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Research Article

FORMULATION AND CHARACTERIZATION OF FLOATING BEADS OF ANTIBIOTIC BY EMULSION GELATION TECHNIQUE

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ABSTRACT

Objective: The study aims at formulation and characterization of floating hydrogel beads of cefdinir for improving its bioavailability.

Methods: Cefdinir is broad-spectrum, oral, third-generation cephalosporin antimicrobial agent active against Gram-positive and Gram-negative bacteria. The floating hydrogel beads of cefdinir were formulated with polymers such as sodium alginate and sodium carboxymethyl cellulose by emulsion gelation technique using olive oil/castor oil. The beads were evaluated for surface morphology, bead size, entrapment efficiency, floating characteristics, *in vitro* swelling, *in vitro* drug release, and stability studies.

Results: On the basis of evaluation, all the beads show good swelling up to 12 h in 0.1 N hydrochloric acid. The swelling was followed by values in order of vegetable oil > mineral oil in case of emulsion gelation method. Scanning electron microscopy study shows that beads were spherical in shape. Comparing all the formulations, formulation FB12 was considered as optimized formulation which shows % yield 94.06±0.11, % floating 87.28±0.90, *in vitro* drug release 94.68, and also stable in stability studies.

Conclusion: From the findings, it may be concluded that cefdinir-loaded floating beads were successfully prepared and proved to be useful for the better bioavailability and patient compliance for enhanced antimicrobial activity.

Keywords: Cefdinir, Emulsion gelation, Floating, Sodium carboxymethyl cellulose, Sodium alginate, Olive oil, Castor oil.

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INTRODUCTION

Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance, and flexibility in formulation [1]. From immediate release to site-specific delivery, oral dosage forms have really progressed [2]. However, it is a well-accepted fact that it is difficult to predict the real *in vivo* time of release with solid, oral controlled release dosage forms. Thus, drug absorption in the gastrointestinal tract (GIT) may be very short and highly variable in certain circumstances [3].

One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GIT is to control the gastric residence time. Dosage forms with a prolonged gastroretentive dosage forms will provide us with new and important therapeutic options [4].

Nowadays, alginate gel beads become post-acceptable vehicle for drug delivery since it is cost-effective, biodegradable, simple process [5]. Floating is the most acceptable approach of gastroretentive drug delivery system (GRDDS). Floating approach is available in single as well as multiparticulate forms such as beads, microspheres, and pellets [6]. Beads spread out more uniformly in the GIT, thus avoiding exposure of the mucosa locally to high concentration of drug [7]. Beads are small, solid, and free-flowing particulate carriers containing dispersed drug particles either in solution or crystalline form. Spherical beads of approximately 2.5 mm in diameter [8].

Cefdinir is a broad-spectrum, oral, third-generation cephalosporin antimicrobial agent active against Gram-positive and Gram-negative bacteria. It is used in treatment of acute chronic bronchitis, rhinosinusitis, pharyngitis, etc. Cefdinir is having half-life of 1.5 h with oral bioavailability 20–30%. Cefdinir is better absorbed from the upper part of the GIT [9].

Therefore, in the present study, an attempt will be made to design and evaluate GRDDS of cefdinir with a view to enhance its bioavailability, duration of action, and convenience of administration in the form of hydrogel beads as floating system leading to improved patient compliance.

MATERIALS AND METHODS

Materials

Cefdinir was purchased from Rajesh Chemicals, Mumbai (India), Sodium alginate, Sodium carboxy methyl cellulose (CMC), Calcium chloride, Aluminum chloride, Calcium Vegetable oil, mineral oil, (SD Fine Chem Ltd., Mumbai). All other chemicals were of analytical grade.

Methods

Standard calibration curve of cefdinir in 0.1 N HCL (pH 1.2) buffer solutions

Preparation of stock solution

Accurately weighed 10 mg of cefdinir was dissolved in small amount of 0.1 N HCL (pH 1.2), and the volume was then made up to 100 ml with the same to obtain a concentration of 100 µg/ml.

Preparation of working standard solution

From the above solution, aliquots of 0.3, 0.6, 0.9, 1.2, 1.5, and 1.8 ml were transferred to a series of 10 ml volumetric flask and diluted up to the mark with 0.1 N HCL (pH 1.2) to give 3, 6, 9, 12, 15, and 18 µg/ml. Absorbance was measured spectrophotometrically at 287 nm against blank using Shimadzu Ultraviolet (UV) Spectrophotometer.

Method of floating bead formulation

Emulsion gelation technique

Solutions of sodium alginate and sodium CMC were prepared by stirring in distilled water. Cefdinir and olive oil/castor oil were added to the solution.

Each mixture with total volume of 100 ml (containing cefdinir 1 g and oil in two different concentrations 10 and 15%v/v) was stirred properly to prepare homogeneous mixtures. The mixture was extruded, using a 20-gauge syringe needle into 200 ml of gently agitated calcium chloride (1%) or aluminum chloride (2%) solution at room temperature. The resulting beads were allowed to stand in the solution for 24 h before being separated and washed twice with 500 ml distilled water. The beads were dried at room temperature for 48 h and were stored in desiccators [10,11].

Characterization of floating beads

Scanning electron microscopy (SEM)

Morphological examination of the surface and internal structure of the dried calcium alginate beads was carried out using a SEM (JEOL JEM-1200 EX II, Japan) equipped with secondary electron detector at an accelerating voltage of 10 kV. The samples were coated with gold to a thickness of about 30 nm in a vacuum evaporator. The internal structure of beads was examined by cutting them with a steel blade [12].

Determination of bead diameter size

Particle size of the prepared beads was determined using an optical microscope fitted with the stage and an ocular micrometer. Twenty dried beads were measured for calculating the mean diameter of beads. The result is expressed as the mean diameter (mm)±standard deviation [13].

Drug content and entrapment efficiency

The drug content and entrapment efficiency of prepared beads were determined by the method of extraction of drug present in beads. The dried beads (100 mg) were taken and extracted in 100 mL of 0.1N HCl (pH 1.2) for 24 h. Then, the dispersion of beads was sonicated for 30 min and the solution was filtered through a 0.45 µm filter. The concentration of drug present in filtrate determined spectrophotometrically at 287 nm (UV-2450, Shimadzu, Japan). Each determination was made in triplicate. The drug content and entrapment efficiency of prepared beads were determined by putting value in the following formula [14].

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

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

In vitro buoyancy

The time interval between the introduction of beads into the dissolution medium and its buoyancy to the top of dissolution medium was taken as floating lag time and floating time was observed visually. The floating abilities of the beads were determined using USP paddle apparatus (50 rpm, 37±0.2°C, 900 ml, 0.1 N HCl). 50 beads were placed in the medium; the time to float and duration of floating (floating time) were measured by visual observation. The percentage of floating pellets was calculated by the following equation: [15].

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

Swelling study

Beads were studied for swelling characteristics. Sample from drug-loaded beads was taken, weighed, and placed in wire basket. Beads were studied for swelling characteristics. Sample from

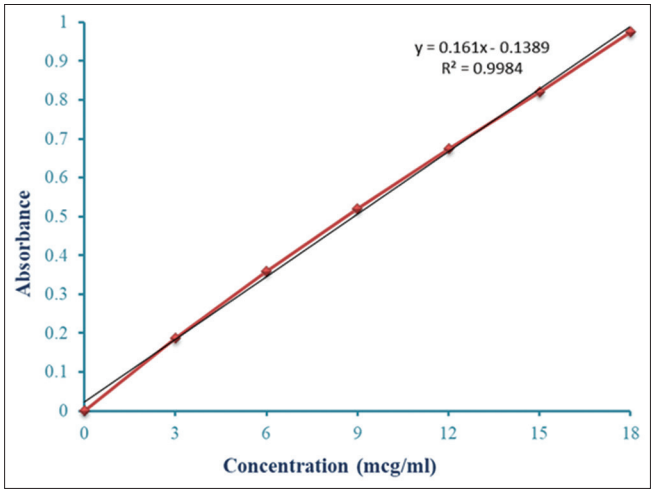

Fig. 1: Calibration curve of cefdinir in 0.1 N HCl

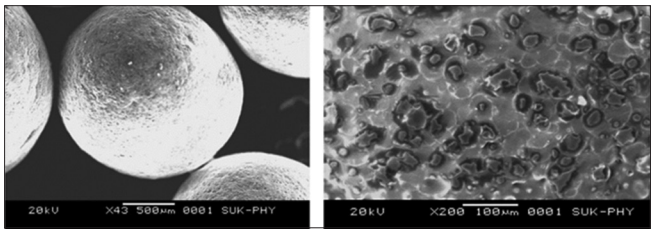

Fig. 2: Scanning electron microscopy of cefdinir-loaded beads

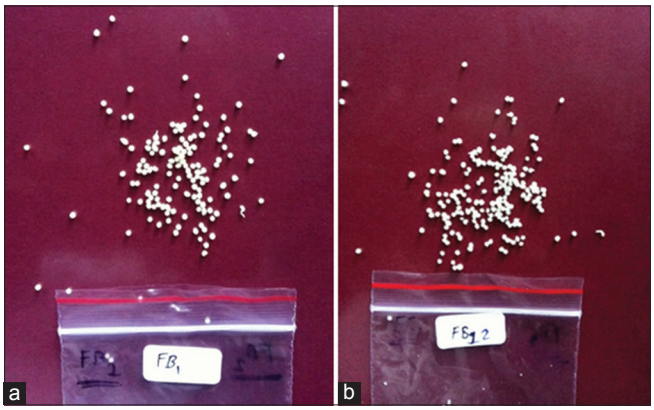

Fig. 3: (a and b) Photographs of prepared cefdinir beads by emulsion gelation method

Table 1: Formulation batches of floating cefdinir floating beads

Ingredients	Formulation code											
	FB1	FB2	FB3	FB4	FB5	FB6	FB7	FB8	FB9	FB10	FB11	FB12
Cefdinir	1	1	1	1	1	1	1	1	1	1	1	1
Sodium alginate	3	3	3	3	3	3	3	3	-	-	-	-
Sodium CMC	-	-	-	-	-	-	-	-	2.5	2.5	2.5	2.5
Vegetable oil	-	-	-	-	10	10	15	15	-	-	10	15
Mineral oil	10	10	15	15	-	-	-	-	10	15	-	-
$CaCl_2$	1	-	1	-	1	-	1	-	-	-	-	-
$AlCl_2$	-	2	-	2	-	2	-	2	2	2	2	2

CMC: Carboxymethyl cellulose

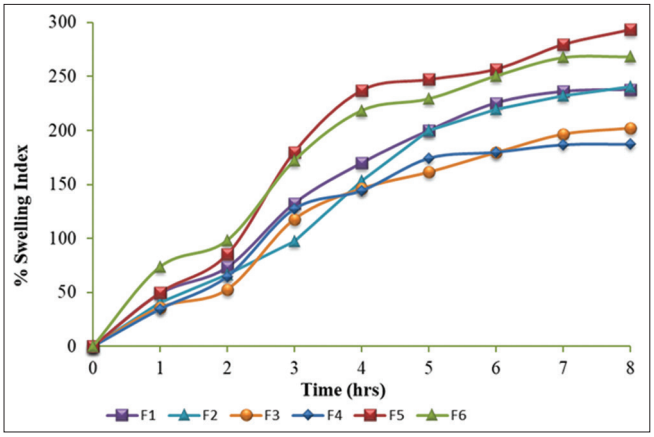

Fig. 4: *In vitro* swelling data of cefdinir beads (FB1–FB4)

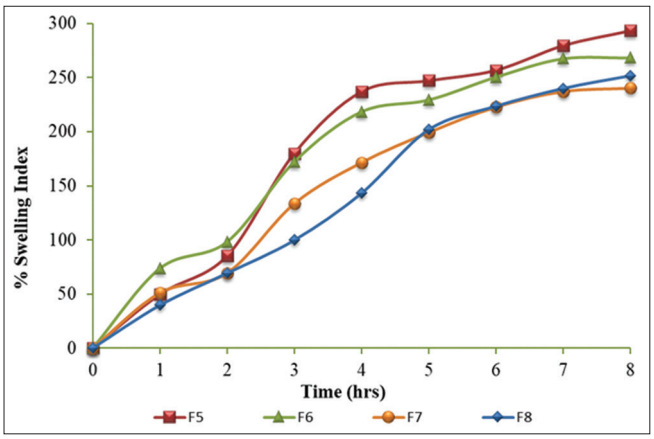

Fig. 5: *In vitro* swelling data of cefdinir beads (FB5–FB8)

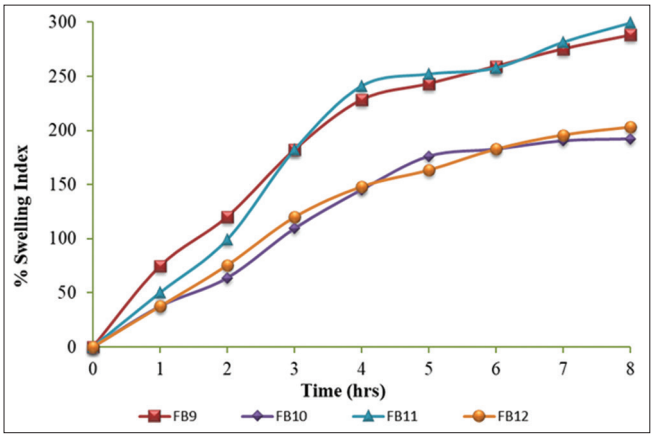

Fig. 6: *In vitro* swelling data of cefdinir beads (FB9–FB12)

drug-loaded beads was taken, weighed, and placed in wire basket of USP dissolution apparatus II. The basket containing beads was placed in a beaker containing 900 ml of HCl solution (pH 1.2) maintained at 37±0.5°C. After 12 h, the beads were removed from their respective swelling media and weighed after drying the water on the surface of the beads using filter paper. Then, the swelling index was calculated as percentage using the following formula [16-19].

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

Table 2: Calibration curve of cefdinir in 0.1 N HCl

Concentration (mcg/ml)	Absorbance (mean±SD)
0	0.000±0.000
3	0.188±0.004
6	0.358±0.002
9	0.519±0.007
12	0.675±0.003
15	0.821±0.005
18	0.975±0.003

SD: Standard deviation

In vitro drug release studies

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 are 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 [20-24].

RESULTS AND DISCUSSION

SEM

The surface morphology of prepared beads was studied by SEM. External and internal surfaces of beads formulation FB12 are shown in Fig. 2. The sodium alginate and sodium CMC beads prepared with calcium chloride were spherical, and the beads prepared with aluminum chloride were spherical with tail. External surface was smooth with slightly rougher surface/shrinkage which could be due to drying. In the drug-loaded beads, the internal surface is slightly sponge like which is due to the drug and rate controlling polymer are uniformly dispersed in the polymer matrix. The internal surface of the oil-entrapped beads shows slightly sponge-like nature with little droplets of entrapped oil which imparts buoyancy to the beads. The surface layer of all beads was denser, and hence, in the preparation process, anionic polymer diffused from the droplet core toward the gelling solution (coagulation medium) to form more heterogeneous structure.

The mean particle size of sodium alginate beads FB9–FB12 was between 1.58 mm and 1.99 mm. Sodium alginate beads were large when compared to sodium CMC due to molecular weight and viscosity. By increasing the oil concentration in the beads, an increase in size of the beads was observed.

Drug entrapment efficiency and floating study

The percentage yield of each batch was calculated on weight basis with respect to the weight of starting material. The percentage production yield of prepared beads was 81.98±0.32–96.10±0.08% for beads FB1–FB12 as shown in Table 4.

The mean drug entrapment efficiency of sodium alginate beads prepared by emulsion gelation technique of batch FB1–FB12 was between 58.14±1.87 and 84.50±0.33%. Hence, sodium alginate shows higher DEE than sodium CMC. Formulation FB1 shows higher DEE in both the methods 84.50±0.33%, suggesting that the emulsion gelation methods are effective for the entrapment of cefdinir.

Beads containing sufficient amount of oil FB1–FB12 demonstrated instantaneous floating ability and % floating was found to be 62.25±1.40–94.60±1.05% (Table 5). Thus, floating ability was found to be directly related to the amount of oil entrapped in the polymer matrix. Furthermore, lower the density of oil, lesser amount of oil is required to float. The beads remained afloat throughout the study period 12 h and the beads continued to float until 24 h.

Table 3: Particle size determination and visual analysis of cefdinir beads prepared by emulsion gelation technique (formulations FB1–FB12)

Formulation code	Particle size (mm) (mean±SD) (n=20)	Shape	Color	Oil leakage
FB1	1.94±0.08	Spherical	Off-white	Yes
FB2	2.02±0.02	Spherical disc	Yellow	Yes
FB3	2.10±0.05	Spherical	Off-white	Yes
FB4	1.98±0.07	Spherical disc	Yellow	Yes and high
FB5	2.08±0.04	Spherical with tail	Off-white	Intermediate
FB6	1.99±0.03	Spherical disc	Off-white	Yes
FB7	1.96±0.02	Spherical	Off-white	Yes
FB8	2.08±0.05	Spherical disc	Off-white	Intermediate
FB9	1.99±0.03	Spherical	White	Intermediate
FB10	1.67±0.06	Spherical	Off-white	Yes and high
FB11	1.97±0.05	Spherical	White	Intermediate
FB12	1.58±0.02	Spherical	Off-white	Yes and high

Table 4: Percentage yield and drug entrapment efficiency study of cefdinir beads prepared by emulsion gelation technique (formulations FB1–FB12)

Formulation code	% yield (w/w) (mean±SD) (n=3)	Percentage drug entrapment (mean±SD) (n=3)
FB1	91.37±0.41	84.50±0.33
FB2	88.26±0.57	80.71±1.78
FB3	81.98±0.32	79.31±1.56
FB4	87.91±0.21	77.08±0.40
FB5	89.54±0.13	68.49±0.87
FB6	96.10±0.08	61.93±0.90
FB7	95.08±0.10	71.28±0.35
FB8	86.57±0.36	69.87±1.14
FB9	87.60±0.25	58.14±1.87
FB10	92.32±0.31	64.42±1.30
FB11	83.78±0.29	67.07±0.67
FB12	94.06±0.11	81.91±0.42

Table 5: *In vitro* buoyancy study of cefdinir beads prepared by emulsion gelation technique (formulations FB1–FB12)

Formulation code	Floating lag time (min)	Floating time (h)	Percentage floating (mean±SD) (n=3)
FB1	<1	>12	86.28±0.28
FB2	<1	>12	90.36±0.08
FB3	<1	>12	78.66±0.78
FB4	<1	>12	84.24±0.17
FB5	<1	>12	94.60±1.05
FB6	<1	>12	93.19±0.34
FB7	<1	>12	93.10±0.76
FB8	<1	>12	89.90±1.30
FB9	<2	>12	68.75±0.78
FB10	<2	>12	62.25±1.40
FB11	<1	>12	69.89±1.37
FB12	<2	>12	87.28±0.90

Table 6: *In vitro* swelling data of cefdinir beads (FB1–FB4)

Time (h)	Swelling index			
	FB1	FB2	FB3	FB4
1	49.01	40.67	36.25	34.65
2	73.34	66.45	52.84	64.71
3	132.5	97.22	117.82	127.35
4	169.95	153.2	146.12	144.26
5	200.02	199.93	161.43	174.21
6	225.47	219.55	179.48	179.84
7	236.21	231.98	196.54	186.75
8	238.04	240.7	202.21	187.21

***In vitro* swelling data of cefdinir beads**

The swelling index of sodium alginate beads containing vegetable oil (olive oil) as floating agent (FB1, FB2, FB3, and FB4) was 238.04, 240.7, 202.21, and 187.21, respectively, and for sodium alginate beads containing mineral oil as floating agent (FB5, FB6, FB7, and FB8) was 293.27, 268.14, 240.17, and 251.77, respectively. The swelling index of sodium CMC beads (FB9, FB10, FB11, and FB12) was 288.14, 192.29, 299.28, and 203.23, respectively. The swelling was followed by values in order of vegetable oil >mineral oil.

Table 7: *In vitro* swelling data of cefdinir beads (FB5–FB8)

Time (h)	Swelling index			
	FB5	FB6	FB7	FB8
1	49.8	73.71	51.11	39.67
2	85.32	98.26	69.41	69.245
3	179.96	172.2	133.5	99.72
4	237.02	218.41	171.5	143.2
5	247.15	229.32	199.27	201.93
6	256.74	250.41	222.7	223.55
7	279.52	267.4	237.12	239.98
8	293.27	268.14	240.17	251.77

Table 8: *In vitro* swelling data of cefdinir beads (FB9–FB12)

Time (h)	Swelling index			
	FB9	FB10	FB11	FB12
1	74.71	37.6	50.18	37.54
2	120.36	63.78	99.22	75.45
3	182.2	109.35	181.96	119.84
4	228.41	145.26	241.02	148.12
5	243.32	176.21	252.15	163.43
6	259.41	182.84	257.74	182.8
7	275.4	190.52	281.52	195.84
8	288.14	192.29	299.28	203.23

***In vitro* drug release data of cefdinir beads**

The percentage cumulative drug release of sodium alginate beads prepared by emulsion gelation method using mineral oil (FB1–FB4) was 76.82, 80.37, 81.81, and 86.34%, while beads prepared by emulsion gelation method using vegetable oil (FB5–FB8) was 64.61, 69.74,and 80.56%, respectively, at the end of 12 h and sodium CMC beads (FB9–FB12) show 84.56, 92.58, 82.42, and 94.68%, respectively, at the end of 12 h. Hence, increase the concentration of gas forming agent or oil concentration, increase the percentage cumulative drug release was observed. Percentage cumulative drug release was followed by value in order of sodium alginate >sodium CMC. Furthermore, it was observed that polymers, sodium alginate and sodium CMC, show delayed release up to 12 h.

The stability data are represented in Table 13, and the stability study was performed for selected formulation FB12 for 3 months, suggesting that FB12 the formulation were stable, with no physical change and also the floating ability, DEE and cumulative % drug release, was not significant changed.

Table 9: *In vitro* drug release data of cefdinir beads (FB1–FB4)

Time (h)	Cumulative % drug release			
	FB1	FB2	FB3	FB4
1	6.6	7.26	7.92	8.58
2	8.25	9.44	10.63	11.82
3	12.68	12.98	15.28	18.58
4	18.12	23.14	24.16	27.18
5	28.94	30.12	31.3	36.48
6	36.72	39.46	42.2	44.94
7	46.88	48.22	50.56	52.9
8	55.76	58.18	62.6	67.02
9	62.36	68.02	69.68	73.34
10	68.58	72.64	74.7	78.76
11	73.33	76.5	79.67	82.88
12	76.82	80.37	81.81	86.34

Table 10: *In vitro* drug release data of cefdinir beads (FB5–FB8)

Time (h)	Cumulative % drug release			
	FB5	FB6	FB7	FB8
1	5.9	6.26	6.62	6.98
2	9.92	10.98	11.04	12.1
3	11.74	13.8	15.86	17.92
4	20.28	22.82	27.36	31.9
5	29.56	32.12	36.68	43.24
6	33.12	38.23	43.34	48.45
7	51.94	50.02	58.1	60.18
8	56.86	59.23	65.6	67.97
9	64.61	69.74	74.87	80.56
10	69.25	74.14	79.03	83.92
11	76.51	77.5	82.49	88.48
12	77.28	82.08	86.88	91.68

Table 11: *In vitro* drug release data of cefdinir beads (FB9–FB12)

Time (h)	Cumulative % drug release			
	FB9	FB10	FB11	FB12
1	6.98	7.32	3.21	5.38
2	9.8	14.88	10.46	12.61
3	16.82	18.9	14.24	15.96
4	27.12	33.4	24.64	32.98
5	38.23	44.39	32.31	46.87
6	48.02	49.76	42.9	54.55
7	54.23	61.98	46.68	63.5
8	65.74	69.47	60.55	76.73
9	74.14	81.78	69.98	82.2
10	77.5	84.92	74.73	89.42
11	82.08	89.38	78.2	92.34
12	84.56	92.58	82.42	94.68

CONCLUSION

Multiparticulate gastroretentive hydrogel beads of cefdinir were formulated with sodium alginate and sodium CMC by emulsion gelation method using olive oil/castor oil. The beads were evaluated for surface morphology, bead size, entrapment efficiency, floating characteristics, *in vitro* swelling, *in vitro* drug release, and stability studies. The prepared beads had a different size and the percentage entrapment efficiency of the drug. The SEM study shows that beads are spherical in shape. Comparing all the formulations, formulation FB12 was considered as optimized formulation which shows % yield 94.06±0.11, % floating 87.28±0.90, *in vitro* drug release 94.68%, and also stable in stability

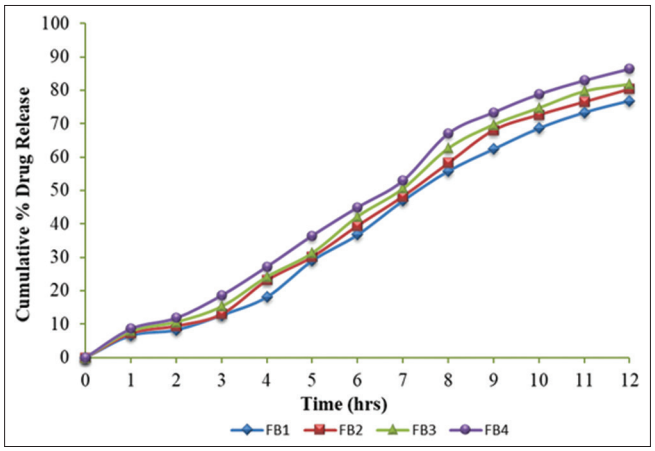

Fig. 7: *In vitro* drug release data of cefdinir beads (FB1–FB4)

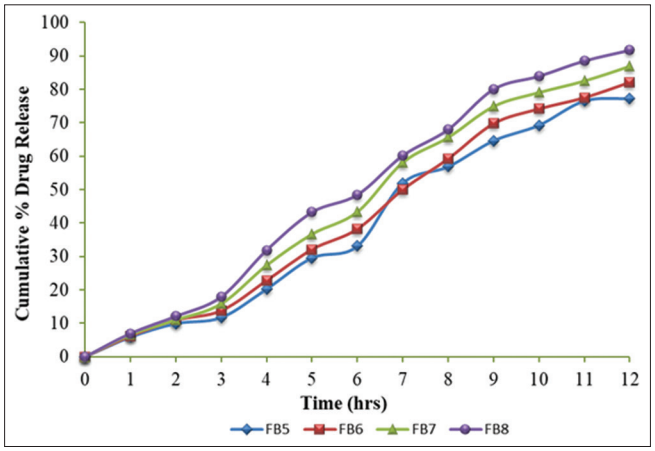

Fig. 8: *In vitro* drug release data of cefdinir beads (FB5–FB8)

Table 12: *In vitro* release data according to various release kinetic models

Formulation code	Zero order (r^2)	First order (r^2)	Higuchi (r^2)	Peppas plot	
				(r^2)	n-value
FB1	0.9502	0.9160	0.9893	0.9948	1.2613
FB2	0.9336	0.7540	0.9956	0.9965	1.2138
FB3	0.9413	0.9970	0.9947	0.9929	1.2934
FB4	0.9141	0.8952	0.9891	0.9761	1.2934
FB5	0.9546	0.9527	0.9731	0.9778	1.1889
FB6	0.8655	0.9634	0.9783	0.9602	1.1802
FB7	0.9375	0.9928	0.9954	0.9936	1.1961
FB8	0.9420	0.9866	0.9909	0.9845	1.2754
FB9	0.9585	0.9810	0.9623	0.9623	1.3621
FB10	0.9750	0.9636	0.9262	0.9264	1.2364
FB11	0.9809	0.9612	0.9204	0.9204	1.1547
FB12	0.9665	0.9690	0.9280	0.9280	1.2067

Table 13: Short-term stability study data of cefdinir-loaded beads (FB1 and FB9)

Sampling time (months)	FB12		
	% floating (mean±SD) (n=3)	% DEE (mean±SD) (n=3)	Cumulative % drug release
0	87.28±0.90	81.91±0.42	94.68
1	86.05±0.31	81.42±0.21	95.69
2	87.91±0.22	81.24±0.17	94.45
3	87.66±0.14	80.13±0.08	93.23

SD: Standard deviation

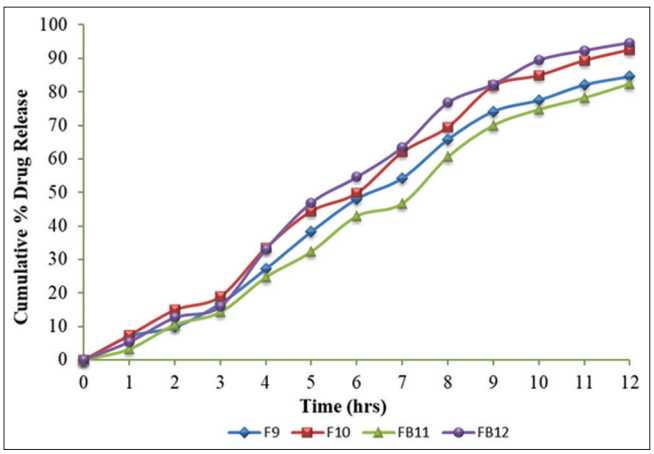

Fig. 9: *In vitro* drug release data of cefdinir beads (FB9–FB12)

studies. From the findings, it may be concluded that cefdinir-loaded floating beads were successfully prepared and proved to be useful for the prolonged gastric residence of the drug, better bioavailability, and patient compliance for enhanced antimicrobial activity.

AUTHORS' CONTRIBUTION

The first author carried out experiments. The second author done preformulation study, made arrangement of drug and polymers, and drafted the manuscript.

CONFLICTS OF INTEREST

Authors declare no conflicts of interest.

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