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PREPARATION AND CHARACTERIZATION OF CINNARIZINE FLOATING OIL ENTRAPPED CALCIUM ALGINATE BEADS

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ABSTRACT

Gastroretentive delivery systems can be retained in the stomach and assist in improving absorption and consequently the bioavailability of drug that has a narrow absorption window in a particular region of gastrointestinal tract. A floatable multiparticulate system with potential for intragastric sustained delivery is one of the approaches to get the gastroretention. Cinnarizine(CNZ), an antihistaminic drug used in vertigo caused by meniere's disease was taken as a model drug for floating beads prepared by non effervescent method. Floating CNZ olive oil-entrapped emulsion gel beads were prepared by the emulsion–gelation method. Different concentrations of sodium alginate (1%, 2%, and 3% w/v), oil (5%, 10%, and 15% v/v), and calcium chloride (0.02, 0.1, and 0.5M) were used and their influence on beads uniformity, buoyancy, and *in vitro* drug release was studied. The results indicated that retardation of drug release was achieved by the oil hydrophobic diffusion barrier, especially in the presence of the compact network of alginate beads. The selected formula of calcium alginate beads using 3% w/v sodium alginate, 15% v/v oil and 0.1 M calcium chloride, showed a higher similarity factor (f_2 =70.1) of CNZ release in comparison to release from standard gastroretentive sustained release floating cinnarizine tablet with good floating over duration of more than 12 hours.

INTRODUCTION: Although the oral route is considered as the most predominant and preferable route of drug delivery since it is easy in administration and economic, the low bioavailability is important limitation [1].

The main disadvantage of traditional oral sustained release dosage forms is the significant fraction of administered drug is not absorbed because only absorption occurs in specific site such as stomach or first part of small intestine [2].

The gastroretentive dosage forms (GRDDS) that recently get interest by scientists can improve therapeutic action by continuously releasing the drug for a prolonged period of time at or before it reaches its absorption site, thus ensuring bioavailability enhancement [3].

One of the approaches to produce GRDDS is Floating Drug Delivery Systems (FDDS) which have a bulk density lower than gastric fluids and thus remain buoyant in the stomach [4].

The aim of preparing a floating multiple unit dosage form is to develop formulation of Cinnarizine (CNZ) that has all the advantages of a floating single unit dosage form but is devoid of all or none phenomenon that accompanied the single unit dosage forms [5].

Cinnarizine, is a piperazine derivative have Ca channel blocking activity with an anti- histaminic activity and high affinity to H_1 receptors (**Fig. 1**), it suffers from incomplete and variable oral absorption which occurs mainly in the proximal small intestine thus it is good candidate to be formulated as a floating multiple unit dosage form [6].

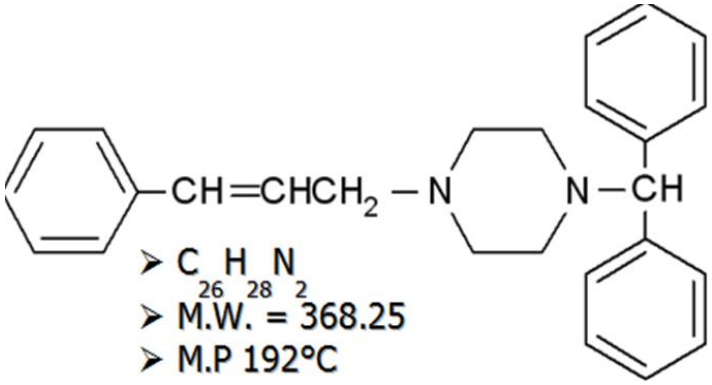

FIGURE 1: STRUCTURE OF CINNARIZINE

The tendency of multiple unit gel beads to possess floating nature as a result of oil incorporation was recently reported in the literatures as non-effervescent FDDS [7-9].

In this regard, the present work deals with the preparation, in vitro evaluation of olive oil-entrapped emulsion gel beads as a delivery system of cinnarizine.

Experimental:

Material: Cinnarizine as gift sample was supplied by Alsafa pharmaceutical industry, Iraq, calcium chloride (chemical LTD), pool, England, BDH, olive oil (chemicals and national factory for lab equipments), Jordan, sodium alginate (Hopkins and Williams LTD), England. All other chemicals were of analytical grade.

Methods:

Preparation of Cinnarizine alginate gel beads: Solutions of sodium alginate were prepared in three different concentrations 1, 2, and 3 **%**w/v by stirring in distilled water**.** CNZ and olive oil were added to the solution. Each mixture with total volume of 25 ml (containing CNZ 2gm and olive oil in three different concentrations 5, 10 and 15**%**v/v) were stirred properly to prepare homogenous mixtures. The mixture was extruded, using a 20 gauge syringe needle into 100 ml of series of gently agitated calcium chloride solution concentrations 0**.**02, 0**.**1, and 0**.**5 M at room temperature.

Calcium alginate gel beads were formed instantly by ionotropic gelation of alginate moiety in the presence of calcium ions. Olive oil and CNZ particles dispersed homogenously in calcium alginate network. The resulting beads were allowed to stand in the solution for 60 min before being separated and washed twice with 500 ml distilled water. The beads were dried at room temperature for 48 and were stored in desiccators [10]. The composition of all formulations was shown in **table 1**.

TABLE 1: FORMULATION COMPOSITION OF CNZ FLOATING ALGINATE GEL BEADS

Formula No	Cinnarizine (g)	Calcium chloride concentration (M)	Sodium alginate concentration (% w\v)	Olive oil concentration (% v/v)
B1	2	0.1	1	10
B2	2	0.1	2	10
B3	2	0.1	3	10
B4	2	0.02	3	10
B5	2	0.5	3	10
B6	2	0.1	3	5
B7	2	0.1	3	15

Effect of calcium chloride concentration on the Gel Beads properties: The effect of calcium chloride concentration, on the beads formations, properties, and release characteristics was studied by varying calcium chloride concentration. Calcium chloride concentrations were 0.02, 0.1 and 0.5M as shown in table 1.

Effect of sodium alginate concentration on the Gel Beads properties: The effect of sodium alginate concentration on the beads formations properties and release characteristics was studied by varying sodium alginate concentration. Sodium alginate solution concentrations were 1, 2, and 3 **%**as shown in table 1.

Effect of olive oil concentration on the Gel Beads properties: The effect of olive oil concentration on the beads formations and properties was studied by varying olive oil concentration. Olive oil concentrations were 5, 10and 15**%** as shown in table 1.

Evaluation of Beads:

Particle Size Analysis and Morphology: The diameter of beads was determined by screw gauge. For this purpose, 20 dried beads were randomly selected from each batch and the mean diameter was calculated [11, 12]. The least count of screw gauge was 0.005 mm. The color and shape of dried beads of each batch was visually observed.

***In Vitro* Buoyancy:** The bead samples (50 mg) were placed in a beaker filled with 100 ml of HCl solution (pH 1.2). Temperature was maintained at 37±0.5^{o}C. The time between the introduction of beads and its buoyancy on the gastric fluid (floating lag time) and the time during which beads remain buoyant (floatation duration) were measured for 12 hrs [13].

The preparation was considered to have buoyancy in the test solution only when all the gel beads floated in the solution (**table 2**).

TABLE 2: CHARACTERIZATION OF THE PREPARED CNZ fIOATING ALGINATE GEL BEADS

Formula No	Entrapment efficiency	Floating lag time (min)	Floating time (hrs)	Swelling index	Size (mm)	shape	f_2
B1	37.81	13	>12	300	0.0825	Spherical	30.52
B2	37.87	14	>12	400	0.0500	Spherical	26.78
B3	37.80	19	>12	400	0.0445	Spherical	67.65
B4	43.28	18	>12	350	0.1240	Spherical	45.08
B5	37.63	15	>12	250	0.0578	Spherical	34.21
B6	41.40	10	>12	375	0.0735	Spherical	48.61
B7	40.15	10	>12	350	0.0919	Spherical	70.10

Entrapment efficiency: One hundred milligram of beads were weighed and crushed in a glass mortar and the crushed material was dissolved in 80 ml of HCl solution (pH 1.2). Volume of this solution was made up to 100 ml with washings of mortar.

Resulting solution was sonicated for 15 minutes, filtered and assayed at 254 nm using double beam UV/Visible spectrometer (Carry UV visible spectrophotometer) and content of Cinnarizine was calculated using following equation [14] (Table 2).

$$\text{Drug Entrapment Efficiency (\%)} = \frac{\text{Experimental Drug Content}}{\text{Theoretical Drug Content}} \times 100$$

Determination of Swelling Index: 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 100 ml of HCl solution (pH 1.2) maintained at 37±0.5^{o}C. After 12hours 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 percent using the following formula [15]:

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

***In Vitro* Drug Release Studies:** The dissolution of CNZ from the prepared beads was studied using USP Type II dissolution apparatus containing 900 ml of HCl solution (pH 1.2) maintained at 37±0.5^{o}C and stirred at 100 rpm. Samples were collected at specified time interval and replaced with a fresh dissolution medium. These

samples were analyzed for CNZ content using spectrometer (Carry UV visible spectrophotometer) at λ max of 254nm [14].

Study of Drug Release Kinetics: The obtained CNZ release data was analyzed to study the release kinetics using zero order, first order, Korsemeyer- Peppas and Higuchi equations.

Zero order ($Q_t = Q_0+Kt$), first order ($\ln Q_t = \ln Q_0+K_1t$), Korsemeyer- Peppas equation (Log drug released = log *k* + n log *t;* where, n = release exponent), and Higuchi ($Q_t = K_H t^{1/2}$) model were fitted to dissolution data of prepared batches, using linear regression analysis.

Zero order kinetics indicates that the drug release is nearly independent of concentration, while first order kinetics indicates time dependent release kinetics.

Korsemeyer- Peppas used to explain the diffusion mechanism by which drug diffuses from dosage form. Higuchi equation explains why the drug diffuses at comparatively slower rate as the distance for diffusion increases, which referred to as square root kinetics [16].

Selection of Best Formula: The selection of best formula depends on comparison the release profiles of CNZ from the prepared formulas to the standard release profile using similarity factor f_2 [17], as well as the formula should provide the buoyancy over 12 hrs and has the accepted physical properties.

$$f_2 = 50 + \log \{[1+ (1/n) \sum_{t=1} * n (R_t-T_t)^2]^{-0.5} *100\}$$

R_t and T_t are the cumulative percentage dissolved at each of the selected n time points of the reference and test product respectively

Stability Studies: The stability studies for beads were done by keeping the sample beads from selected optimized batch (B7) at room temperature for 90 days. The beads were stored in tightly closed containers at room temperature only because the polymer used in preparation of beads (sodium alginate) is not stable at higher temperature. Every month, the beads were evaluated for different parameters like morphology, floating time, swelling index and drug release studies according to procedures mentioned previously.

Statistical Analysis: The results were expressed as the mean of three experiments. Students't-test was applied to determine the level of significance. The analysis of variance (ANOVA) was also applied to check significance difference in the drug release from different formulations. Difference was considered statistically significant when $p < 0.05$.

RESULT AND DISCUSSION:

Preparation of Cinnarizine Floating Alginate Gel Beads:

Beads Formation and Cross Linking: It is well known that the gelation and cross-linking of alginate molecules are due to the stacking of the guluronate blocks in the alginate chains with the formation of the 'egg-box junction' upon adding chelating divalent cations such as calcium ion (Ca^{2+}) [18]. The resulting beads were spherical, regular and float to different extent over the calcium chloride solution during the formulation process as shown in **Fig. 2**, except those prepared from sodium alginate concentration of 7 % with olive oil concentration of 20 % v/v in different calcium chloride concentrations which manifested in the preliminary formulation trials. This may be due to inability of calcium ions to penetrate the thick and viscous dispersions of these concentrations of sodium alginate and olive oil mixtures to form rigid gel matrix. So these formulations were excluded from characterization and not mentioned in method section.

***In vitro* Buoyancy Study:** All the prepared formulations show the floating time more than twelve hours which is sufficient to achieve sustained release action with variable floating lag time of range (19-10 min) according to the density of calcium alginate network and percent of oil entrapped.

FIG. 2: BUOYANCY STUDY OF THE SELECTED FORMULA OF CNZ FLOATING ALGINATE GEL BEADS

Entrapment Efficiency (EE): Low EE of range (37.63-44.31%) was seen in the prepared formulations as shown in table 2. This may be due to the high solubility of CNZ, resulting in high drug loss into the solution during the preparation. Also this may be due to leaching of the drug during the gelation process, during the curing process or drying process [19].

Drug Release Studies: Cinnarizine is a weak basic drug, at the pH of simulated gastric fluid (pH 1.2), the extent of ionization is high, resulting in an increase in drug solubility. Being consisting of small soluble molecules and the good ionization in the dissolution medium, CNZ has the tendency to diffuse out easily from the gel matrix, and this account for the reasonable release seen in this medium even though it is not the favorable pH for calcium alginate dissolution [20].

Effect of calcium chloride concentration: The EE of alginate gel beads with low concentration of calcium chloride was greater than that with higher one using the same concentration of sodium alginate and olive oil series (table 1). These results were probably due to more extended gel bead shrinkage during gelation by calcium ion. This result is in agreement with those found by Sriamornsak *et al* [21].

The data shown in Fig. 3 show that the release of CNZ encapsulated in alginate beads with different $CaCl_2$ concentration has been prolonged with increasing $CaCl_2$ concentration. That can be explained by considering the structure of the gel beads. Low Ca^{2+} concentration leads probably to a loose gel. As a consequence, the drug can be easily released from the beads, as the steric entanglements do not constitute a strong barrier. Further addition of Ca^{2+} gives more structured gel and the drug is more retained inside the beads due to steric reason, since the existence of physical entanglements of cross-linked alginate-Ca^{2+} of lower dimensions controlling the drug diffusion flow within the beads .

At high concentration of calcium chloride, strong and rigid gel is formed around the matrix and this strong gel does not allow the dissolution medium to penetrate into the matrix at a high speed, resulting in a reduction in the release rate.

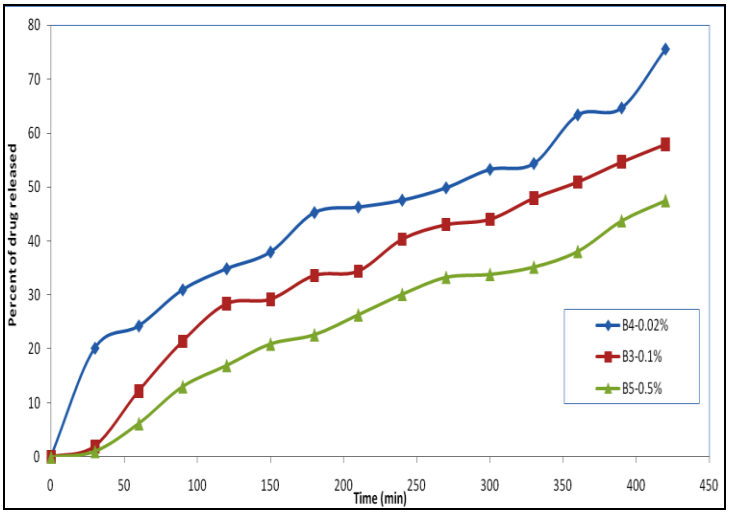

FIG. 3: EFFECT OF THE $CACL_2$ CONCENTRATION ON THE RELEASE OF CNZ IN PH 1.2 FROM FLOATING ALGINATE GEL BEADS

Effect of Sodium Alginate Concentration: The results revealed that the variation in the concentrations of alginate had no significant effect on the entrapment of CNZ in alginate gel beads, and could be due to abundant availability of alginate for gelation process. Rapid and rigid gel matrix was formed even at 3 % sodium alginate concentration to react with calcium ions and form sufficient cross-linking.

The release rate of CNZ was high with low sodium alginate concentrations. The weight of the beads was found to increase with the increasing in the concentration of alginate suggesting the formation of a thicker alginate layer. At high sodium alginate concentration the hindrance to drug diffusion from the polymer matrix would be rather high making the diffusion process more difficult and this is reflected in the slowing down of the drug release.

These results are in agreement with those found by Kesavan *et al* [22]. Floating lag time was extended since denser beads were formed with higher sodium alginate concentrations as could be seen in formulas B1, B2 and B3 from table 2.

It was observed that drug release for formulas B1, B2 and B3 was prolonged, and the release rates were proportional to the increase of alginate concentration. The release percent of the loaded drug was 88.3, 84.4, and 50.9% for B1, B2 and B3 beads in 6 h with alginate concentrations 1, 2 and 3% (w/v), respectively (**Fig. 4**).

The prolongation of the release rate from the alginate hydrogel beads with increase of alginate concentration reflects the concomitant increases in gel strength which is a determining factor in this case since the release of drugs in alginate matrices are mainly through the diffusion of the drug through the pores of the polymer network which can be significantly reduced in size by increasing the alginate concentration.

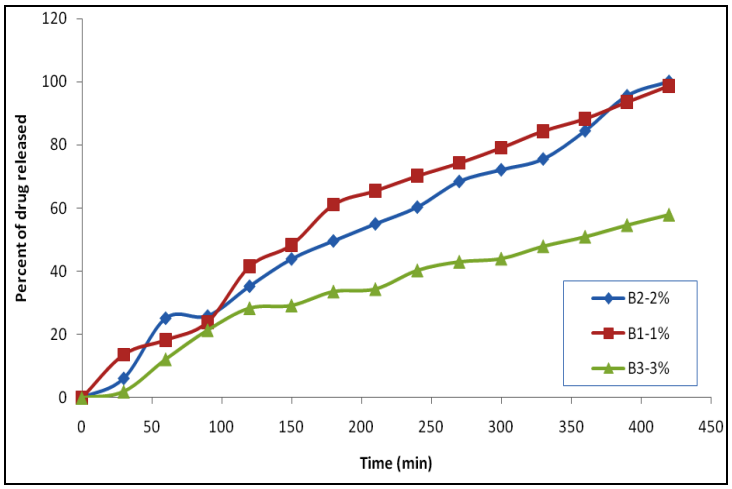

FIG. 4: EFFECT OF THE SODIUM ALGINATE CONCENTRATION ON THE RELEASE OF CNZ IN pH 1.2 FROM FLOATING ALGINATE GEL BEADS

Effect of Olive Oil Concentration: The incorporation of olive oil in the alginate gel beads seems to extend the release process of the drug. Alginate gel beads containing 15% olive oil produced slower drug release profiles, compared with those of 10% and 5% concentrations (**Fig. 5**).

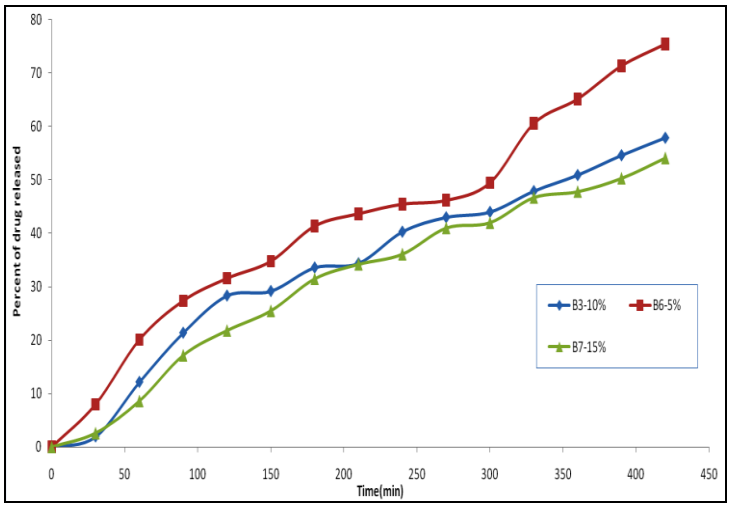

FIG. 5: EFFECT OF THE OLIVE OIL CONCENTRATION ON THE RELEASE OF CNZ IN pH 1.2 FROM FLOATING ALGINATE GEL BEADS

The release profile indicated that the sustaining action was more pronounced with oil entrapped beads than conventional alginate beads. As compared to conventional (no oil) beads, the release of the drug was sustained sufficiently for longer time in simulated gastric juice. An additional property of buoyancy was observed for the oil-entrapped beads, which was due to incorporation of oil having density less than water. The lower the density of the oil, the lesser was the amount of the oil required to give it a buoyant nature.

The effect of addition of oil in the formulation created an additional barrier. The pores of the beads containing oil limited the release of drug. This could be attributed to an additional diffusion layer to the release of the drug. When calcium ions are added to a sodium alginate solution, alignment of the G-blocks occurs; and the calcium ions are bound between the two chains like eggs in an egg box.

Thus, the calcium reactivity of algins is the result of calcium-induced dimeric association of the G-block regions. Depending on the amount of calcium present in the system, these inter-chain associations can be either temporary or permanent. With low levels of calcium, temporary associations are obtained, giving rise to highly viscous, thixotropic solutions. At higher calcium levels, precipitation or gelation results from permanent associations of the chains.

By the use of alginate and employing oil entrapment technique, drug can be retarded in the stomach.

Kinetic analysis of the Release Data: The kinetic analysis of release data of all the prepared formulations indicated fitting to different model of drug release and according to diffusion exponent value, the mechanism of diffusion can be classified as follows; 0.45=Fickian diffusion, 0.45 < n < 0.89=Anomalous (non-Fickian) diffusion, 0.89= Case-II transport, n > 0.89=Super case-II transport (table 3).

The values of *n* for the release of CNZ from the beads of selected formula B7 indicated Super case-II transport [23].

TABLE 3: KINETIC MODELING OF CNZ RELEASE PROFILE FROM FORMULATIONS B1-B7

Formula no.	Zero	First	Higuchi	Korsemyer-Peppas	
	Correlation coefficient R^2				n
B1	0.986	0.829	0.951	0.953	0.81
B2	0.963	0.957	0.964	0.972	0.92
B3	0.951	0.979	0.967	0.874	0.21
B4	0.931	0.961	0.971	0.971	0.47
B5	0.978	0.943	0.947	0.914	1.23
B6	0.964	0.947	0.954	0.962	0.74
B7	0.968	0.99	0.963	0.992	1.04

Selection of Best Formula: Since all the prepared formulations has acceptable physical properties and enough total floating for sustained release action, therefore the main criteria for selection is the short floating lag time and higher similarity *f*2 value which consequently leading to select formula B7 as the best formula as shown in **Fig. 6** and it was subjected to stability study.

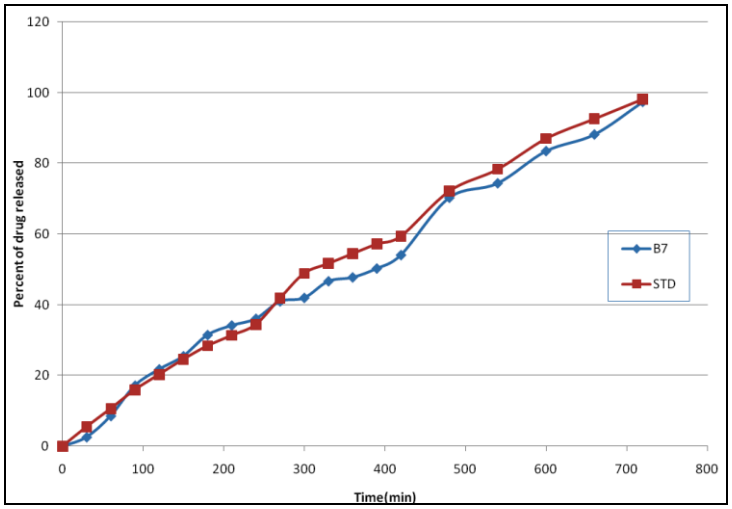

FIG. 6: RELEASE PROFILE OF CNZ IN pH 1.2 FROM THE SELECTED FORMULA (B7) OF FLOATING ALGINATE GEL BEADS IN COMPARISON TO STANDARD RELEASE PROFILE

Stability study: The results of this study indicated that the selected formula was stable at the end of three months and no physical changes were occur during the studying time in addition no significant changes ($p<0.05$) in buoyancy and release properties were observed

CONCLUSION: In conclusion, the present study reveals the characteristics of CNZ-loaded alginate bead formulations. The ionotropic gelation can be used in producing CNZ-loaded alginate beads. The formulation variables influenced the mean particle size and in vitro drug release characteristics of the prepared beads. The data suggest that CNZ-loaded alginate bead is a potentially useful delivery system for making controlled release gastroretentive floating beads by the ionotropic gelation technique.

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