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ORIGINAL PAPER

PREPARATION, OPTIMIZATION AND CHARACTERIZATION OF GASTRORETENTIVE RANITIDINE HYDROCHLORIDE ALGINATE BEADS

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Abstract. Gastroretentive drug delivery system of RHCl using floating alginate beads as an approach for prolonged release was prepared and the results of factorial design indicated that the dissolution profile is significantly depended on the alginate: drug ratio and hydroxy proprylmethylcellulose(HPMC): alginate ratio. The determined drug loading % of optimized formula was 33% which means that the weight of floating beads equivalent to 336 mg of RHCl is 1018.18 mg.
Keywords: alginate beads, hydroxy proprylmethylcellulose(HPMC), Ranitidine hydrochloride

Introduction

Oral drug administration has been predominate route for drug delivery. During the past two decades, numerous oral delivery systems have been developed to act as drug reservoirs from which the active substance can release over defined period of time at a predetermined and controlled rate [1]. Controlled-release drug delivery system (CRDDS) provides drug release at a predetermined, predictable, and controlled rate[2]. An important requisite for successful performance of oral CRDDS is that the drug should have good absorption throughout the gastrointestinal tract GIT, preferably by passive diffusion, to ensure continuous absorption of the released drug[3]. Gastroretentive drug delivery systems (GRDDS) as a new approach can be defined as dosage forms that can be retained in the stomach[4]. GRDDS can improve the controlled delivery of drugs that have as absorption window by continuously releasing the drug for prolonged period of time before reaching its absorption site [5], thus ensuring its optimal bioavailability[5]. Density determines the location of the system in the stomach. Systems with density lower than gastric content can float to the surface, while high density systems sink to the bottom of the stomach. Both positions may isolate the dosage system from the pylorus [6]. Furthermore diffusion of different drugs through the mucus to the epithelium is dependent on their size. For instance, Saha*et el* showed that gastric mucus was more permeable to metronidazole (171 Da) than amoxicilline (365.4 Da)[7].

The main disadvantage of traditional oral sustained release dosage forms is the significant fraction of administered drug is not absorbed because absorption only occurs in specific site such as stomach or first part of small intestine[8]. 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 [9]. 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 [10]. The aim of preparing a floating multiple unit dosage form is to develop formulation of Ranitidine hydrochloride (RHCl) 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[11] .

Ranitidine hydrochloride (RHCl) as model drug for GRDDS

Ranitidine HCl (RHCl) is class III compound and histamine H_2 receptor antagonist. Chemically it is N-[2-[[[5-[(dimethyamino)methyl]- 2-furanyl] methyl]thio]ethyl]-N-methyl-2-nitro-1,1-

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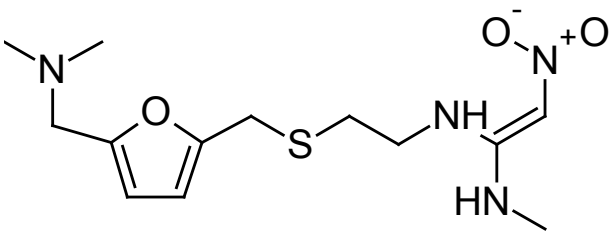
ethendiamine,HCl. It has the following structure formula [12].



Chemical formula	$C_{13}H_{22}N_4O_3S.HCl$
H_2O solubility	Very soluble
Melting point	136-142ºC
pKa	2.3 and 8.2

It is widely prescribed in active duodenal ulcers, gastric ulcers, Zoellinger-Ellison syndrome, gastroesophegeal reflux disease, and erosive esophagitis. The recommended adult oral dose of RHCl is 150 mg twice daily or 300 mg once daily [13]. Despite a short biological half-life of 2.5-3 h, gastric inhibitory effect lasts for 5-7 h probably because a part of the drug, after absorption, is stored in depot (bile and parenchyma tissues), which is released after food intake. The secondary peak in plasma concentration time curves in human volunteers supports this phenomenon. An alternative dose of 300 mg leads to plasma fluctuations; therefore, a sustained- release drug delivery system of drug (for 12 h), which will act in combination with the depot phenomena in the body, will ensure a biological effect of greater than 80-20 h without saturation of the absorption process [14].The GRDDS can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability. It also increases the stomach wall receptor site bioavailability and drugs ability to reduce acid secretion [15]. This principle may be applied for improving systemic as well as local delivery of RHCl, which would efficiently reduce gastric acid secretion.

Optimization of drug formulation using factorial designs

Recently, most of pharmaceutical researchers use an experimental design in the formulation studies. Experimental design involves the arrangement of experiments in the design space such that the reliable and consistent information is achievable with minimum of experiments [16]. Factorial design (FD, full or fractional), also known as experimental design, are the most popular response surface design. Full factorial design involve studying the effect of all factors (n) at various level (x), including the interactions amongst them with total no. of experiments as x^n. The simplest class of FDs involves factors at two levels with factor level suitably coded. A 2^3 factorial design was employed in formulating gastric floating drug delivery system (GFDDS) containing metoprolol tatrate[17]. Response surface methodology was used in the study of effect of hydrophilic swellable polymers on dissolution enhancement of carbamazepine SD [18].

Experimental

Material

Ranitidine HCl powder USP 30 as gift sample was supplied by Changzhou Longcheng pharmaceutical Co., Ltd., China. Calcium carbonate, Calcium chloride was purchased from Merck, Germany. All other chemicals were of analytical grade.

Methods

Preparation of standard curve of Ranitidine hydrochloride spectrophotometrically:

Standard curve in 0.1 N HCl.

Standard curve was made from stock solution of RHCl which was prepared by dissolving 50 mg of RHCl in 100 ml of 0.1 N HCl and then different concentrations out stock solution using 0.1 N HCl for dilution was prepared. The samples were filtered through a 0.22 um cellulose nitrate membrane filter. The filtrate was analyzed spectrophotometrically for RHCl at its λ max 315 nm. The analysis was performed in triplicate.

HPLC analysis of Ranitidine hydrochloride.

The HPLC value system which was used consisted of an Agilent G1310A isocratic pump with solvent cabinet, an Agilent G1328 A manual injector (MI) plus autosampler and an Agilent G1314A variable wave length detector (Agilent Technologies Inc., DE, USA)[19].

Preparation of gastroretenative using floating alginate beads

Exact weight of RHCl was dissolved in distilled water. This solution was dispersed in three different volume of 1.6% w/v alginate solution to give three alginate to drug ratio of (1:1, 1.5:1 and 2:1), the alginate to drug ratio was considered as factor 1 (X1) while the alginate solution containing HPMC in three level of ratio of HPMC to alginate (0,0.1and 0.2) was utilize as factor 2(X2). Then, the gas-forming agent calcium carbonate ($CaCO_3$) was added to the solution in weight ratio of 5:1($CaCO_3$: alginate w/w). The resulting solution was dropped through a 26-G syringe needle into calcium chlo-

ride solution (15% w/v) containing 10 % v/v acetic acid[20].The volume of calcium chloride used was four times the volume of alginate solution.

The beads were allowed to remain in the same solution for 2 hours to improve their mechanical strength. The formed beads were separated, and freeze- dried [21]. Blank beads without RHCl were also prepared using the same technique. The composition of the factorial design batches D1 to D9 is shown in table (I).

Characterization of the prepared floating alginate beads

Drug loading and drug entrapment efficiency

The percent drug loading was calculated by dividing the amount of drug in the sampled beads by weight of beads [22]. The drug entrapment efficiency was calculated using the following the equation:

$$\textit{Drug entrapment efficiency}\ (\%) = \frac{M\ actual}{M\ theoretical} \times 100$$

Where M *actual* is the actual amount of drug in beads and the M *theoretical* is the amount of drug in the beads calculated from the quantity added in the process [23].

In vitro dissolution studies

The dissolution studies were performed for all prepared formulas in triplicate using USP XXIV dissolution apparatus II [24]. An accurately weighed sample (equivalent to 336 mg of RHCl) of floating alginate beads formula D1 to D9 was dropped into 900 ml of 0.1 N HCl maintained at a temperature of 37 ±0.5 °C and stirred at speed of 50 rpm. At different time intervals, a 5-ml aliquot of the sample was withdrawn and the volume was replaced with an equivalent amount of plain dissolution medium which was kept at 37°C [25].

X1 indicated the alginate to drug ratio; X2, HPMC to alginate ratio; p1, p5, and p10 Values represented the drug release after 1, 5, and 10 hours, respectively. DEE indicates the drug entrapment efficiency.

Floating properties

The time between the introduction of the floating alginate bead into the medium and its buoyancy to upper one third of dissolution vessel (buoyancy lag time) and the time for which the formulation constantly floated on the surface of the medium (duration of buoyancy) were measured simultaneously as a part of dissolution studies [20].

Particle size analysis

Particle size and size distribution of selected optimized floating beads formula were measured using an optical microscope, and the mean particle size was calculated by measuring 500 particles with the help of calibrated ocular micrometre [26].

Statistical analysis

Result of release studies of RHCl were expressed as mean ± SD where n =3 in all cases. Regression and correlation were used in determining the calibration curve of RHCl. Student (t-test) was used in case of investigation of significance of difference of the mean of two sets of values using 5% as level of confidence interval.

Results And Discussions

For purposes of drug assay and release profile studies, two calibration curves were conducted. The data of the absorbance were plotted as a function of concentration of RHCl in distilled water and 0.1 N HCl. A linear correlation coefficient (R^2= 0.9999) was obtained in both solvents as shown in Figure 1 and 2 respectively.

Full factorial design analysis of GRDDS

Gastroretentive RHCl by using floating alginate beads.

A multiple unit floating gastroretentive dosage form was designed, keeping in view the all or nothing response of single-unit systems. Literature reports indicated widespread use sodium alginate for achieving sustained release of drugs [27], because of sodium alginate's ability to form stable and bioadhesive gel with calcium ions [28].

Results of GRDDS by floating alginate batches (D1-D9) are listed in Table I which includes P_1, P_5, P_{10} and DEE; values represent the drug release after 1, 5, 10 h, and the drug entrapment efficiency respectively. These values are obtained from dissolution profile that is shown in Figure 3. The data clearly indicated that P_1, P_5, and P10 are significantly dependent on X_1 (alginate to drug ratio) and X_2 (HPMC to alginate ratio) while DEE % depends only on X_1. The fitted equations relating the response to X_1 and X_2 were generated by putting the estimated values of coefficient (Table III) in equation 2. The values of correlation coefficient shown in Table III indicted a good fitting of suggested model.

$$Y = b_0+b_1X_1+b_2X_2+b_{12}X_1X_2+ b_{11}(X_1)^2+ b_{22}(X_2)^2$$

Figures (4, 5, 6 and 7) show the response surface plot of alginate to drug ratio (X_1) and HPMC to alginate ratio (X_2) versus P_1, P_5, P_{10}, and DEE%, respectively. The data demonstrate that both X_1 and X_2 affect the drug dissolution profile (P_1, P5, and P10) while only X_1 affects the DEE %. The most significant terms ($P<0.05$) in model suggested by software are (b_1, b_2, b_{11}); (b_1,b_2) and (b_1, b_2, b_{12}) for P_1 , P_5, P_{10} responses respectively. It may be concluded that high level of X_2 favour the preparation of gastroretentive sustained release RHCl, the value of X_1X_2 (b_{12})

	Variables Levels in coded		Response			
Batch Code	X_1	X_2	P1	P5	P10	DEE
D1	-1	-1	45.30±0.39	81.26±0.63	100.0±0.22	75.71±0.44
D2	-1	0	44.50±0.53	79.12±0.45	99.72±0.31	77.42±0.62
D3	-1	+1	43.98±0.72	72.90±0.63	96.26±0.46	76.31±0.53
D4	0	-1	30.90±0.66	66.86±0.41	87.65±0.29	78.43±0.33
D5	0	0	30.10±0.25	64.72±0.71	87.32±0.67	80.25±0.29
D6	0	+1	26.10±0.34	60.52±0.26	83.12±0.55	79.76±0.75
D7	+1	-1	23.48±0.28	53.40±0.37	78.76±0.49	81.96±0.64
D8	+1	0	21.48±0.46	51.40±0.59	73.76±0.77	84.54±0.42
D9	+1	+1	20.07±0.74	44.14±0.35	67.37±0.37	82.56±0.78
	Actual values					
Coded terms	X_1	X_2				
-1	1:1	0:1				
0	1.5:1	0.1:1				
+1	2:1	0.2:1				

Table I. Results of Factorial Design Batches of Floating Alginate Beads

X1 indicated the alginate to drug ratio; X2, HPMC to alginate ratio; p1, p5, and p10 Values represented the drug release after 1, 5, and 10 hours, respectively. DEE indicates the drug entrapment efficiency

Response	Coefficients estimates						R^2
	$.b_0$	$.b_1$	$.b_2$	$.b_{12}$	$.b_{11}$	$.b_{22}$	
P1	29.29	-11.46	-1.59	-0.52	4.10	-0.39	0.9959
P value		0.0001*	0.0361*	0.4018	0.0124*	0.6440	
P5	65.3	-14.06	-3.99	-0.225	-0.33	-1.9	0.9918
P value		<0.0001*	0.0003*	0.6786	0.6678	0.0021*	
P10	86.96	-12.68	-3.28	-1.91	-0.052	-1.41	0.9928
P value		<0.0001*	0.0013*	0.0266*	0.9511	0.1677	
DEE	80.56	3.27	0.42	0.0000	0.27	-1.62	0.9910
P value		0.0004*	0.1116	1.0000	0.4695	0.0159*	

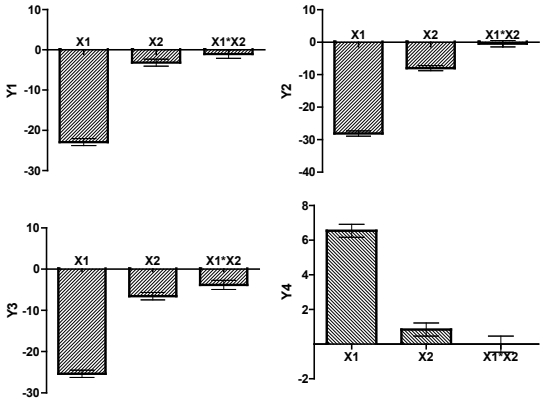


Table II. Results of Regression Analysis of Floating Alginate Beads

Response		df(1,3)	SS	MS	F	R^2
P1	Regression	5	837.94	167.59	145.62	0.9959
	Error	3	3.45	1.15		
P5	Regression	2	1281.22	640.61	364.44	0.9918
	Error	6	10.55	1.76		
P10	Regression	3	1044.00	348.00	229.57	0.9928
	Error	5	7.58	1.52		
DEE	Regression	5	70.59	14.12	66.02	0.9910
	Error	3	0.64	0.12		

Table III. The Results of ANOVA of Floating Alginate Beads

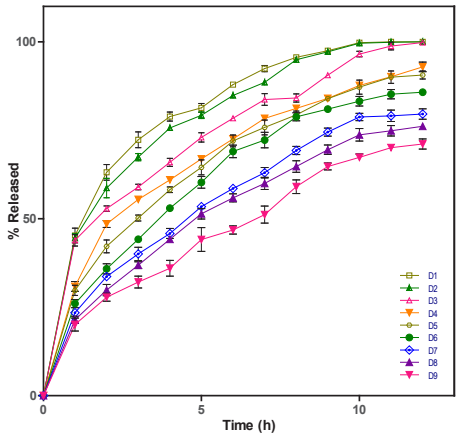


Figure 3. Dissolution profile in 0.1 N HCl at 37°C of batches D1-D9 prepared as gastroretenativeRHCl using floating beads

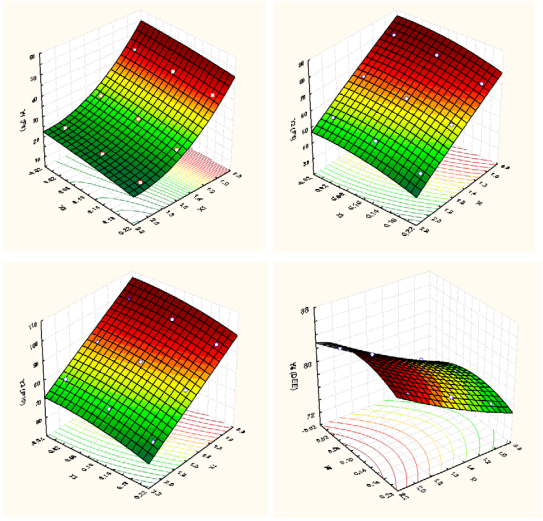


Figure 4. Response surface plot for effect of variables on percentRHCl released after 1 h(P1) from floating alginate beads. **Figure 5.** Response surface plot for effect of variables on percent RHCl.released after 5 h(P5) from floating alginate beads. **Figure 6.** Response surface plot for effect of variables on percentRHCl released after 10h(P10) from floating alginate beads **Figure 7.** Response surface plot for effect of variables on RHCl entrapment efficiency (DEE) of floating alginate beads.

also suggest that interaction between X_1 and X_2 has a significant effect on P_{10}.

For DEE % response, the significant terms ($P<0.05$) in the model suggested by software are b_1 and b_{22} meaning that DEE % is significantly affected by alginate drug ratio (X_1) with no significant affect of HPMC to alginate ratio (X_2). Also the polynomial terms $(X_2)^2$ which represents of non linearity has significant effect on DEE %. It was clear that the DEE % was higher at higher alginate ratio (X_1). This may be due to the highly dense internal structure of alginate matrix.

The ability of alginate, sodium salts, to rapidly form viscous solutions and gels on contact with aqueous media has been exploited by the pharmaceutical industry in sodium alginate's wide application as ac carrier in hydrophilic matrix controlled release oral dosage forms. Matrices incorporating alginate salts have been employed to successfully prolong the release of many drugs [29].

The significant retardation effect of alginate observed from the results is in agreement with Prajapati ST *et al*[30] study on modification of domperidone release byalginate. On the hand the retarding effect of HPMC was also observed by Varshosz J *et al*[31] in formulation of tramadol hydrochloride using HPMC with natural gum.

So using the polynomial equation the software predicts the best formula to prepare gastroretentive sustained release RHCl targeting P_1 value of (32.17 %), P_5 value of (56.65 %), P_{10} value of (87.61 %), depending on theoretical dissolution profile calculated from pharmacokinetic parameters to obtained sustained release for 12 h, and higher DEE % which contains alginate to drug ratio of (1.42:1) and HPMC to alginate ratio of (0.11:1) to prepare sustained release floating RHCl using alginate beads.

Figure 8 shows the dissolution profile of optimized formula prepared by using alginate beads in compression standard theoretical dissolution profile. The similarity factor f_2 equals 71.29, which means the optimized formula

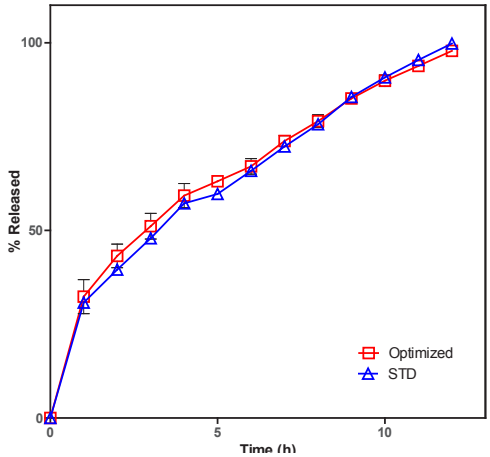


Figure 8. Comparison of dissolution profiles in 0.1 NHCl at 37°C of optimized formula of floating alginate beads of RHCl and standard sustained release profile

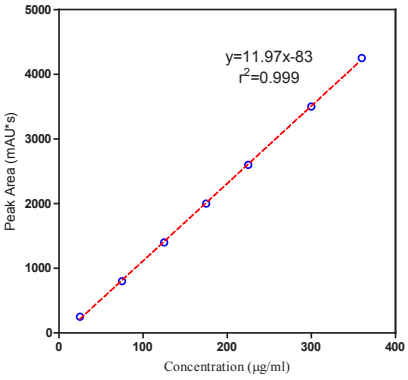


Figure 9. The HPLC chromatogram of Ranitidine HCl

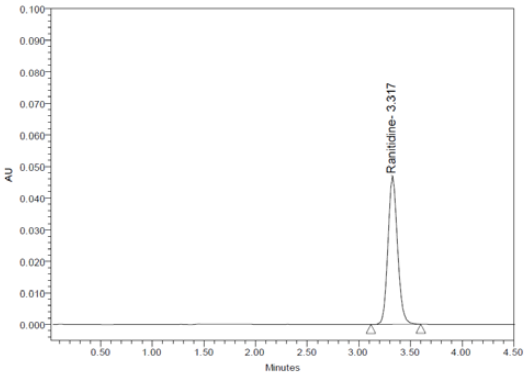
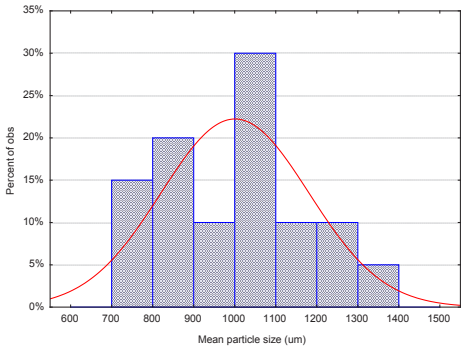


Figure 10. Calibration curve of Ranitidine HCl using HPLC.Figure 11 Photograph of floating alginate beads of RHCl by digital camera

Figure 11. Photograph of floating alginate beads of RHCl by digital camera



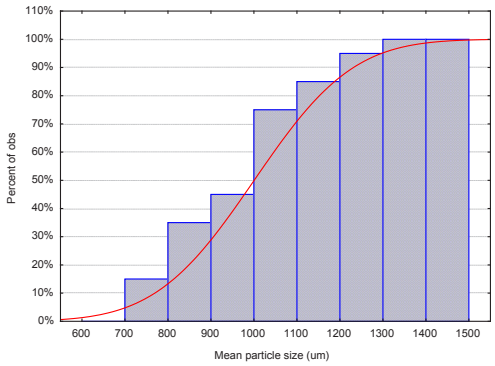


Figure 12. Cumulative distribution curve of particle size analysis of floating alginate beads of RHCl

could produce sustained release over 12 h .The dissolution studies and loading % of optimized formula of floating alginate beads were also done using the HPLC analytical method; a sharp peak of RHCl was obtained at 2.389 min. retention time as shown in Figure (9). The peak area was linear as a function of drug concentration with a correlation coefficient of 0.9993 as shown in Figure (10). The results indicate that there is no significant difference ($p<0.05$) between the two analytical methods.

Furthermore the morphology of optimized formula was spherical as shown in Figure 11 with particle size distribution of average 1048.2 um± 175.4 (Figure 12) and this observation is also demonstrated by Smardel P *et al*[31] in the study of parameters that effects alginate beads. On the other hand, the DEE % of optimized

formula was 79.17, buoyancy over 12 h, and practical loading % of 33 which means the weighed of floating beads equivalent to 336 mg of RHCl is 1018.18 mg. the results indicate that the GRDDS of RHCl could be obtained using floating alginate beads, but the high excipient weight is not appropriate.

Batch Code	Loading %	DEE %	Duration of floating
D1	40.30±0.12	75.71±0.44	12h
D2	39.22±0.41	77.42±0.62	12h
D3	37.10±0.29	76.31±0.53	12h
D4	34.21±0.53	78.43±0.33	12h
D5	32.11±0.62	80.25±0.29	12h
D6	30.73±0.38	79.76±0.75	12h
D7	29.63±0.46	81.96±0.64	12h
D8	28.71±0.48	84.54±0.42	12h
D9	26.41±0.29	82.56±0.78	12h
Optimized formula	33.00±0.54	79.17±0.58	12h

Table IV. Characterization of Batches of Floating Alginate Beads

Conclusion

Results of GRDDS batches of RHCl prepared by floating alginate beads showed that the dissolution profile is significantly dependent on the ration of alginate to drug and ratio of HPMC to alginate while DEE% depends only on the ratio of alginate to drug. The selected formula which consists of alginate to drug ratio of (1.42:1) and HPMC to alginate ratio of (0.11:1) provides sustained release floating of RHCl using alginate beads with similarity factor f_2 equal to 71.29 in comparison to the theoretical dissolution profile. The data show that the GRDDS of RHCl could be obtained using floating alginate beads, but the high excipient weight is not appropriate.

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