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Research Article

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Formulation and evaluation of low cost sustained release floating alginatebeads

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ABSTRACT

Floating beads are the micro-beads/ spheres prepared by ionic gelation technique. They can be either of sustained release or immediate release type. Sustained release type of floating drug delivery systems generally employ a high viscosity polymer like the hydroxyl propyl methyl cellulose (HPMC) or ethyl cellulose as the matrixing agent. These polymers are generally very expensive, and their use in the formulation leads to increased cost of the formulation, which is the main reason that limits the wide-spread usage of this dosage form. In this study, we have tried to produce low cost floating alginate beads by substituting high-cost polymers like HPMC with low cost polymer like carboxy methyl cellulose (CMC). Comparative studies were carried out to determine the efficacy of formulations containing CMC with that of formulations containing HPMC as the matrixing agent. We have also studied the effect of physicochemical properties of the drugs on the drug release pattern of the dosage form i.e. floating alginate beads.

Keywords: Floating Beads; Hydroxy propyl methyl cellulose; Sodium Alginate; Counter ion effect; Carboxy methyl cellulose; Clarithromycin; Paracetamol; Aluminium Hydroxide

INTRODUCTION

Floating drug delivery systems are those dosage forms which float on the contents in the stomach and release the drug (Arora et al., 2005). They can be either of sustained release or immediate release type. Sustained release type of floating dosage form is used for increasing the gastro-intestinal transit time (Deshpande et al., 1997) of the drug whereas immediate release types of floating dosage form are used for localized effect on the stomach.

Sometimes sustained release type can be used to release the drugs which are absorbed only in the acidic environment of the stomach (Adrian et al., 1957) for a prolonged period of time. Sustained release type of floating drug delivery system is of special importance when compared to immediate drug release type because immediate release forms need not be of floating type to elicit their maximum pharmacological effect.

Advantages

These dosage forms increase the overall GI transit time of sustained release formulations. Thus, the dosing frequency of the drug can be reduced to a great extent.

These can be used to administer the drugs which get absorbed only in the acidic environment of the stomach. This dosage from can also be used for administering the drugs which show the local effect on the stomach.

Even after having all these advantages floating drug delivery systems could not be used widely because of their high cost. This high cost of these formulations is mainly due to the high cost of polymers used in the preparation of these formulations. The most commonly used polymers in the preparation of these dosage forms are hydroxyl propyl methyl cellulose (HPMC), carbapol, ethyl cellulose.

In this study, we have tried to reduce the cost of the floating dosage forms by formulating low cost alginate beads and evaluating them for their efficiency by comparative studies. In our study, we have used low cost polymers like carboxy methyl cellulose (CMC) and sodium alginate in place of polymers like hydroxyl propyl methyl cellulose (HPMC) and ethyl cellulose. To increase the efficiency of CMC, we have used a polymer solution of high concentration in place of very dilute solution of polymers that are generally used.

Materials and Methods

Materials

Hydroxylpropyl methyl cellulose (K100M) was obtained as a gift sample from Mc Loyds pharmaceuticals

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Table 1: Composition of formulations from F1-F5

Formulation No.	Sodium alginate (gm)	Carboxy methyl cellulose (gm)	Sodium bicarbonate (mg)	Paracetamol (gm)	Distilled water up to (ml)
F1	1	0.2	200	1	10
F2	0.9	0.1	100	1	10
F3	1.1	0.15	150	1	10
F4	0.8	0.09	90	1	10
F5	1.2	0.16	160	1	10

Table 2: Composition of formulations from S1-S5

Formulation No.	Sodium alginate (gm)	Carboxy methyl cellulose (gm)	Sodium bicarbonate(mg)	Clarithromycin (gm)	Distilled water Up to (ml)
S1	1	0. 2	200	1	10
S2	0.9	0.1	100	1	10
S3	1.1	0.15	150	1	10
S4	0.8	0.09	90	1	10
S5	1.2	0.16	160	1	10

Table 3: Composition of formulations from V1-V2

Formulation No.	Sodium alginate(gm)	Carboxy methyl cellulose(gm)	Sodium bicarbonate (mg)	Aluminum hydroxide (gm)	Distilled water Up to (ml)
V1	1	0.2	200	1	10
V2	0.9	0.1	100	1	10

Table 4: Composition of formulations from I1-I5

Formulation No.	Sodium alginate (gm)	Hydroxyl propyl methyl cellulose $K_{100}M$ (gm)	Sodium bicarbonate (mg)	paracetamol (gm)	Distilled water Up to (ml)
I1	1	0.2	200	1	10
I2	0.9	0.1	100	1	10
I3	1.1	0.15	150	1	10
I4	0.8	0.09	90	1	10
I5	1.2	0.16	160	1	10

pvt.Ltd, Mumbai, Carboxy methyl cellulose (high viscosity grade) was bought from S.D. Fine Chemicals pvt.Ltd. Paracetamol (pure drug) was obtained as a gift sample from Dr. Ready Laboratories Hyderabad, Clarithromycin (pure drug) was obtained as a gift sample from Dr. Reddys Laboratories Hyderabad, Aluminum hydroxide (purified form) was obtained as a gift sample from Dr. Reddys Laboratories Hyderabad.

Methods

Preparation of floating alginate beads

Different formulations of Alginate beads were prepared by using the same quantity of drug, but all of them varied in the composition of excipients. Details about composition of all the formulations are given in tables 1-6, and the procedure followed for their preparation was as follows:

1 gm of drug was dissolved in 10ml of water followed by a weighed quantity of CMC, which was mixed in this solution with the help of a magnetic stirrer. To this mixture, a weighed quantity of sodium alginate powder was added with continuous stirring. Then this mixture was loaded into a syringe and was released drop wise into a beaker containing 5% calcium chloride solution. This led to the formation of alginate beads by ionic gelation (Kunjachan et al 2010).

Plotting of calibration curves

Calibration curve of paracetamol at pH-2:

10 mg of paracetamol was dissolved in 10ml of HCL buffer of pH-2; this gave us a solution that contains 1000µg/ml of drug. From this solution, 1ml was withdrawn and mixed with 9ml of fresh buffer, which gave us a solution of 100µg/ml. From this solution 1, 2, 3, 4, 5ml of solutions were withdrawn separately and mixed with 9, 8, 7, 6, 5ml of fresh buffer; this gave us the solutions that contain 10, 20, 30, 40, 50µg/ml of paracetamol.

The absorbance values of 10, 20, 30, 40, 50µg/ml solutions of paracetamol were measured by using a double beam U.V-Visible spectrophotometer at a λmax of 247nm (Indian pharmacopeia 1996b), using HCL Buffer of pH-2 as reference. The absorbance values were plotted against the concentration of solution and then linear regression was applied to the graph obtained, so as to obtain a linear calibration curve.

Table 5: Composition of formulations from M1-M5

Formulation No.	Sodium alginate(gm)	Hydroxyl propyl methyl cellulose $K_{100}M$ (gm)	Sodium bicarbonate(mg)	Clarithromycin (gm)	Distilled water Up to (ml)
M1	1	0.2	200	1	10
M2	0.9	0.1	100	1	10
M3	1.1	0.15	150	1	10
M4	0.8	0.09	90	1	10
M5	1.2	0.16	160	1	10

Table 6: Composition of formulations from K1-K2

Formulation No.	Sodium alginate(gm)	Hydroxyl propyl methyl cellulose $K_{100}M$ (gm)	Sodium bicarbonate(mg)	Aluminium hydroxide (gm)	Distilled water Up to (ml)
K1	1	0.2	200	1	10
K2	0.9	0.1	100	1	10

Same procedure was followed to plot a calibration curve for paracetamol at pH-7.4 but in this case phosphate buffer of pH-7.4 was used to prepare samples and also as reference solvent. Same procedure was followed to plot the calibration curve for clarithromycin both at pH-2 and pH-7.4, but the absorbance values were observed at λmax of 211nm (Rajesh kumar et al 2011) in the UV visible spectrophotometer.

Calibration curve of aluminum hydroxide at pH-2

5 gm of aluminum hydroxide was weighed and dissolved in 3ml of HCL by warming on a water bath. This solution was cooled to about 25^{o} C and then diluted to 100ml with distilled water; the pH of the final solution was adjusted to 2 by adding required amount of hydrochloric acid. 0.2 ml of this solution was taken and to this 0.4 ml of 0.05 M disodium edetate, 800ml of distilled water and a drop of methyl red solutions were added. This solution was neutralized by continuous drop by drop addition of 0.1M sodium hydroxide solution. The resultant solution after neutralization was warmed on a water bath for about 30mins, and to this solution 30mg of hexamine was added. This final solution was titrated with 0.05M lead nitrate solution using xylenol orange solution as an indicator (Indian Pharmacopoeia 1996a).

Each ml of 0.005M disodium edetate is equivalent to 0.0002549 gm of aluminum hydroxide. This gives us the titre value for 10µg of aluminum hydroxide. Similarly titre values were obtained for 10, 20 and 30 up to 150µg of aluminum hydroxide and were plotted against concentration to obtain calibration curve.

Calibration curve of aluminum hydroxide at pH-7.4

The procedure followed for plotting this curve was same as the procedure for plotting curve at pH 2 but, before titrating the pH of initial solution was adjusted to 7.4 with the help of sodium hydroxide solution.

Evaluation of drug release pattern

The drug release pattern of alginate beads prepared by using various drugs was evaluated in a single stage dissolution test apparatus with a container capacity of 900ml at a temperature of 37.5 ± 0.2° C and 50 ± 5rpm. HCL buffer of pH-2 and phosphate buffer of pH-7.4 were used as dissolution media. Samples of 1ml each were withdrawn at regular intervals of 30 minutes each and was analyzed in UV visible spectrophotometer in case of paracetamol and clarithromycin and by titrimetry in case of aluminum hydroxide. Sink conditions were maintained throughout the process.

Determination of swelling index

Swelling index was determined by taking 1gm of beads of each formulation and these beads were submerged in 10ml of water and were allowed to absorb water and at regular intervals, water was drained and the beads were weighed. Same process was repeated until a constant weight was obtained. At this particular point, we got the value of maximum water absorbing capacity of the beads and because water absorbing capacity is directly proportional to percentage swelling it directly indicates the swelling index, which was calculated by using the following formula.

Swelling index = weight of wet beads/weight of dry beads

Determination of floating lag time

Floating lag time was determined by visual observation by dropping the beads into the dissolution media and noting the time taken by the beads to come to the surface.

Determination of total floating time

Total floating time was determined by dropping the beads in HCl buffer of pH-2 and noting the time for which the beads stayed afloat.

Determination of percentage drug content

1gm of beads were accurately weighed and powdered. This powder was then dissolved in 10ml of distilled water. 1ml of this solution was taken and was diluted to 100ml with distilled water from this solution 1ml was taken and diluted to 100ml with distilled water

Table 7: Time taken for the complete drug release from the formulations F1, S1, V1, I_1, M_1, K_1 at pH- 2 and pH- 7.4

Formulation No.	F1		S1		V1	
pH Condition	pH-2	pH-7.4	pH-2	pH-7.4	pH-2	pH-7.4
Time taken for total drug release (hrs)	12	11.5	15	14.5	9.5	15
	I1		M1		K1	
	24	23	30	29	19	30

Table 8: Swelling index of various formulations

Formulation No.	Swelling index (Mean± SD)	Formulation No.	Swelling index (Mean± SD)	Formulation No.	Swelling index (Mean± SD)
F1	2 ± 0.1	V1	2.0 ±0.1	M1	2.8 ± 0.1
F2	1.3 ± 0.2	V2	1.3 ± 0.2	M2	2.1 ± 0.1
F3	1.5 ± 0.2			M3	1.8 ± 0.1
F4	1.2 ± 0.3			M4	1.45 ± 0.2
F5	1.6 ± 0.1			M5	1.85 ± 0.1
S1	2.0 ± 0.1	I1	2.8 ± 0.1	K1	2.8 ± 0.1
S2	1.3 ± 0.2	I2	2.1 ± 0.1	K2	2.1 ± 0.1
S3	1.5 ± 0.1	I3	1.8 ± 0.2		
S4	1.2 ± 0.2	I4	1.45 ± o.2		
S5	1.6 ± 0.1	I5	1.85 ± 0.1		

Table 9: Floating lag time of various formulations

Formulation no.	Floating lag time (mins)	Formulation no.	Floating lag time (mins)	Formulation no.	Floating lag time (mins)
F1	7	V1	7	M1	4
F2	11	V2	11	M2	7
F3	9.5			M3	5.5
F4	12			M4	8.5
F5	10			M5	6.3
S1	7	I1	4	K1	4
S2	11	I2	7	K2	7
S3	9.5	I3	5.5		
S4	12	I4	8.5		
S5	10	I5	6.3		

Table 10: Total floating time of various formulations

Formulation no.	Total floating time (hrs)	Formulation no.	Total floating time (hrs)	Formulation no.	Total floating time (hrs)
F1	14	V1	14	M1	28
F2	12	V2	12	M2	24
F3	13			M3	26
F4	10			M4	20
F5	13.3			M5	26.6
S1	14	I1	28	K1	28
S2	12	I2	24	K2	24
S3	13	I3	26		
S4	10	I4	20		
S5	13.3	I5	26.6		

and 1ml of this solution was taken and analyzed for the quantity of the drug present in it by spectrophotometry for paracetamol and clarithromycin and by titrimetry for aluminium hydroxide. The quantity of drug thus obtained was multiplied with dilution factor given above. Thus, the percentage drug content in 1gm of beads was obtained.

RESULTS

Until otherwise stated all the results were obtained only after repeating all the experimental procedures thrice and calculating the corresponding standard deviation or by deducing the average of three values in case of time values.

Table 11: Percentage drug content of various formulations

Formulation No.	Percentage drug content (Mean ± SD)	Formulation No.	Percentage drug content (Mean± SD)	Formulation No.	Percentage drug content (Mean± SD)
F1	99 ± 0.1	V1	98.7 ± 0.3	M1	98.7 ± 0.1
F2	101 ± 0.3	V2	99.8 ± 0.1	M2	101.4 ± 0.4
F3	98.7 ± 0.2			M3	99.6 ± 0.2
F4	99.3 ± 0.4			M4	100.1 ± 0.3
F5	100.7 ± 0.2			M5	101.4 ± 0.4
S1	99.8 ± 0.2	I1	99.5 ±0.2	K1	100.1 ± 0.2
S2	100.2 ± 0.1	I2	100.6 ± 0.3	K2	99.6 ± 0.4
S3	98.9 ± 0.3	I3	99.1 ± 0.2		
S4	99.9 ± 0.2	I4	99.9 ± 0.1		
S5	101.2 ± 0.2	I5	100.9 ± 0.3		

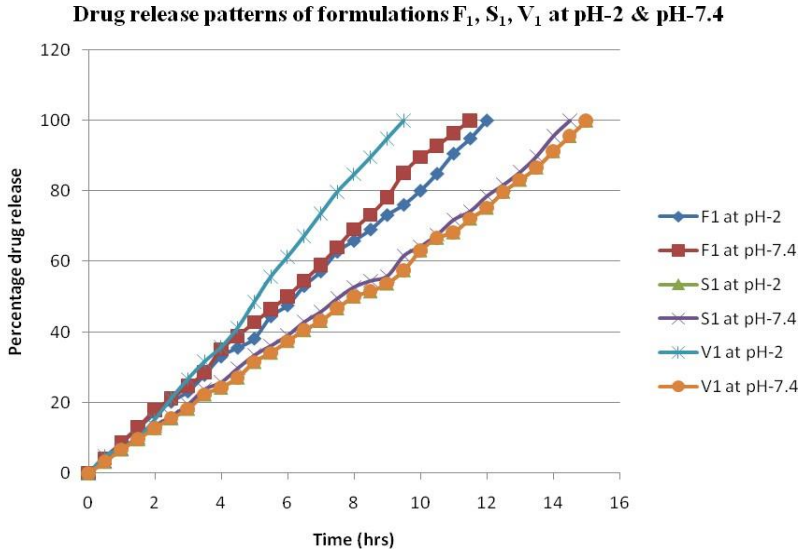

Figure 1: Drug release pattern of the formulations F1, S1, V1 at pH- 2 and pH- 7.4

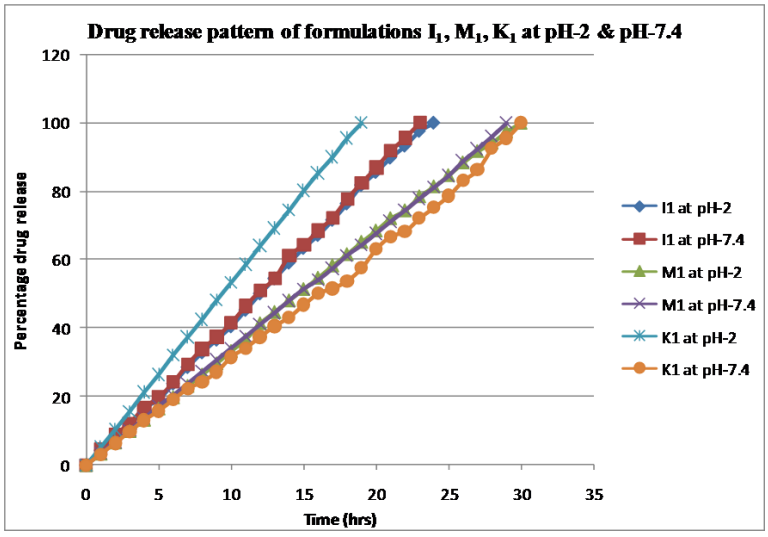

Figure 2: Drug release pattern of the formulations I1, M1, K1 at pH- 2 and pH- 7.4

The drug release patterns of all the formulations have been determined and of all the formulations the formulations F1, S1, V1 Fig-1 & I1, M1, K1 (results shown in table-7, Fig-2) have shown the best drug release profile. Swelling Index was determined for all the formulations, and all the formulations have shown the swelling index value which is sufficient for proper floatation of the dosage form (results shown in table-8). The following are the results of various floating properties like floating lag time (results shown in table-9) and total floating time (results shown in table-10).

Percentage drug content of the all the formulations have been evaluated (results shown in table-11). All the formulations except F3, S3, S5, V1, M1.M2, M5, were found to be within the limits of Indian Pharmacopoeia. The formulations F3, S3, S5, V1, M1.M2, M5, deviate from the pharmacopoeial limits because as per the Indian pharmacopoeia limits the percentage drug content should not be less than 99% and more than 101%.

DISCUSSIONS

From the dissolution study of various formulations prepared by us, it is clear that the rate of drug release is maximum from formulations employing carboxy methyl cellulose sodium salt as the matrixing agent and is minimum from formulations employing HPMC K_{100}M as the matrixing agent. This shows that the gel formed from HPMC is more viscous and less erodable than the gel formed from CMC. Even though we have used CMC sodium salt of high viscosity, it is clear from the results that the rate of release is maximum with this polymer. This can be because of its higher solubility in water when compared to HPMC K_{100}M, due to which it is easily erodable when compared to HPMC K_{100}M. However, among the formulations containing CMC the rate of drug release was highly affected by the quantity of CMC used and more the quantity used less, was the drug release rate. Same was the case with formulations containing HPMC. Thus, we can say that the quantity of polymer used as a matrixing agent plays an important role in determining the sustained release action of a dosage form. This is the reason why only the formulations F_1, S_1, V_1& I_1, M_1, K1 showed the best drug release profile.

The quantity of polymer also influences various floating properties, and it is clear from the results that the total floating time is more in case of formulations containing HPMC instead of CMC. It is also clear from the results that the other floating property, like the floating lag time is not entirely dependent on the quantity of polymers alone. The floating lag time of a formulation was found to be less if the quantity of gas forming agents is more and floating lag time was found to be the maximum; if the quantity of gas forming agent is less/ absent in a formulation.

However, it was observed that even though the quantity of all the excipients used was same in case of formulations F1, S1, V1 the rate of drug release was different and this difference was mainly due to the difference in the properties of drugs incorporated into these formulations. As the solubility of paracetamol in gastric contents is more when compared to clarithromycin the rate of release of paracetamol is more when compared to clarithromycin. As aluminium hydroxide is highly soluble in acidic environment of the stomach, its release rate is more at pH-2 when compared to pH-7.4.

CONCLUSIONS

The formulations employing a mixture of sodium alginate powder and CMC can be used only in certain situations like the one in which the administered drug is absorbed effectively from both stomach and intestine. This is because these formulations continue to release the drug, even after they sink and enter into the intestine. These formulations can be employed to administer drugs, which are intended for localized effect in the stomach for a short duration of time. They can also be used in conditions where the drug is absorbed only from the stomach but the duration of steady state plasma concentration required is in between 12 - 13 hours.

In all these cases, the formulations employing CMC can be used where the total floating time is 12-14 hours and in case of drugs like paracetamol almost 100% of drug is released within that period. In case of drugs like clarithromycin, these formulations are less effective because only about 80 - 95% of the drug is released when the beads are still afloat, and this is mainly due to its lower solubility than paracetamol.

Hence, it can be concluded by saying that, while designing a dosage form it is essential to consider the characteristics of the drug to be administered along with the nature and characteristics of excipients used for designing the dosage form

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