



STOMACH-SPECIFIC DRUG DELIVERY OF RIBOFLAVIN USING FLOATING ALGINATE BEADS

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ABSTRACT

A multiple-unit-type oral floating dosage form (FDF) of Riboflavin was developed to prolong gastric residence time, and increase drug bioavailability. The floating bead formulations were prepared by dispersing Riboflavin together with calcium carbonate into a mixture of sodium alginate and hydroxypropyl methylcellulose solution and then dripping the dispersion into an acidified solution of 1% (w/v) calcium chloride. The formulations were optimized for different weight ratios of gas-forming agent and sodium alginate. Prepared microbeads were evaluated for Particle size, Scanning electron microscopy, In-Vitro buoyancy study, Drug entrapment efficiency and In-Vitro drug release. The beads containing higher amounts of calcium carbonate demonstrated instantaneous, complete, and excellent floating ability. All the formulations remained buoyant and controlled release for up to 10 hrs. The mechanism of drug release was found to follow Higuchi matrix order release. Results indicate that FDF performed significantly better than the simple tablet dosage form.

Keywords: Riboflavin, Sodium alginate, Hydroxypropylmethylcellulose, Gastroretentive dosage forms, Narrow absorption window.

INTRODUCTION

The need for gastroretentive dosage forms (GRDFs) has led to extensive efforts in both academia and industry towards the development of such drug delivery systems¹. Prolonging the gastric residence of a dosage form may be of therapeutic value. Amongst the methods available to achieve this, floating dosage forms show considerable promise².

However, the use of gastro-retentive dosage forms could avoid these associated problems. Further, the extended GRDFs are also required if either drug action is required at stomach or if the drug is not absorbed through the small intestine. In such cases the dosage form that can spend much time in stomach such as microbeads, floating tablets etc., are well employed. Floating systems have the property of retaining the dosage units in the stomach for prolonged period of time and are useful for drugs acting locally in the gastro intestinal tract (GIT), drugs which are poorly soluble and unstable in intestinal fluids. Floating drug delivery systems (FDDS) remain buoyant due to lower density than the gastric and intestinal fluids. Multiple unit FDDS such as microspheres have the advantage of not being subjected to 'all or nothing' gastric emptying nature of single unit systems³.

Literature reports indicate widespread use of sodium alginate for achieving sustained release of drugs^{4, 5}, targeting gastric mucosa^{6, 7}, and increasing the bioavailability of drugs⁸ because of sodium alginate's ability to form a stable and bioadhesive gel with calcium ions⁹. Hydroxypropyl methylcellulose (HPMC) has been reported to enhance the sustained-release properties of alginate by providing a denser inner matrix¹⁰. Also, the preparative methodology of alginate beads involves the use of aqueous solvents, avoiding exposure of ingredients to high temperatures and toxic organic solvents^{11, 12}.

Riboflavin, a model of narrow absorption window drug was used to demonstrate the impact of controlled drug release from the prototype gastro retentive dosage forms on its pharmacokinetics. This model drug is advantageous because it lacks adverse effects and has no pharmaceutical effect on gastric motility. Riboflavin is used for the treatment of Ariboflavinosis associated with weakness, throat soreness/swelling, tongue swelling (glossitis), angular stomatitis/cheilosis (skin cracking or sores at the corners of the mouth), dermatitis (skin irritation), and anemia. It is readily absorbed from the upper GIT being its absorption window, 60% of drug is bound to plasma proteins, its $t_{1/2}$ 66-84 min, 9% of drug is excreted unchanged in urine make it a suitable candidate for floating drug delivery system¹³.

In context of the above principles, a strong need was recognized for the development of floating dosage form to deliver Riboflavin

(model drug) in stomach to increase the efficiency of the drug, providing sustained release.

MATERIALS AND METHODS

Materials

Riboflavin was purchased from Dr. Reddy's Laboratories (Hyderabad, India). Sodium alginate (low viscosity grade; 250 cp in 2% solution at 25°C) and Hydroxypropylmethylcellulose (HPMC) were received as gift samples from FDC Limited, Mumbai. Calcium carbonate was purchased from Poona chemical laboratory (Pune, India). All other reagents and chemicals used were of analytical reagent grade.

Preparation of floating alginate beads of Riboflavin¹⁴:

A solution was prepared by dissolving 0.1 g Riboflavin in 5 ml distilled water. The solution was dispersed in 30 ml alginate solution (3%, w/v) containing HPMC (alginate:HPMC=9:1, w/w). Then gas forming agent such as CaCO₃ was added to the solution with levels from 0:1 to 1:1 (gas-forming agent/alginate, w/w). The mixture was then degassed under vacuum. The formulation compositions are shown in Table 1. The resulting solution was dropped through a 26G syringe needle into 1% (w/v) CaCl₂ solution containing 10% (v/v) acetic acid. The solution containing suspend beads was stirred with a magnetic stir bar for 10 min to improve the mechanical strength of the beads and allowed to complete the reaction to produce gas. Since the carbonate salts are insoluble at neutral pH, the divalent ions were only released in the presence of acid, thereby preventing premature gelation. The fully formed beads were collected, washed with ethanol and distilled water. **Evaluation of floating alginate beads of Riboflavin**

Size analysis¹⁵

The average diameter of ten wet and dry beads was determined using a caliper (Mitutoyo, Japan) in triplicate.

Morphology of the beads¹⁵

Surface and cross-sectional morphologies of beads were examined with a scanning electron microscope (SEM) (JSM-5310LV Scanning Microscope, Tokyo, Japan).

Drug entrapment efficiency¹⁶

The prepared beads were evaluated for drug entrapment efficiency. An accurately weighed sample of beads (10 mg) was crushed in a mortar and added to 10 ml of water for complete swelling and was sonicated for 2 min at 60 MHz of frequency. About 20 ml of methanol was added to precipitate sodium alginate which was removed by centrifuging for 5min at a rotational speed of 1000 rpm.

The drug content was analyzed by a UV spectrophotometer at 444 nm after suitable dilution with 0.1 N HCL (pH 1.2). The percentage entrapment efficiency was calculated as

$$\text{Percentage entrapment efficiency} = \frac{\text{Practical drug loading} \times 100}{\text{Theoretical drug loading}}$$

In-vitro buoyancy study¹⁶:

Floating properties of wet and dry alginate beads were evaluated using USP dissolution apparatus containing 900 ml acidic buffer (pH 1.2) at rotational speed of 75 rpm. The temperature of medium was maintained at $37 \pm 2^\circ\text{C}$. Fifty beads were placed in the media and the total floating time was measured by visual observation (n=3).

Table 1: Floating Alginate beads of Riboflavin

Ingredients	Formulation				
	C1	C2	C3	C4	C5
Riboflavin (g)	0.1	0.1	0.1	0.1	0.1
Alginate (% w/v)	3	3	3	3	3
Alginate: HPMC (w/w)	9:1	9:1	9:1	9:1	9:1
CaCO ₃ : Alginate (w/w)	0:1	0.25:1	0.5:1	0.75:1	1:1

In-vitro drug release¹⁷:

Dissolution studies were carried in triplicate for all the formulations, employing USP paddle dissolution apparatus containing 900 ml of 0.1 N HCL dissolution media (pH 1.2) at 100 rpm, $37 \pm 2^\circ\text{C}$ temperature. 5 ml of sample was periodically withdrawn at suitable time intervals and same volume was replaced with fresh dissolution medium. The samples were analyzed spectrophotometrically at 444 nm after suitable dilution.

RESULTS AND DISCUSSION

Size analysis

A range of weight ratios of CaCO₃ was used to determine the effect of the gas forming process on the size of beads formed (Table 2). Results show that gas forming agent significantly increased the size of the beads. By increasing the gas forming agent in alginate solution, spherical beads could not be formed because released CO₂ gas burst the bead before the wall was sufficiently hardened. Wet beads are showing greater size than dry beads due to swelling of polymer matrix.

Morphology of the beads

Scanning electron photographs of the formulations is shown in figure 1. Increased ratios of incorporated CaCO₃ made the bead surface smoother (figure 1B & 1C). It is suggested that the presence of Ca²⁺ ions contributed to homogenous alginate bead formation.

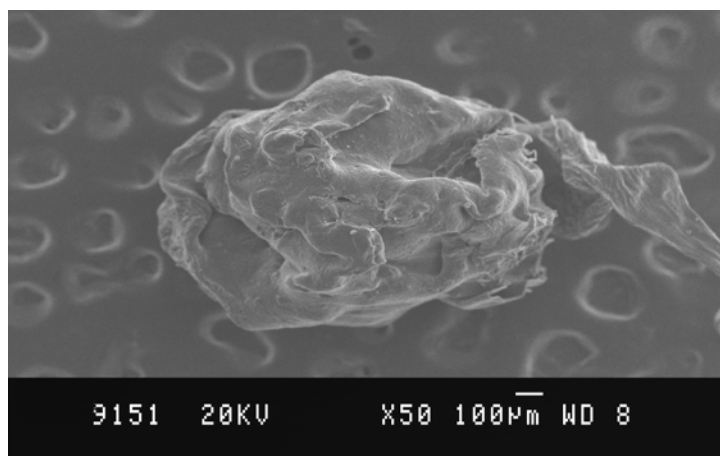
Drug entrapment efficiency

The entrapment efficiency for various Riboflavin floating bead formulations was found to vary between 61.50% and 81.12% (Table 3). It was observed that an increase in the ratio of gas forming agent : alginate from 0:1 to 1:1 resulted in a decrease in the entrapment efficiency of Riboflavin in floating beads. The beads without gas forming agent, because of the highly dense internal structure of the alginate matrix, were able to retain Riboflavin more effectively. During the preparation of beads, gas forming agent reacts with acetic acid to release carbon dioxide, which permeates the alginate matrix, leaving pores. These porous beads, with a less dense internal structure, result in decreased entrapment efficiency of the drug.

Table 2: The effect of weight ratios of CaCO₃ on bead size in wet and dry conditions

Formulation	Wet AVE (mm)±S.D	Dry AVE (mm)±S.D
C1	2.15±0.02	1.05±0.08
C2	2.23±0.05	1.20±0.03
C3	2.35±0.08	1.36±0.04
C4	2.47±0.02	1.54±0.09
C5	2.62±0.04	1.61±0.04

± S.D- Standard deviation for (n=3)



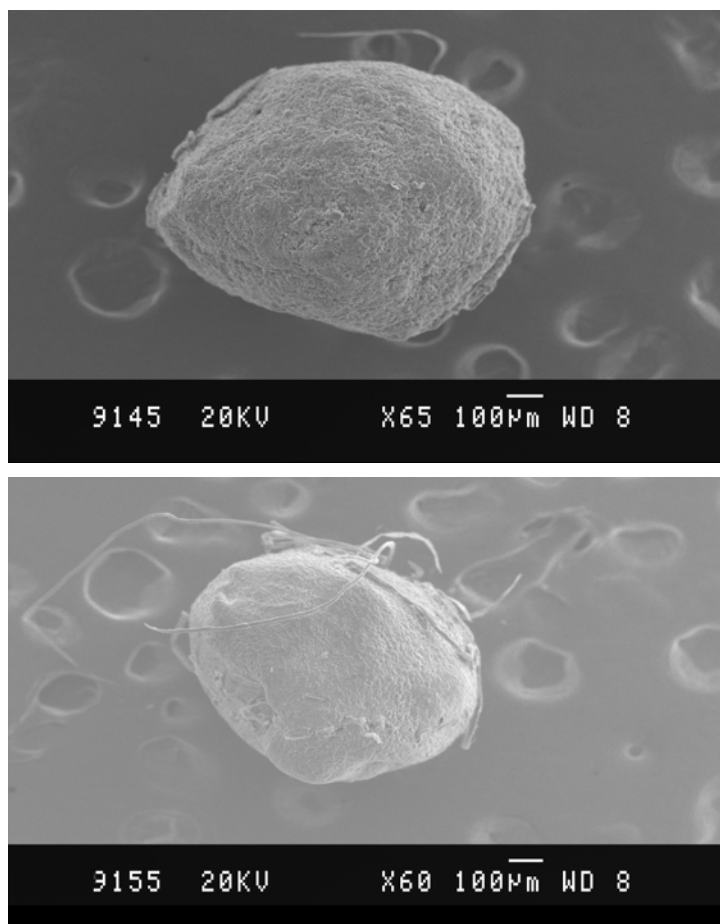


Fig. 1: A) Scanning electron microscopy photomicrograph of formulation C1, B) Scanning electron microscopy photomicrograph of formulation C3, C) Scanning electron microscopy photomicrograph of formulation C5,

In-vitro buoyancy study

The floating ability of prepared beads was evaluated using USP dissolution apparatus containing 900 ml acidic buffer (pH 1.2) at rotational speed of 75 rpm. The results are shown in Table 3. While gas forming agent free beads sink uniformly in media, beads containing gas forming agents in proportion ranging from 0.5:1 – 1:1 ratios showing excellent floating ability. The wet beads (0.25 gas forming agent/alginate, w/w) had better floating ability than dry beads. Wet bead contain a greater proportion of CO₂ gas than dry ones and are thus more buoyant.

In-vitro drug release

The plot of cumulative % drug released Vs time plotted for all formulations are depicted in Figure 2. In the absence of gas forming agent the release rate was very slow due to the high dense internal structure of alginate beads and was expected to retain the drug more effectively. Increasing the CaCO₃ weight ratio prolongs the

release rate of riboflavin from alginate matrix. Beads without gas forming agents shows better controlled release than gas forming agent contain formulations.

The results of dissolution data was fitted into various drug release kinetic equations. Correlation coefficient (r) value was highest for Higuchi matrix order release equation in all batches, thus indicating matrix release kinetics.

CONCLUSION

A successful attempt has been made to formulate floating alginate microbeads of Riboflavin using gas forming agent Calcium carbonate as a gastroretentive drug delivery system. The formulation C3 exhibited the optimum sustained release of Riboflavin over a period of at least 10 h., with excellent floating properties.

From above studies it is concluded that floating alginate microbeads can be a suitable approach to improve oral bioavailability of drugs having narrow absorption window in stomach.

Table 3: Floating ability (Wet and Dry beads), Drug entrapment efficiency (%), In Vitro drug released (%) of Riboflavin microbeads

Formulation	Floating ability		Drug entrapment efficiency (%)	In-Vitro drug released (%) Mean ± (S.D.)
	Wet beads	Dry beads		
C1	-	-	81.12	66.45±2.45
C2	+	+/-	75.45	71.407±2.89
C3	++	++	71.65	76.12±3.12
C4	++	++	64.71	81.85±3.45
C5	++	++	61.50	85.45±4.18

- ; Completely sink, +/- ; Partially sink or float, ++ ; Completely float, ± S.D- Standard deviation for (n=3)

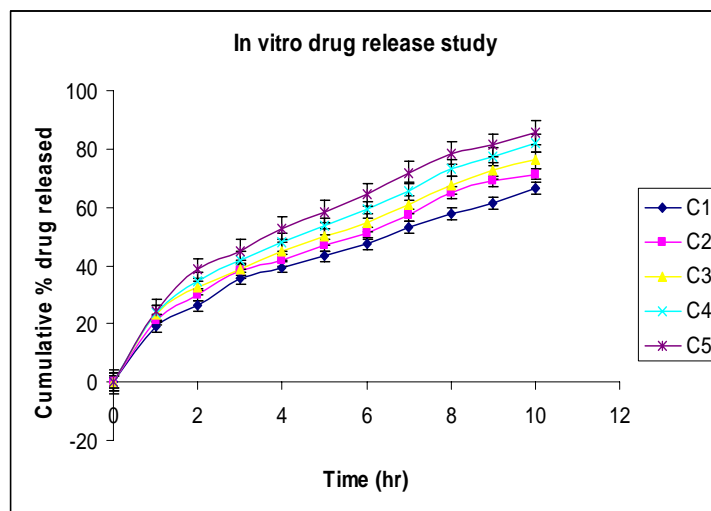


Fig. 2: In vitro drug release study (Cumulative % drug released)

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