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FORMULATION AND CHARACTERIZATION OF FLOATING BEADS TO DELIVER ASPIRIN

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ABSTRACT

Floating drug delivery systems have gained importance during the last few decades. The floating beads dosage form with lower density as compared to the gastric juice gains buoyancy as well as greater bioavailability with less adverse effects. It has the potential to combat the limitations of other novel drug delivery systems. Multiparticulate systems offer an added advantage of spreading uniformly throughout the gastric fluid and each unit behaves as a single unit. Floating beads for model drug aspirin were developed in this study using two different techniques to maintain buoyancy using olive oil and calcium carbonate. It was hypothesized that olive oil entrapped alginate beads being lighter than aqueous medium would float on the surface of gastric fluid while, calcium carbonate used in the other formulation would generate effervescence and keep the granules floating. Both the methods were used simultaneously in the present study and compared. The formulations were characterized with respect to drug loading, yield, floating time, drug release and release kinetics. The different floating techniques applied showed promising results with effective buoyancy. Carbopol and sodium alginate accentuated the property of sustained release from the formulation. The further in-vivo studies on animal models might help in the evaluation of safety and efficacy of the developed formulation.

Keywords:*Floating beads, Controlled drug delivery, Aspirin, Sodium alginate, Carbopol 940, Olive oil.*

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1. INTRODUCTION

Oral drug delivery is the most popular and convenient route, the route has proved to be the most suitable over any other form of conventional drug delivery system. Several advantages like non-invasiveness; patient compliance and cost effectiveness make it the most convenient method of drug delivery over decades [1]. Gastro retentive drug delivery through oral route gives a controlled release drug profile which is beneficial but at the same time challenging due to variable gastric emptying time. The formulation resides in the gastric region for a long duration of time and thereby enhances its bioavailability thus avoiding multiple dosing of the drug and helps to overcome the adverse effects [2]. Among all of those, the floating beads may be formulated easily without the need of high temperature and high drug entrapment [3]. The beads are of lower density compared to that of the gastric fluid which imparts the required buoyancy, and it further helps to release the drug in a controlled manner. Therefore, the dosage form can release the drug independently without any hinderance mostly occurred due to variable gastric emptying time. The accurate placing of the beads over the gastric fluid also helps to target site specific release for different pathophysiological conditions such as gastric ulcers, duodenal ulcers, gastroesophageal reflux disease. The controlled release pattern can also be achieved in the gastric area by different alternative

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methods such as mucoadhesion, sedimentation, expansion and modified shape system.

The stomach has three major anatomical regions that are fundus, body and antrum. The action of the gastric juices over the undigested food takes place in the body area while antrum is the area where mixing motions and pumping action occurs, which accounts for the gastric emptying time. The contraction of the stomach occurs at fasting as well as fed state with different electrical events and patterns. The contractions result in the reduction of particle size (less than 1 mm) of the food as well as drug which are sent forward in the suspension form [4]. The controlled release dosage form faces two major challenges; those are short-lived gastric residence time and unpredictable gastric emptying time. The gastric emptying rate depends upon the volume of the fluid present in meal. The nutritive density and caloric content in the food help to determine the gastric emptying time. It also varies with the variance in biological factors such as age, BMI (Body Mass Index), gender and diseased state. Controlled drug delivery through oral route has been challenging especially due to variable gastric emptying characteristics. Floating drug delivery systems help to achieve controlled drug delivery through the oral route by simple technique. The delivery systems generally have lower density than the gastric fluid which helps them to float and release the entrapped drug in a controlled manner. Thus, the dosage form becomes independent of the emptying of the gastric contents and can achieve prolonged release. Floating drug delivery systems have been especially beneficial for prolonging drug release. Besides, they also help to achieve site specific drug release for disease of the stomach like ulcers and also to improve bioavailability and absorption for poorly soluble drugs.

In this work we have used Aspirin (2-Acetoxybenzoic acid) [5] as a model drug for the development of floating drug delivery system using calcium carbonate and olive oil as a base. Aspirin is a conventional non-steroidal anti-inflammatory drug which can be given either alone or in combination to reduce pain, fever and inflammation. Chronic low dose therapy (75-150 mg per day) of aspirin can also prevent heart attacks, strokes and blood clot formation [6]. The drug acts by inhibiting cyclooxygenase enzyme which further reduces the synthesis of pro-inflammatory prostaglandins (PGs) [7]. Platelet aggregation in the blood generally takes place with thromboxane which simultaneously helps in the clot formation, the inhibition of thromboxane with aspirin can be one of the pharmacological bases of the benefit against cardiovascular disease [8]. Aspirin undergoes high first pass metabolism which decreases its bioavailability. Aspirin gets absorbed in the upper part of the gastrointestinal tract very rapidly. Therefore, floating drug formulations are designed to improve the bioavailability of aspirin and to release the drug very slowly in the gastric region to improve its absorption [9].

Two types of floating beads of aspirin were prepared using calcium carbonate with glacial acetic acid and olive oil, respectively. The formulations were characterized with respect to yield, drug content, encapsulation efficiency, drug release and release kinetics [10]. The main objectives of the study were to prepare and characterize the floating beads by the two methods and compare the efficacy of the systems to maintain buoyancy as well as to achieve controlled drug release.

2. MATERIALS

Aspirin (2-Acetoxybenzoic acid), Carbopol 940, hydroxyl propyl methylcellulose (HPMC), sodium alginate, calcium carbonate, calcium chloride, acetic acid, olive oil, distilled water.

3. METHODS

3.1 Preparation of floating beads with calcium carbonate

Table 1: Formulation batches (FB1-FB6) of Aspirin floating beads

Formulation code	Sodium alginate: Carbopol 940	$CaCO_3$ (%w/v)	$CaCl_2$ (%w/v)	Glacial acetic acid (% v/v)	Olive oil (% v/v)
FB1	4:0	4	1	10	-
FB2	5:1	4	2	10	-
FB3	5:1	4	1	10	-
FB4	3:0	-	1	-	20
FB5	4:1	-	1	-	20
FB6	8:1	-	1	-	20

For preparation of floating beads with calcium carbonate at first, weighed amount of drug was dissolved in required amounts of purified hot water (heated to a temperature of 60°C on water bath). Weighed required amount of polymer was dissolved in suitable amount of water in a separate beaker. Suitable amount of calcium carbonate was added to the polymer solution. Thereafter the drug solution was added to the polymer solution and volume made up to 100 ml. In another beaker, 10% acetic acid solution was prepared containing 1% calcium chloride. The drug-polymer solution was added drop wise in to the acetic acid-calcium chloride solution with the help of 25 G needle and stirred for 30 minutes to obtain the beads. Thereafter, the mixture was filtered to collect the beads and washed multiple times with purified water and air dried overnight.

3.2 Preparation of floating beads with olive oil

For preparation of floating beads with olive oil, weighed amount of drug was dissolved in required amounts of purified hot water (heated to a temperature of 60°C on water bath). Weighed required amount of polymer was dissolved in suitable amount of water in a separate beaker. Suitable amount of olive oil was added to the polymer solution. Thereafter the aspirin solution was added to the polymer solution and volume made up to 100 ml. In another beaker a solution was prepared containing 1% calcium chloride. The drug-polymer solution was added drop wise in to the calcium chloride solution with the help of 25 G needle and stirred for 30 minutes to obtain the beads. Thereafter, the mixture was filtered to collect the beads and washed multiple times with purified water and air dried overnight. The compositions of the various formulations are given in Table 1.

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3.3 Characterization of beads

The bead formulations were characterized with respect to their yield, size and drug encapsulation efficiency. Twenty dried floating beads were taken for estimating mean diameter of the beads. The particle size of the prepared beads was estimated using optical microscope fitted along with the stage and an ocular micrometer. The result is expressed as the mean diameter (mm±standard deviation) [11].

3.3.1 Drug content and entrapment efficiency

The drug content in the formulation and entrapment efficiency were determined by extraction method. For extraction process dried beads (100 mg) were taken and extracted in 100 ml of 0.1 N HCl (pH1.2) for 24 h. Then, the beads were sonicated for 30 min and the solution was filtered through 0.4 µm filter paper. The filtrate was then taken and concentration of drug present is estimated in triplicate using spectrophotometrically at 287 nm (UV-2450- Shimadzu spectrophotometer). The drug content and entrapment efficiency of beads were estimated by putting value in the following formula [12].

Calculated drug content Drug content

$$= \frac{\text{Calculated drug content} \times 100}{\text{Total amount of beads}}$$

Calculated drug content Entrapment efficiency

$$= \frac{\text{Calculated drug content} \times 100}{\text{Theoretical drug content}}$$

3.3.2. Estimation of drug release mechanism

The drug dissolution data were fit into various equations for estimation of drug release kinetics like zero order, first order and Higuchi kinetics and determination of drug release mechanism was done. Release studies were performed in triplicate using the USP basket method at 100 rpm and 37±0.5°C in 1000 mL of test medium (i.e., SGF). Approximately, 50 beads were used for each experiment. The samples were withdrawn at specific time interval and assayed spectrophotometrically at the wavelength of maximum absorbance. The percentage of the drug release is calculated with respect to the drug content of the beads. The drug content is expressed as the percentage of drug encapsulated in a unit weight of beads. The experiments are carried out in triplicate and the results were averaged [13].

3.3.3. *In vitro* buoyancy

In- vitro buoyancy test was performed using USP paddle apparatus (50 rpm, 37±0.2°C, 900 ml, 0.1 N HCl). The prepared beads were taken and placed in the medium, the time taken by the beads to come over the top of dissolution media was noted down as floating lag time which was observed visually. The percentage of floating pellets was calculated by the following equation [14].

Floating beads (%)

$$= \frac{\text{Number of floating beads at the measure time} \times 100}{\text{Initial number of beads}}$$

3.3.4. Swelling study

For swelling study, the beads were weighed and placed inside the wire basket of USP dissolution apparatus II. The basket containing beads were placed inside the beaker filled with 900 ml of HCl (pH 1.2) maintained at temperature 37±0.5°C. After 12 h, the beads were removed from the swelling media study and studied for swelling characteristics. Beads were studied for swelling characteristics. The beads were removed after 12 h from their media and weighed after drying the beads with filter paper [15]. At last, the swelling index was estimated as percentage using the formula given below:

% Swelling index

$$= \frac{\text{Final wt. of beads - Initial wt. of beads}}{\text{Initial wt. of beads}} \times 100$$

4. RESULTS AND DISCUSSIONS

4.1. Determination of particle size by optical micrsocopy

The mean particle size of the beads ranged from 1.48 to 2.01 mm (Table 2).

Table 2: Particle size determination of Aspirin beads

Formulation code	Particle size (mm) (mean±SD) (n=20)
FB1	1.98±0.04
FB2	1.84±0.05
FB3	2.01±0.04
FB4	1.48±0.01
FB5	1.55±0.01
FB6	1.66±0.02

4.2. Percentage yield and drug entrapment efficiency

The percentage yield of each formulation was calculated with taking weight of the starting material into consideration. The percentage yield of prepared beads was 61.9 to 84.9% (Table 3) for beads FB1-FB6. The range of mean drug entrapment efficiency of batch FB1-FB6 was between 51.3±0.05 to 70.3±0.01. The formulation prepared with olive oil shows higher drug entrapment efficiency as compared to glacial acetic acid. The formulation incorporating good amount of oil shows instant floating ability. The beads remained afloat throughout the study period 12 h and the beads continued to float until 24 h. The percentage floating for formulation FB4 was highest i.e., 82.3±0.02. (Table 3)

Table 3: Percentage yield and drug entrapment efficiency study of Aspirin beads (formulations FB1–FB6)

Formulation Code	% yield (w/w) (Mean±SD) (n=3)	Percentage drug entrapment (Mean±SD) (n=3)
FB1	65.9±0.04	54.3±0.02
FB2	78.9±0.01	62.3±0.01
FB3	61.9±0.05	51.32±0.01
FB4	84.9±0.01	70.3±0.01
FB5	80.9±0.02	68.3±0.02
FB6	82.9±0.03	65.3±0.02

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4.3. Swelling study

The *in vitro* swelling indices of the formulated beads FB1-FB6 were 298.3, 295.3, 299.3, 206.23, 298.25, and 267.6 respectively. The prepared formulation showed good swelling index with mineral oil which might be due to the olive oil used as a floating agent.

Table 4: *In vitro* swelling data of Aspirin beads (FB1–FB6)

Time (h)	% Swelling index					
	FB1	FB2	FB3	FB4	FB5	FB6
1	51.2	45.3	36.6	32.33	50.03	32.01
2	63.45	64.3	49.5	78.21	96.43	52.03
3	122.3	164.3	143.3	108.53	178.22	107.54
4	155.3	205.2	229.3	143.02	234.65	148.21
5	203.2	265.3	235.8	167.03	267.98	189.84
6	257.4	277.3	258.9	185.07	275.02	209.21
7	289.1	285.3	273.4	194.56	284.03	298.02
8	298.3	295.3	299.3	206.23	298.25	267.06

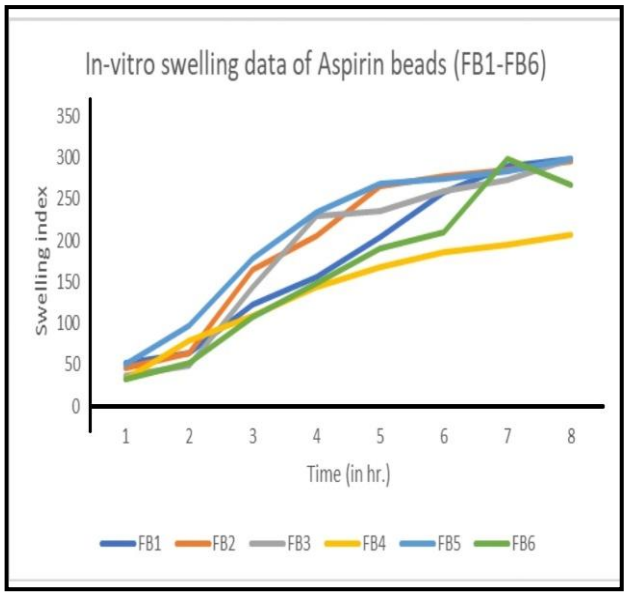

Fig. 1:*In vitro* swelling of Aspirin beads

4.4. Drug release study

The drug release data showed controlled release from all the formulations. The formulations prepared with glacial acetic acid and calcium carbonate (FB1-FB3) released about 79 to 85.54 % drug in 12 hrs, with FB3 showing the best profile containing the highest amount of carbopol 940 together with sodium alginate (Table 5). On the other hand the formulations containing olive oil released drug in the range of 82.23 to 96.43 % in 12 hours. FB6 had the best release profile with highest amount of olive oil (Fig 2).

From the study of drug release mechanism it was observed that formulations with glacial acetic acid and calcium carbonate FB3 followed zero order release mechanism. The n value indicated non–fickian transport. In case of oilve oil containing formulation FB6, the Higuchi model of matrix mechanism was followed and non fickian transport was determined from the n value derived from KorsemeyerPeppas model.

Table 5: In vitro drug release data of Aspirin beads (FB1–FB6)

Time (h)	Cumulative % drug release					
	FB1	FB2	FB3	FB4	FB5	FB6
1	7.9	6.3	5.6	6.54	5.78	6.46
2	9.45	10.76	9.7	10.03	12.67	14.02
3	10.67	16.24	11.43	15.76	18.45	20.23
4	18.67	28.45	23.4	36.54	23.21	24.02
5	27.56	35.56	27.5	48.44	34.67	33.45
6	36.78	43.24	34.2	58.96	59.54	56.87
7	54.98	51.67	58.6	68.35	65.34	63.98
8	57.56	69.24	63.2	74.36	72.22	66.32
9	68.73	73.76	65.6	85.37	87.56	70.45
10	75.79	79.89	69.3	89.57	89.01	76.54
11	78.05	84.67	78.5	93.02	92.54	78.45
12	84.65	85.54	79	96.43	94.04	82.23

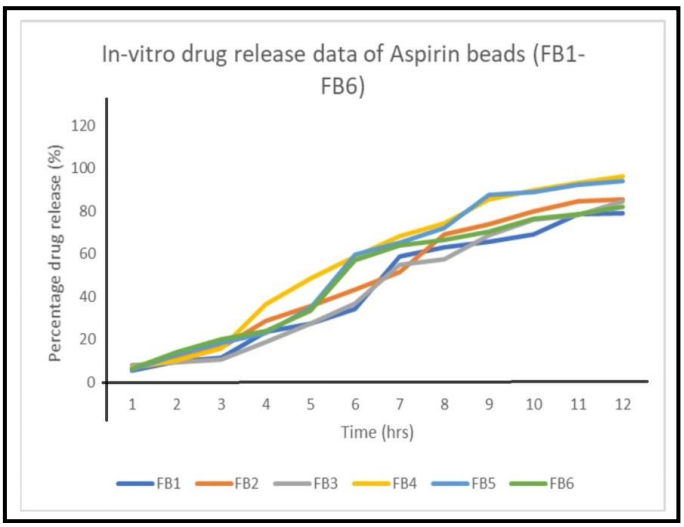

Fig. 2: In vitro drug release of beads

Table 6: Drug release mechanism studies

Kinetic model	FB3	FB6
Zero order	0.96	0.946
First order	0.897	0.85
Higuchi model	0.938	0.954
KorsemeyerPeppas	0.942	0.968
N value	1.2	1.15

4.5. *In vitro* buoyancy study of aspirin beads

Beads containing olive oil FB4–FB6 have shown good floating ability and percentage floating was found to be 62.3±0.02-82.3±0.02. The floating ability of the formulations was found to be directly proportional to the amount of oil entrapped in their polymer matrix. If the density of oil is low, very less amount of oil is required. The beads floated for 12 h and beyond. The percentage floating for formulation containing glacial acetic acid (FB1, FB2, FB3) were 74.3±0.02, 73.3±0.01, 67.3±0.04 and the percentage floating for formulation containing olive oil (FB4, FB5, FB6) was 82.3±0.02, 80.3±0.01 and 62.3±0.01 respectively.

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Table 7: *In vitro* buoyancy study of Aspirin beads (formulations FB1–FB6)

Formulation Code	Floating lag time (min)	Floating Time (h)	Percentage Floating (mean±SD) (n=3)
FB1	<1	>12	74.3±0.02
FB2	<2	>12	73.3±0.01
FB3	<2	>10	67.3±0.04
FB4	<1	>12	82.3±0.02
FB5	<1	>12	80.3±0.01
FB6	<1	>12	62.3±0.01

CONCLUSIONS:

The floating beads prepared were characterized which gave promising results. The shape of beads was spherical for nearly all the batches. Percentage yield and drug entrapment efficiency were found to be greater for FB4, FB5 and FB6 (batches prepared with olive oil) compared to FB1, FB2 and FB3 (batches prepared with calcium carbonate). The floating time was also greater than 12 hours for all the formulations. Swelling studies indicated a gradual increase in swelling with time. Regarding the drug release, all the batches sustained drug release for around 12 hours. Among the batches prepared with calcium carbonate, FB3 gave the best sustained release and among the batches prepared with olive oil, FB6 showed the best sustained release. Overall all the formulations prepared showed good controlled release properties, swelling and floating characteristics and thus the formulations can be successfully employed to achieve controlled release of aspirin.

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