Research Article

Preparation and evaluation of gastroretentive hydrogel beads of Cefdinir by ionotropic gelation method

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Abstract

Objective: The purpose of the present study was to develop and evaluate gastroretentive hydrogel beads of Cefdinir using polymers like Sodium alginate and Sodium CMC by ionotropic gelation method using Calcium carbonate or sodium bicarbonate as a gas forming agent. **Materials and Methods:** Twelve formulated beads evaluated physically in terms of surface morphology, bead size, entrapment efficiency, floating characteristics, Fourier transform infrared spectroscopy, in vitro swelling, and in *vitro* drug release and stability studies. **Results:** The surface morphology revealed that the prepared beads are spherical, having rough and dense surface with microscopic cracks and wrinkles on the surface. According to nature of coagulation medium the shape of beads was changed. Formulations F5 shows higher drug entrapment efficiency (i.e. 94.60%) suggesting that the ionotropic gelation method is effective for the entrapment of Cefdinir. All the beads formulation remained float throughout the study up to 24 h with the range of 62.25-96.40% suggesting that calcium carbonate and sodium bicarbonate can be used as buoyant. All the beads show good swelling up to 12 hrs in 0.1 N HCL. The swelling followed values in order of sodium carboxy methyl cellulose > sodium alginate. The in vitro drug release indicated that increase the concentration of gas forming agent increase the drug release and drug release followed values in order of sodium alginate > sodium CMC. Also increase in concentration of the polymer resulted in decreased drug release. **Conclusion:** It can be concluded that the floating beads of cefdinir can be prepared by using $CaCO_3$ and $NaHCO_3$as buoyant along with hydrogel forming polymer like sodium alginate and sodium carboxy methylcellulose as a release modifier for improved oral bioavailability of Cefdinir.

Keywords: Cefdinir, ionotropic gelation, gas forming agent, oil entrapment, sodium alginate, sodium carboxy methyl cellulose

Introduction

It is widely known that gastric residence time is one of the important factors affecting the drug bioavailability of pharmaceutical dosage forms. Variable and short gastric emptying time can result in incomplete drug release from the drug delivery system above the absorption zone (stomach or upper part of small intestine), leading to a diminished efficacy of the administered dose (Sungthongjeen et al., 2006). One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract is to control the gastric residence time. Dosage forms with a prolonged gastro retentive dosage forms will provide us with new and important therapeutic options. Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability reduces drug waste (Shaikh et al., 2016). It has applications also for local drug delivery to the stomach and proximal small intestines. Gastroretention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients (Sharma et al., 2011). . During the last few years, most popular approach of Gastroretention is floating drug delivery systems .Among these, the use of floating hydrogel beads is the simplest approach.

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Cefdinir is a semi-synthetic third generation oral antibiotic in the cephalosporin family of antibiotics. Cefdinir is used to treat a wide variety of bacterial infections. It has biological half-life of 1.5h so, administration of drug is six times per days for acute and sub-acute conditions, its having 35-54%% of bioavailability. It exhibits lower bioavailability when given in conventional dosage forms due to diminished absorption and degradation in lower part of the GIT. So there is need to prepare gastroretentive hydrogel beads of cefdinir to increase its bioavailability & therapeutic efficacy (Chandra et al., 2018).

Materials and methods

Materials

Cefdinir was purchased from Rajesh chemical Mumbai (India), Sodium alginate, Sodium carboxy methyl cellulose, Calcium chloride, Aluminium chloride, Calcium Carbonate, sodium bicarbonate, (SD Fine Chem Ltd., Mumbai). All other chemicals were of analytical grade.

Formulation of gastroretentive beads

In the first scheme the Cefdinir beads were prepared by using single polymer like sodium alginate (3%) and sodium Carboxymethyl cellulose (3%). For the preparation of sodium alginate and sodium Carboxymethyl cellulose solution; the polymer was dissolved in distilled water and the gas forming agent such as $CaCO_3$, $NaHCO_3$ was added to the solution with levels from 1:0.5 to 1:1 (alginate: gas forming agent w/w) the formulation composition are shown in table 1. The resulting solution was dropped through a 20G syringe needle into 1% $CaCl_2$ or 2% $AlCl_3$. The solution containing suspended beads were kept overnight and then filtered, washed twice with 500 ml distilled water. The beads were dried at room temperature for 48 hrs and were stored in desiccators (Yellanki et al., 2010).

Characterization of floating beads

Fourier-transformation infrared (FTIR) spectroscopy

Fourier Transformation Infrared spectra of pure drug, polymer and drug loaded floating beads were obtained in KBr pellets at moderate scanning speed between 4000-200 cm^{-1} in a Perkin-Elmer Fourier Transformation Infrared Spectroscope (Hrsoliya et al., 2012).

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 (Pasparakis et al., 2002).

Drug content and Entrapment efficiency

The drug content and entrapment efficiency of prepared beads was determined by method of extraction of drug present in beads. The dried beads (100mg) were taken and extracted in 100 mL of 0.1N HCl (pH 1.2) for 24 hours. 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 was determined by putting value in given below formula (Varshosaz et al., 2007).

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

$$\text{Entrapping efficiency} = \frac{\text{Calculated Drug content}}{\text{Theoretical Drug content}} \times 100$$

In-vitro buoyancy

The floating abilities of the beads were determined using USP paddle apparatus (50 rpm,37 ±0.2 °C, 900 ml, 0.1N HCl). 50beads were placed in the medium; the time to float

Table 1. Formulation table for floating beads of Cefdinir by ionic gelation method

Ingredients	Formulation Code											
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}	F_{11}	F_{12}
Cefdinir	1	1	1	1	1	1	1	1	1	1	1	1
Na. Alginate	3	3	3	3	3	3	3	3	-	-	-	-
Na. CMC	-	-	-	-	-	-	-	-	2.5	2.5	2.5	2.5
$NaHCO_3$	1	1	1.5	1.5	-	-	-	-	1	1.5	-	-
$CaCO_3$	-	-	-	-	1.5	1.5	3	3	-	-	1.5	3
$CaCl_2$	1	-	1	-	1	-	1	-	-	-	-	-
$AlCl_2$	-	2	-	2	-	2	-	2	2	2	2	2

and duration of floating (floating time) were measured by visual observation. The percentage of floating pellets was calculated by the following equation: (Chandra et al., 2018).

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

Swelling Study

Beads were studied for swelling characteristics. Sample from drug-loaded beads were taken, weighed and placed in wire basket Beads were studied for swelling characteristics. Sample from drug-loaded beads were 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. After12hours the beads were removed from their respective swelling media and weighed after drying the water on the surface of the beads using filter paper (Singhal et al., 2010; Hari, 2010; Sriamornsak, 2007). Then the swelling index was calculated and represented as percent.

Scanning electron microscopy (SEM)

Morphological examination of the surface and internal structure of the dried Calcium alginate beads was carried out using a scanning electron microscope (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 (Shaikh et al., 2018).

***In-vitro* drug release studies**

Release studies were performed in triplicate using the USP basket method at 100 rpm and 37±0.5°Cin 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 averaged (Chaturvedi et al., 2012; Piyakulawat, 2007; Bhattarai, 2011).

Results and discussion

Fourier-transformation infrared (FTIR) spectroscopy

The drug-polymer interaction was studied using FTIR spectroscopy for selected combination of drug with different polymers used. The FTIR spectra obtained is illustrated in figure 1. The IR spectrum of cefdinir give absorption peak at

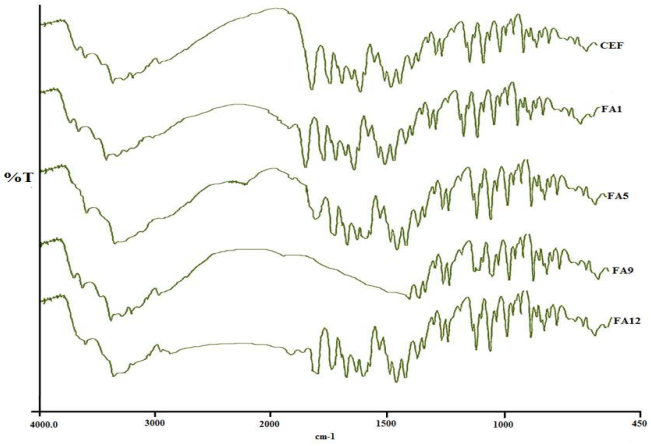

Figure 1. FTIR of formulation blends

Table 2. Particle size determination and visual analysis

Formulation code	Particle size (mm) (mean ± SD) (n = 20)	Shape	Colour
F1	0.99 ± 0.04	Spherical	Off white
F2	1.37 ± 0.08	Spherical with tail	Off white
F3	1.41 ± 0.06	Spherical	White
F4	1.58 ± 0.07	Spherical with tail	Off white
F5	1.32 ± 0.05	Spherical	White
F6	0.88 ± 0.04	Spherical with tail	Off white
F7	1.32 ± 0.05	Spherical	Off white
F8	1.98 ± 0.07	Spherical	Off white
F9	0.98 ± 0.03	Spherical with tail	Yellow
F10	1.06 ± 0.04	Spherical	White
F11	1.43 ± 0.06	Spherical with tail	Light Yellow
F12	1.69 ± 0.02	Spherical	Off white

3271 cm^{-1} due to Alkene groups (=C–H stretching) with absorption peak at 1710 cm^{-1} and 1544-1756cm^{-1} due to Ketone groups (-C=O). The IR spectrum of the F1 and F5 containing sodium alginate exhibit a broad hump around 3346cm^{-1} to 3242 cm^{-1} corresponds to -OH of the -COOH. Strong absorption peak is observed at1641cm^{-1}. The IR spectrum of sodium alginate show a broad hump due to presence of O-H group along with C=O absorption peak. The IR spectrum of F9 and F12 containing sodium CMC gives broad hump at 3170cm^{-1}.

Particle size determination and visual analysis of cefdinir beads

The particle size of beads is represented in table 2. The sizes of beads were influenced by the orifice of the needle, extrusion rate and concentration of polymer. The mean particle size of sodium alginate beads prepared by ionotropic gelation method (F1-F8) was between 0.88 to 1.98mm and sodium CMC beads prepared by ionotropic gelation method (F9-F12) were between 0.98 to 1.69mm. The sodium alginate and sodium CMC beads prepared with calcium chloride were spherical and the beads prepared with aluminum chloride were spherical with tail.

Figure 2. Photograph showing prepared floating beads

Table 3. Drug entrapment efficiency and floating study

Formulation code	%Drug Entrapment (mean ± SD) (n = 3)	Floating lag time (min.)	Floating time (hrs)	Percentage floating (mean ± SD) (n = 3)
F1	88.28 ± 0.28	< 1	> 12	88.34 ± 0.84
F2	90.36 ± 0.08	< 1	> 12	89. 60 ± 0.65
F3	78.66 ± 0.78	< 1	> 12	79.92 ± 0. 34
F4	84.24 ± 0.17	< 1	> 12	82.24 ± 0. 87
F5	94.60 ± 1.05	< 1	> 12	96.42± 1.02
F6	93.19 ± 0.34	< 1	> 12	91.69 ± 0.31
F7	93.10 ± 0.76	< 1	> 12	95.24± 0.30
F8	89.90 ± 1.30	< 1	> 12	87.32 ± 0.98
F9	68.75 ± 0.78	< 2	> 12	66.95 ± 0.14
F10	62.25 ± 1.40	< 2	> 12	64.74 ± 1.04
F11	69.89 ± 1.37	< 2	> 12	68.00 ± 1.72
F12	67.28 ± 0.90	< 2	> 12	70.80 ± 0.87

Table 4. *In vitro* swelling data of Cefdinir beads (F1-F6)

Time (hrs)	Swelling Index					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
1	68.8	51.87	55.3	48.91	53.27	45.42
2	95.32	75.23	92.29	71.36	82.845	64.36
3	169.96	110.59	167.2	119.2	127.82	108.25
4	210.02	139.95	195.41	145.41	178.1	124.26
5	295.15	201.31	271.37	191.32	205.43	155.28
6	321.74	272.67	302.11	259.41	249.59	233.84
7	338.52	296.03	329.69	271.4	266.95	250.21
8	362.24	310.39	340.01	292.11	280.99	262.91

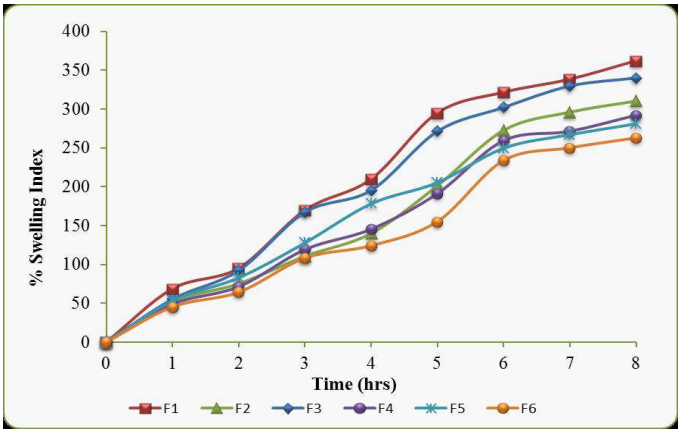

Figure 3. *In vitro* swelling data of Cefdinir beads (F1-F6)

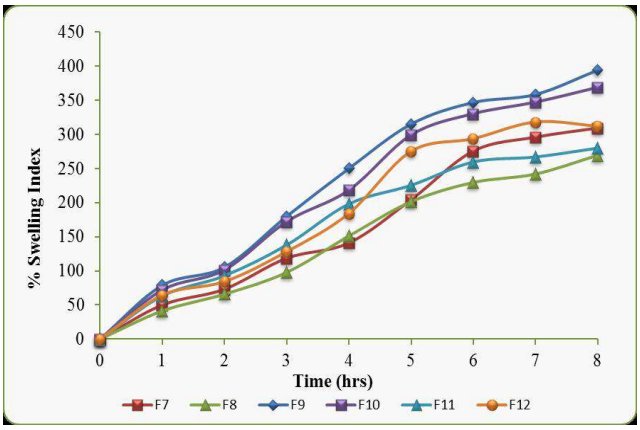

Figure 4. *In vitro* swelling data of Cefdinir beads (F7-F12)

Table 5. *In vitro* swelling data of Cefdinir beads (F7-F12)

Time (hrs)	Swelling Index					
	F7	F8	F9	F10	F11	F12
1	49.97	41.27	78.8	71.91	63.27	64.43
2	73.23	65.845	105.32	101.36	92.845	84.31
3	118.59	97.82	179.96	172.2	137.82	128.25
4	140.95	151.1	250.02	218.41	198.12	184.26
5	204.31	201.43	315.15	299.32	225.43	275.29
6	275.67	229.595	346.74	330.41	259.59	293.84
7	296.03	241.985	358.52	347.4	266.98	318.26
8	309.39	269.38	394.24	369.11	279.99	312.18

Drug entrapment efficiency and floating study

The results of entrapment efficiency are presented in table 3. The mean drug entrapment efficiency (DEE) of sodium alginate beads prepared by ionotropic gelation method (F1-F8) was between 78.66 to 94.60% and sodium CMC beads (F9-F12) was between 62.25 to 69.89%. The floating ability of prepared beads was evaluated along with dissolution studies. The beads containing gas forming agent (F1-F12) sank immediately and float with lag time not more than 2min in 0.1 N HCl (pH 1.2), and % floating was between 64.74-96.42%, floating ability of $CaCO_3$ was higher than $NaHCO_3$as a gas forming agent was observed.

In vitro swelling data of Cefdinir beads

The swelling data of sodium alginate and sodium carboxy methyl cellulose beads are represented in table 4-5 and illustrated in figure 3-4. All the formulations showed good swelling in pH 1.2 HCL.

Scanning electron microscopy (SEM)

The surface morphology of prepared beads was studied by scanning electron microscopy. External and internal surfaces of

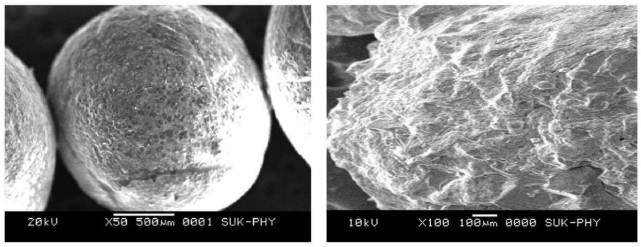

Figure 5. SEM study of F4 formulation

beads formulation F4, are shown in figure 5. 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.

In-vitro drug release studies

In-vitro drug release studies of cefdinir from floating beads were performed in 0.1 N HCL for 12 hours using USP Type I

Table 6. *In vitro* drug release data of Cefdinir beads (F1-F6)

Time (hrs)	Cumulative % Drug Release					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
1	1.6	1.65	1.91	2.95	1.4	1.86
2	4.25	2.7	5.25	5.65	2.75	3.02
3	12.56	8.57	12.56	14.68	8.56	10.57
4	32.12	33.66	31.12	35.89	31.12	34.96
5	38.94	42.4	44.94	54.02	40.94	44.8
6	46.72	52.58	56.72	70.94	46.72	55.61
7	58.88	64.3	68.88	80.78	56.88	67.43
8	63.76	76.17	80.76	88.25	62.76	76.17
9	76.36	83.15	86.36	90.47	74.36	84.19
10	80.58	85.12	90.58	92.35	81.58	87.28
11	83.33	88.41	92.33	94.12	83.33	88.46
12	88.02	89.61	93.89	94.98	84.23	88.56

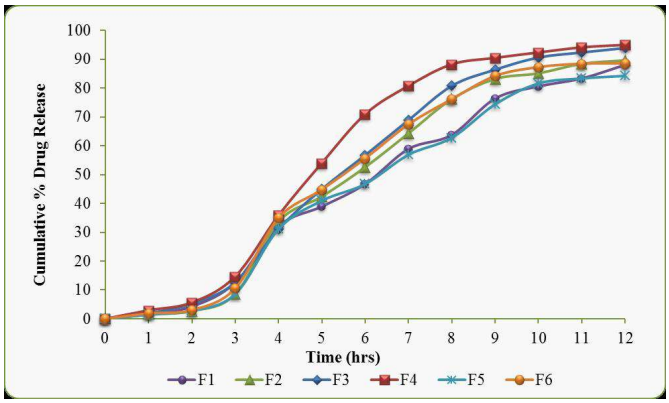

Figure 6. *In vitro* drug release data of Cefdinir beads (F1-F6)

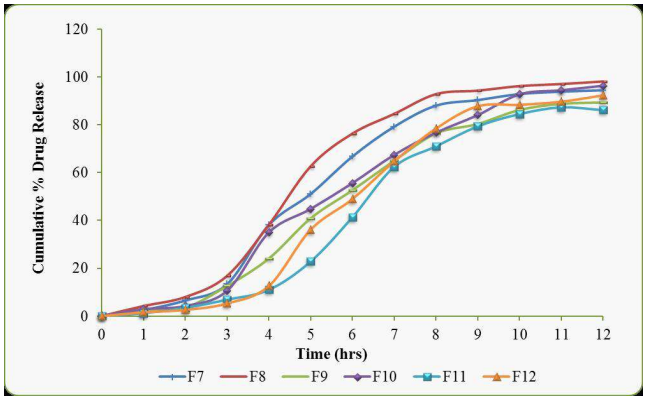

Figure 7. *In vitro* drug release data of Cefdinir beads (F7-F12)

Table 7. *In vitro* drug release data of Cefdinir beads (F7-F12)

Time (hrs)	Cumulative % Drug Release					
	F7	**F8**	**F9**	**F10**	**F11**	**F12**
1	2.56	4.2	2.06	2.86	1.2	1.54
2	6.5	7.96	3.56	4.2	3.4	2.56
3	13.31	16.8	12.57	10.57	6.86	5.25
4	38.12	38.16	24.06	34.96	10.96	12.56
5	51.04	62.64	40.87	44.8	22.8	36.12
6	66.72	76.34	52.61	55.61	41.32	48.94
7	79.23	84.58	64.98	67.43	62.4	64.72
8	88.02	92.84	76.4	76.72	70.98	78.44
9	90.34	94.3	80.34	84.06	79.35	87.76
10	92.88	96.21	86.22	92.76	84.5	88.36
11	93.86	97.06	88.76	94.47	87.32	89.68
12	94.47	98.14	89.36	96.34	86.12	92.33

dissolution test apparatus.The *in vitro* release data was represented in Table 6-7 and illustrated in Fig.6-7.The *in vitro* release of cefdinir was mainly affected by nature and amount of polymer, swelling behaviour of the polymers.

Conclusion

A successful attempt has been made to formulate floating alginate and sodium CMC beads of Cefdinir by ionotropic gelation method. From the results of FT-IR, it can be concluded that there is no interaction between the drug and the polymers used. The formulation F8 shows highest release of Cefdinir 98.14% over a period of 12 hrs with excellent floating properties. Hence, the floating beads of Cefdinir can be prepared by using $CaCO_3$ and $NaHCO_3$ as buoyant along with hydrogel forming polymer like sodium alginate and sodium carboxy methylcellulose as a release modifier for improved oral bioavailability of Cefdinir.

Conflicts of interest: Not declared.

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