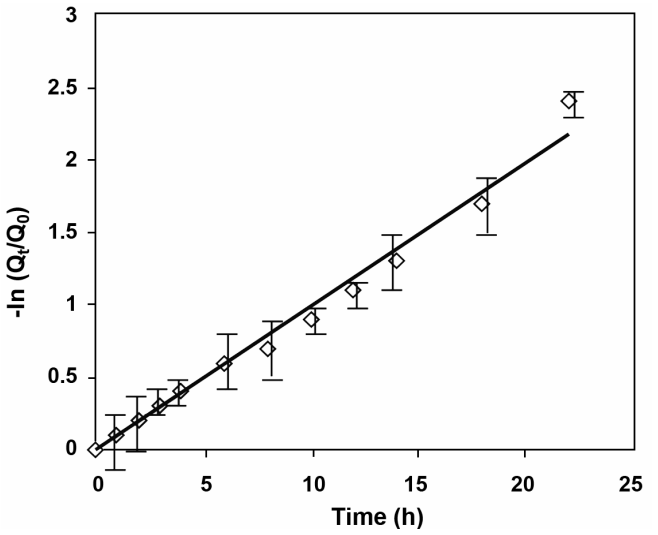

Figure 5. First-order kinetic plot of the release of B2 from sample HG (0.58) in SGF of pH 1.2 at 37°C.

non-linear. Moreover, the lower value of R^2 (i.e., 0.9679) also indicated non-suitability of this model in the present study. This may also be justified on the basis of the fact that the aspect ratio of the circular discs (i.e., D/L) is nearly 0.26 and hence Higuchi model could not be fairly applicable to the release data. Since R^2 value for the first order kinetic model is much closer to unity and the plot obtained shows fair linearity it can be concluded that the long term release of model drug B2 from the floating disc HG(0.58) follows the first order kinetics.

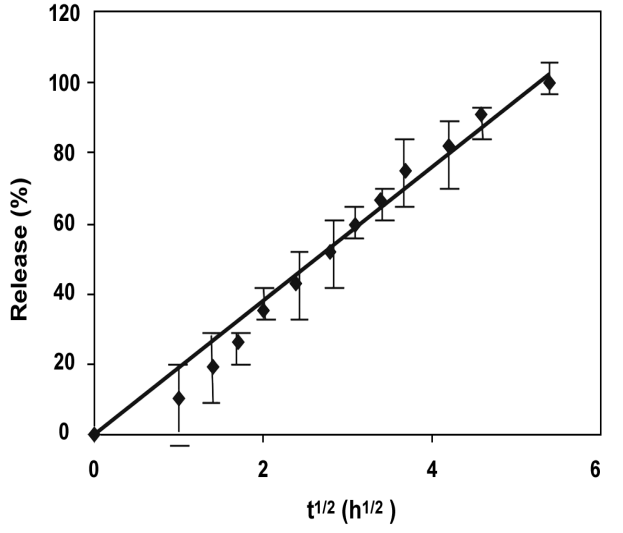

Figure 6. Higuchi plot of the sample HG (0.58).

CONCLUSION

The study describes the variations in the release rate from poly(acrylamide-*co*-acrylic acid) porous floating gels by varying degrees of cross-linking of the gels. The gel, cross-linked with 0.58 mM of cross-linker demonstrated slower release, extended over the duration of nearly 30 h. On the other hand, the loosely cross-linked gel, namely HG (0.12) showed faster release. However, both samples remained buoyant for 96 h. It can be concluded from this study that the duration of drug release from a floating gastro retentive device can be easily controlled by varying the degree of cross-linking of the device as per requirements.

REFERENCES

1. El-Gibaly I., Development and in vitro evaluation of novel floating chitosan microcapsules for oral use: Comparison with non-floating chitosan microspheres, *Int. J. Pharm*., **249**, 7-21, 2002**.**
2. Whitehead L., Fell J.T., Collett J.H., Sharma H.L., Smith A.M., Floating dosage form: An in vivo study demonstrating prolonged gastric retention, *J. Cont. Rel*., **55**, 3-12, 1998.
3. Baumgartner S., Kristl J., Vrecer F., Vodopivec P., Zorko B., Optimization of floating matrix tablets and evaluation of their gastric residence time, *Int. J. Pharm.*, **195**, 125-135, 2000.
4. Arora S., Ali J., Ahuja A., Khar R.K., Baboota, S., Floating drug delivery systems: A review, *AAPS Pharm. Sci. Tech*., **6**, E 372, 2005.
5. Shimpi S., Chouhan B., Mahadik K.R., Paradkar A., Preparation and evaluation of Diltiazen hydrochloride gelucire 43/01 floating granules prepared by melt granulation, AAPS *Pharm. Sci.Tech*., **5**, 1Q, 2004**.**
6. Durig T., Fassihi R., Evaluation of floating and sticking extended release delivery systems: An unconventional dissolution test, *J. Cont. Rel*., **67**, 37-44, 2000.
7. Bulgarelli E., Forni F., Bernabei M.T., Effect of matrix composition and process conditions on casein-gelatin beads floating properties, *Int. J. Pharm*., **198**, 157-165, 2000.
8. Bajpai S.K., Bajpai M., Sharma L., Investigation of

water uptake behavior and mechanical properties of superporous hydrogels, *J. Macromol. Sci. Pure Appl. Chem. A*, **43**, 507-524, 2006.
9. Lee D.-H., Kim J.-W., Suh K.-D., Amphiphillic urethan acrylate hydrogels: pH Sensitivity and releasing behaviors, *J. Appl. Polym. Sci*., **72**, 1305-1311, 1999.
10. Bajpai S.K., Sing S., Analysis of swelling behavior of poly (methacrylamide-*co*-methacrylic acid) hydrogels and effect of synthesis condition on water uptake, *React. Funct. Polym.*, **66**, 431- 440, 2006.
11. Singla A.K., Medirate D.K., Influence of sodium lauryl sulfate on indomethacin release patterns, *Drug. Dev. Int. Pharm*., **107**, 1838- 888, 1988.
12. Higuchi T., Mechanism of sustained action medication: theoretical analysis of rate of release of solid drugs dispersed in solid matrices, *J. Pharm. Sci*., **52**, 1145- 1149, 1963.