



## **FORMULATION AND EVALUATION OF OIL ENTRAPPED FLOATING ALGINATE BEADS OF RANITIDINE HYDROCHLORIDE**

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### **ABSTRACT**

The objective of this investigation is to develop a multi-unit gastroretentive sustained release dosage form of a water soluble drug, Ranitidine hydrochloride, from a completely aqueous environment avoiding the use of any organic solvent, which could cure peptic ulcer more efficiently by releasing the drug especially in stomach and also for a prolonged duration of time. A new emulsion gelation technique was used to prepare emulsion gel beads using sodium alginate as the polymer. The gel beads containing oil was prepared by gently mixing or homogenizing oil and water phase containing sodium alginate which was then extruded in to calcium chloride solution. The effects of factors like concentration of oil, curing time, drug: polymer ratio, alginate: pectin ratio and curing agent on drug entrapment efficiency, floating lag time, morphology and drug release were studied. Minimizing the curing time of beads led to enhanced drug entrapment efficiency. The use of sodium alginate and combinations of sodium alginate and pectin were used to study the effect on the sustaining property of the formed beads. It was found that sodium alginate was not sufficient to sustain the drug release at gastric pH. Instead of it, appropriate combination of alginate and pectin could provide the sustain release of drug. The results show that these beads can entrap even a water soluble drug as Ranitidine hydrochloride in sufficient amount and also can successfully deliver the drug in stomach for a prolonged duration of time without using any organic solvent and any time consuming step in the preparation.

**Keywords:** Floating Beads, Ranitidine hydrochloride, Floating Drug Delivery.

### **INTRODUCTION**

A drug that is released from a dosage form in a controlled manner in the stomach will empty together with fluids and will have the whole surface area of the small intestine available for absorption<sup>1</sup>. These considerations have led to the development of oral controlled gastroretentive dosage forms possessing gastric retention capabilities. Thus Gastroretentive dosage forms, i.e. those designed to exhibit a prolonged gastric residence time (GRT), have been a topic of interest in terms of their potential for controlled drug delivery<sup>2,3,4,5</sup>.

Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs<sup>6,7</sup>. Such retention systems are

important for drugs that are degraded in the intestine or for drugs like antacids or certain antibiotics, enzymes that should act locally in the stomach<sup>8</sup>. If drug is poorly soluble in intestine due to alkaline pH and then its retention in gastric region may increase the solubility before they are emptied, resulting in increased bioavailability<sup>9</sup>. Such systems are more advantageous in improving G.I. absorption of drugs with narrow absorption windows as well as for controlled release of the drugs having site-specific absorption limitation. Retention of drug delivery system in stomach prolongs over all G.I. transit time, thereby resulting in improved bioavailability for some drugs<sup>6,10</sup>.

The patient always wants to minimize the frequency of dosing without compromising the therapeutic benefit. Use of sustained release dosage forms can fulfill this requirement. Ranitidine hydrochloride is an antiulcer drug and works on H<sub>2</sub>-receptor mainly in stomach. The primary absorption region of this drug is stomach. Since it is an antiulcer drug, it will be beneficial to retain the drug in gastric region. The half life of RHCL is approximately 2.1 hr and the dose of drug is also low which make it a suitable candidate for sustained release dosage form. By retaining it in stomach and by sustaining its release, the absorption of drug and its efficacy can be enhanced. Formulation of RHCL as a sustained release dosage form can also minimize the loss of drug in comparison of conventional tablets.

The design of gastroretentive drug delivery systems depends upon physicochemical properties, dose and purpose of controlling the drug release, constraining pathophysiological factors. Various approaches have been pursued including low density dosage form that remains buoyant above gastric fluid or high density dosage form that is retained at the bottom of the stomach, imparting bioadhesion to the stomach mucosa, utilizing ion-exchange resin which adheres to mucosa, expanding the dosage form by swelling or unfolding to a large size which limits emptying of dosage form through pyloric sphincter, using modified shape system, or other effervescent systems using a gas generating material like sodium bicarbonate and calcium carbonate or the same with citric acid<sup>11-16</sup>. Preparation of floating alginate beads is more suitable because it is a multiparticulate system, utilizes cheap and

nontoxic polymers and there is no use of any organic solvent. These beads having a sustained release composition and formulation of ranitidine hydrochloride capable of providing release drug release over 12 hr was formulated using expandable, gelling, swellable, hydrocolloid polymer along with light liquid paraffin. Sodium alginate has been used as thickening and gelling agent. Additionally it also reduces interfacial tension between an oil and water phase and is efficient for preparation of emulsion. Alginate is a linear co-polymer composed of two monomeric units. D-mannuronic acid and L-guluronic acid. They occur in alginate molecule as regions made up exclusively of one unit or the other referred to M block or G block or as a region in which monomer approximates an alternating sequence. Gels form when a calcium salt is added to a solution of sodium alginate in water. The gel forms by chemical reaction, the calcium displaces the sodium from the alginate, holds the long alginate molecules together and a gel is the result<sup>17,18,19</sup>. No heat is required and the gels do not melt when heated. The polyguluronate block of alginate is known to be responsible for this gelling feature<sup>20</sup>. Pectin was also used in combination with alginate to study its effect on different parameters. It is a complex polysaccharide comprising mainly esterified D-galacturonic acid residues in an  $\alpha$ -(1-4) chain. The acid groups along the chain are largely esterified with methoxy groups in the natural product. The USP 28 describes pectin as a purified carbohydrate product obtained from the dilute acid extract of the inner portion of the rind of citrus fruits or from apple pomace. It is also gelled when react with calcium ion.

## **MATERIALS AND METHODS**

### **Materials**

Gift sample of Ranitidine hydrochloride (RHCl) was obtained from Orchev Pharma Pvt Ltd, Rajkot, Gujarat, India. Sodium alginate, pectin-pure (poly D-galarturonic acid methyl ester, methoxy content 6%) and light liquid paraffin were purchased from Central drug house (P) Ltd; New Delhi. Calcium chloride (anhydrous) was purchased from Ranbaxy fine chemicals limited, New Delhi. All other ingredients used were of analytical grade.

### **Method**

#### **Preparation of ranitidine hydrochloride floating emulsion gel beads with sodium alginate**

The technique involved in the preparation of oil entrapped floating alginate beads was emulsion gelation technique. Polymer was dissolved in water with stirring. Oil was added to polymer solution and the drug was then added. The mixture was homogenized for 15 minutes and was extruded via a needle having diameter of 0.8 mm from a distance of 5 cm in to 5% calcium chloride solution with gentle agitation at room temperature. The dropping rate was kept 2ml/min. The formed beads were cured for different duration to optimize curing time, separated by filtration. After washing the beads, they were dried in a tray dryer at temperature of 40<sup>0</sup>C. The time of drying was optimized by weighing the beads repeatedly, until they obtained a constant weight. The formulations of the different batches (A-1 to D-2) are shown in Table-1.

#### **Preparation of ranitidine hydrochloride floating emulsion gel beads with sodium alginate and pectin blend**

The technique involved was similar, only the different combination of sodium alginate and

pectin in each drug polymer ratio was added. Homogenizing time, needle diameter, distance of needle from the surface of solution, strength of calcium chloride solution and dropping rate were kept constant. Optimized Curing time was used here to cure the beads. After washing the beads, they were dried in a tray dryer at temperature of 40<sup>0</sup>C. The time of drying was optimized by weighing the beads repeatedly, until they obtained a constant weight. The formulations of these batches (E1 to K2) are shown in Table-2.

## **EVALUATION AND CHARACTERIZATION OF BEADS**

### **Study of size and morphology of emulsion gel beads**

The diameter of beads was determined by screw gauge<sup>21, 22</sup>. For this purpose, 20 dried beads were randomly selected from each batch and the mean diameter was determined by screw gauge. The least count of screw gauge was 0.005 mm. Colour and shape of dried beads of each batch was noted.

### **Floating time of emulsion gel beads**

The gel bead samples (n=10) were placed in a beaker filled with 50 ml of 0.1 N HCl solution. Temperature was maintained at 37<sup>0</sup>C. The floating time of beads was observed for 20 hrs. The preparation was considered to have buoyancy in the test solution only when all the gel beads floated in it<sup>21</sup>.

### **Determination of drug content**

50 mg of beads were weighed and crushed in a pastel mortar and the crushed material was dissolved in 25 ml of water. Volume of this solution was made up to 50 ml with washings of mortar. This solution was shaken with the help of wrist action shaking machine for 5 hrs and then kept for 24 hrs. Then it was filtered. The filtrate was assayed by

spectrophotometrically at 313.5 nm. The drug content and the encapsulation efficiency were determined.

#### **Swelling studies<sup>23</sup>**

Beads were studied for swelling characteristics. Only those batches were selected which have good drug content and entrapment efficiency more than 50%. Sample from drug-loaded beads were taken, weighed and placed in wire basket of USP dissolution apparatus II. The basket containing beads was put in a beaker containing 100 ml of 0.1 N HCl (pH 1.2) maintained at 37°C. The beads were periodically removed at predetermined intervals and weighed. Then the swelling ratio was calculated as per the following formula:

Swelling ratio = weight of wet beads/weight of dried beads

#### **Drug release studies**

The dissolution of Ranitidine hydrochloride-loaded calcium alginate beads was studied using USP Type II dissolution apparatus (Hicon, Grover enterprises Delhi) containing 900 ml of 0.1 N HCl (pH 1.2) maintained at 37±0.5°C and stirred at 50 rpm. Samples were collected periodically and replaced with a fresh dissolution medium. These samples were analyzed for the drug present in them with help of UV spectrophotometer (UV-1700, Pharmaspace, Shimadzu). Only those batches were selected for the release study, which have good drug content and drug entrapment efficiency more than 50%.

#### **Study of drug release kinetics<sup>24</sup>**

Study of release kinetics of RHCl from beads was done. The optimized batch was selected for drug release kinetics study. Zero order ( $Q_t = Q_0 + K_0t$ ), first order ( $\ln Q_t = \ln Q_0 + K_1t$ ) and Higuchi ( $Q_t = K_{11}t^{1/2}$ ) model were fitted to dissolution data of optimized batch i.e. H-1,

using linear regression analysis. Zero order kinetics indicates that the concentration is nearly independent of drug release, while first order kinetics indicates time dependent release kinetics. Higuchi equation explains why the drug diffuses at comparatively slower rate at the distance for diffusion increases, which referred to as square root kinetics.

#### **Stability studies**

The stability studies for beads were done by keeping the sample beads from optimized batches at room temperature for 90 days. The beads were filled in capsules and these capsules were packed in vials. The vials were sealed and stored at room temperature only because the polymer used in preparation of beads i.e. sodium alginate is not stable at higher temperature. The selected batches for stability study were batch H-1 and K-1. The samples were put for 90 days. In the end of one month the beads were evaluated for different parameters like morphology, floating time, swelling ratios and drug release studies. Methods followed to evaluate these parameters were similar as followed previously.

### **RESULTS AND DISCUSSION**

The floating RHCL beads were prepared according to the formulations shown in table 1 and 2. The observations of evaluation of RHCL beads are given in Table3 & Table4. The shape of beads varies from spherical to disc shape with changing concentration and ratio of polymers. As the total concentration of polymer reduced from 5% to 4% and then 3% w/v, shape of beads also became spherical to disc like. In the case of beads prepared with the combination of sodium alginate and pectin, as the part of alginate was reduced, the spherical shape was lost and beads became disc like or of irregular shape. The results

show as the amount of oil and drug content increased, the size increased gradually (Fig.1 & Fig.2). Colour of sodium alginate beads crosslinked with glutaraldehyde was white in

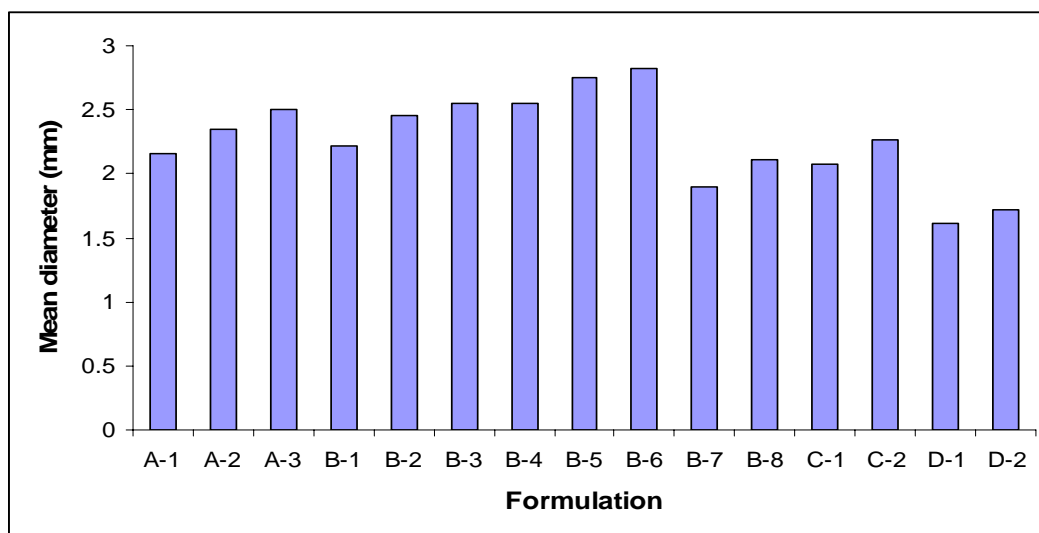
solution but it changed in reddish brown after drying. The colour of pectin beads prepared in similar way was somewhat darker than that of sodium alginate beads.

**Table 1: Formulation of Ranitidine Hydrochloride Floating Emulsion Gel Beads with sodium alginate**

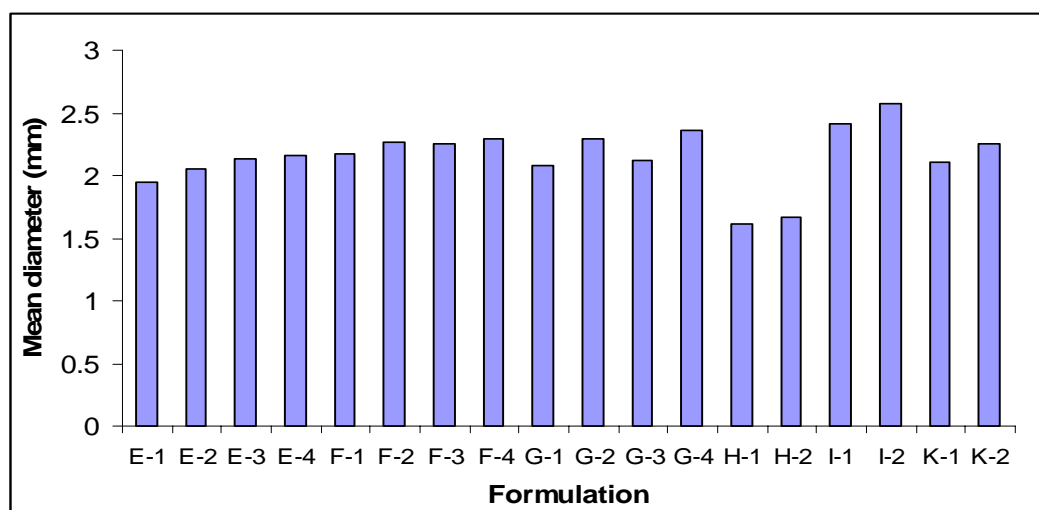
Batch code	Polymer Concentration (%)	Drug: Polymer	Oil Concentration (%)	Curing Time (min)
A-1	5	1:1	10	10
A-2	5	1:1	20	
A-3	5	1:1	30	
B-1	5	1:1	10	2
B-2	5	1:1	20	
B-3	5	1:1	30	
B-4	5	1:0.5	10	
B-5	5	1:0.5	20	
B-6	5	1:0.5	30	
B-7	5	1:1	15	
B-8	5	1:0.5	15	
C-1	4	1:0.4	15	
C-2	4	1:0.4	20	
D-1	3	1:0.3	15	
D-2	3	1:0.3	20	

**Table 2: Formulation of Ca<sup>2+</sup> crosslinked alginate – pectin blend gel beads**

Batch code	Polymer (%)	Drug: Polymer	Alginate: Pectin	Oil Concentration (%)
E-1	5	1:1	3:2	15
E-2	5	1:1	3:2	20
E-3	5	1:0.5	3:2	15
E-4	5	1:0.5	3:2	20
F-1	5	1:1	1:1	15
F-2	5	1:1	1:1	20
F-3	5	1:0.5	1:1	15
F-4	5	1:0.5	1:1	20
G-1	5	1:1	2:3	15
G-2	5	1:1	2:3	20
G-3	5	1:0.5	2:3	15
G-4	5	1:0.5	2:3	20
H-1	4	1:0.4	3:2	15
H-2	4	1:0.4	3:2	20
I-1	4	1:0.4	1:1	15
I-2	4	1:0.4	1:1	20
J-1	4	1:0.4	2:3	15
J-2	4	1:0.4	2:3	20
K-1	3	1:0.3	3:2	15
K-2	3	1:0.3	3:2	20



**Fig. 1: Particle size distribution of Emulsion gel beads of RHCl(Batch A-1 to D-2)**



**Fig. 2: Particle size distribution of Emulsion gel beads of RHCl (Batch E-1 to K-2)**

Most of the batches had floating time more than 20 hrs as given in Table 3, but they have different floating lag time. Light liquid paraffin has lower relative density (0.86). It helped the beads to become buoyant. As the amount of oil was increased in the preparation of a batch, amount of oil also increased in individual bead. Due to this extra amount of oil, beads floated immediately or with a very short lag time. Again as the drug content of

beads increased, the floating lag time also increased. But for floating lag time the effect of drug content and amount of oil must be considered jointly. The third factor responsible for difference in floating lag time is polymer concentration. The results show when the batches, among which all parameters except polymer concentration were same, are taken in consideration, floating lag time was governed by polymer concentration.

The drug entrapment efficiency of the dried beads was varied from 2.11 to 75.18% and drug content of beads had range from 0.5% to 26.75%. Curing time is major factor, which governs the % drug content and % entrapment efficiency. Being Ranitidine hydrochloride a freely water soluble drug, most of the drug diffused in the surrounding aqueous medium resulting a very low % drug content and % entrapment efficiency. To overcome this problem, curing time was optimized at 2 min. The second important parameter, which was utilized to improve % drug content and % entrapment efficiency, was amount of oil used in preparation of each batch. Use of 10 % and 30% oil were discarded because batches prepared with 10% oil were floated with a long floating lag time and batches with 30% of oil was not taken in consideration because of the problem of leakage of oil. After preparation of these batches, two oil concentrations were selected, one was 15% and another one was 20%. When batch B-1, B-7, B-2 and B-3 were observed for its drug content results, their respective % drug contents were found 11.25%, 15.12%, 10.68% and 9.21%. It can be seen that when the amount of oil was increased from 10% to 15%, the % drug content was also increased from 11.25% to 15.12% but further increment of oil caused reduction in % drug content. The reason behind this, when amount of oil used was 10%, some amount of drug diffused in surrounding medium during gellification of beads. But when this amount was increased up to 15%, the barrier action of entrapped droplets of oil were increased and protected more drug against diffusion, resulting in increased drug content of beads. When the amount of oil was increased up to 20% and 30%, this enhanced volume of oil occupied the most of the volume of a single bead and

prevented the entrapment of sufficient amount of drug. Thus it can be concluded that an intermediate optimum level of oil is necessary for preparation of beads with maximum drug content. The third factor, which affected the % drug content and % entrapment efficiency, was drug: polymer ratio. When the amount of drug is greater, lesser amount of drug diffusion in surrounding aqueous medium was taken place during a definite curing time. After the above decision, the effect of polymer concentration in preparation of each batch was analyzed. The results show that more the concentration of polymer was there; more was the capacity of beads to hold the drug with itself.

The next effort to enhance the drug content and drug entrapment efficiency was done by preparing the beads with combination of polymers. The results indicate that the drug content and the drug entrapment efficiency was less when the beads were prepared with a single type of polymer (sod.alginate) in comparison of the beads prepared with two types of polymers (sod.alginate and pectin). This might be due to the presence of two types of protective layers in beads, one of calcium pectinate and other one of calcium alginate, which prevented the diffusion of drug more effectively than a single type of layer only. But as the proportion of alginate was reduced in the combination of these two polymers, the drug content of beads started to reduce. It can be explained that in combination of two layers calcium alginate layer was more effective in prevention of diffusion of drug than the calcium pectinate layer and also there was an optimum ratio of these two polymers (i.e. alginate: pectin 3:2), which was responsible for the maximum drug content.

**Table 3: Characterization of emulsion gel beads of RHCL of batch A- 1 to E-3**

S. No.	Batch code	Mean diameter (mm)±S.D. (n=20)	Floating lag time	Floating Time (hrs)	Drug content (%)	Entrapment efficiency (%)
1	A-1	2.16±0.07	40min-1hr	>20	0.8	3.32
2	A-2	2.35±0.06	0	>20	0.5	2.11
3	A-3	2.5±0.06	0	>20	1.8	7.28
4	B-1	2.22±0.08	40min-1hr	>20	11.25	36.12
5	B-2	2.45±0.05	1-2min	>20	10.68	45.24
6	B-3	2.55±0.05	0	>20	9.21	49.35
7	B-4	2.55±0.09	40min-1hr	>20	21.56	56.56
8	B-5	2.75±0.08	3-4min	>20	22.5	57.38
9	B-6	2.82±0.06	2-3 min	>20	21.41	58.32
10	B-7	1.90±0.29	0	>20	15.12	54.08
11	B-8	2.11±0.1	3-4 min	>20	23.00	62.65
12	C-1	2.08±0.17	0-30 sec	>20	22.23	60.15
13	C-2	2.26±0.17	0-30sec	>20	21.05	55.24
14	D-1	1.61±0.38	0-30sec	>20	20.95	55.00
15	D-2	1.72±0.31	0	>20	20.33	51.00
16	E-1	1.95±0.08	3-4min	>20	14.45	59.02
17	E-2	2.06±0.06	0	>20	8.89	47.19
18	E-3	2.13±0.08	30sec-1min	>20	26.67	75.18

**Table 4: Characterization of emulsion gel beads of RHCL of batch E-4 to K-2**

S. No.	Batch code	Mean diameter (mm)±S.D. (n=20)	Floating lag time	Floating Time (hrs)	Drug content (%)	Entrapment efficiency (%)
1	E-4	2.16±0.07	0-30sec	>20	24.44	58.68
2	F-1	2.18±0.23	0	>20	9.5	36.45
3	F-2	2.27±0.08	0	>20	8.89	42.56
4	F-3	2.25±0.05	4-5min	>20	24.45	54.62
5	F-4	2.29±0.07	3-4min	>20	23.34	50.12
6	G-1	2.08±0.16	0	>20	12.2	47.32
7	G-2	2.29±0.11	0	>20	12.67	56.62
8	G-3	2.12±0.14	0-30sec	>20	24.45	52.02
9	G-4	2.36±0.1	0-30sec	>20	22.23	59.56
10	H-1	1.61±0.16	30sec-1min	>20	23.92	70.76
11	H-2	1.67±0.12	30sec-1min	>20	22.5	65.52
12	I-1	2.41±0.18	0-30sec	>20	18.5	48.5
13	I-2	2.58±0.16	0-30sec	>20	18	45.3
14	K-1	2.11±0.15	0-30sec	>20	22.1	65
15	K-2	2.25±0.11	0-30sec	>20	21.44	61.79



In the present study it was observed that in each batch there was a maximum swelling of beads followed by sudden reduction in weight in next observation. This effect might be owing to acid solubility of drug that might have influenced the swelling behavior of beads. The polymer concentration has significant effect on swelling ratio of beads. As the amount of polymer was increased, the swelling ratio of beads decreased. This result may be because of maximum crosslinking of polymers that yielded compact beads. The polymer mixture is also responsible for different swelling behavior

of beads. As the proportion of alginate was reduced, the maximum swelling ratio as well as the time of rehydration increased. It proves that alginate makes compact structured beads in comparison to pectin. Oil has also a little effect on swelling behavior. In batch B-8 & B-5, batch C-1 & C-2, batch D-1 & D-2, batch E-3 & E-4, batch F-3 & F-4, batch G-3 & G-4, batch H-1 & H-2 and batch K-1 & K-2, the increased amount of oil in each pair of batches caused a slower swelling of beads. Thus the oil acted as a barrier for water absorption (Fig. 3 & Fig. 4).

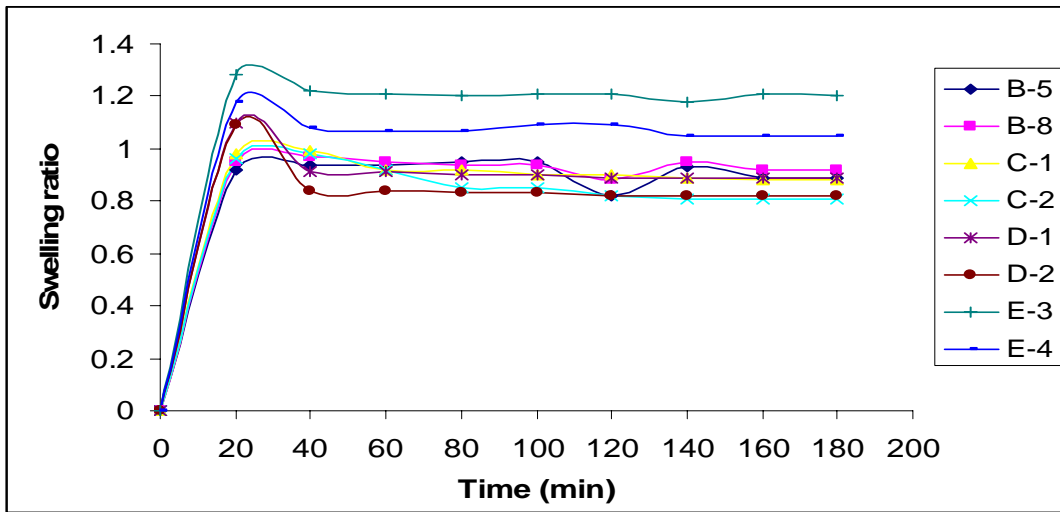


Fig. 3: Swelling ratio in 0.1N HCl vs time relationship of RHCl loaded emulsion gel beads of batch B-5 (◆), B-8 (■), C-1(▲), C-2(×), D-1(\*), D-2 (●),E-3(+)& E-4 (—)

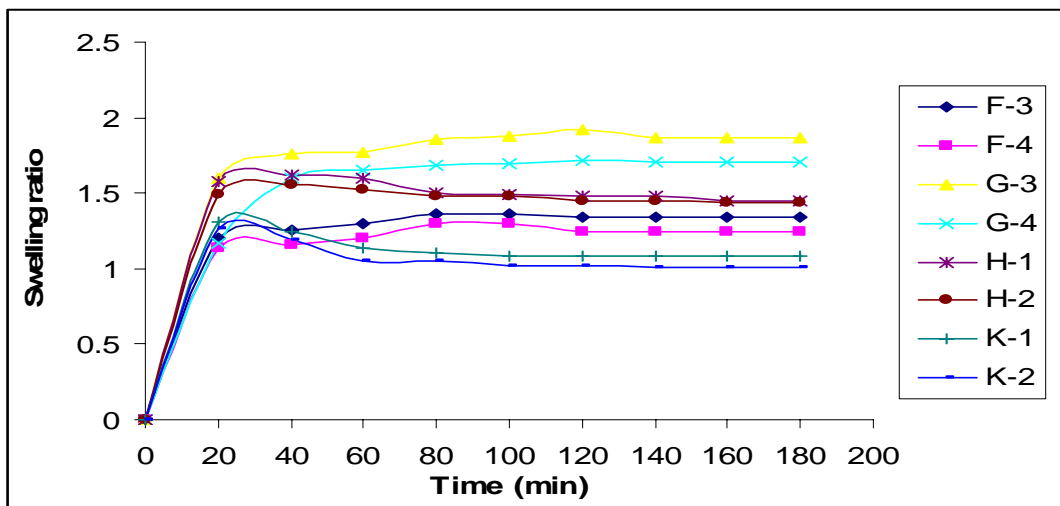


Fig. 4: Swelling ratio in 0.1N HCl vs time relationship of RHCl loaded emulsion gel beads of batch F-3(◆), F-4(■), G-3(▲), G-4(×), H-1(\*), H-2(●), K-1(+)& K-2(—)

Drug release pattern was affected by polymer concentration, ratio of polymer mixture and amount of oil. All the batches showed the initial burst release. This may be due to the water-soluble nature of the drug. It may also be possible that drug particles were dragged on the surface of the beads during curing in aqueous surrounding medium, which resulted in initial burst release. The results indicate that the drug release slows down with increasing polymer concentration. It can be explained that greater the amount of polymer, thicker the layer of polymer was formed around the drug particles and more effectively the polymer would hold the drug with itself. This had also been proved with the result of drug content. The same reason is also true for the batches prepared with combination of polymers.

The release pattern of drug from batches prepared with combination of polymers i.e. with alginate and pectin was entirely different than that of from batches prepared with single

polymer (Fig.5 & Fig.6). Results showed that alginate alone was not sufficient to sustain the drug release. After observing the release pattern of batch E-3, F-3 and B-5, a great difference was found. This difference might be due to the presence of an additional barrier layer of calcium pectinate in the beads of former batches, which caused the slow release of drug from beads. The difference in % cumulative release of batch H-1 & H-2 from that of C-1 and C-2 and the difference in % cumulative release of batch K-1 & K-2 from that of D-1 and D-2 have same explanation. It is observed that as the proportion of sodium alginate was reduced and proportion of pectin was increased in a batch, the release of drug became fast. So it may be explained that calcium alginate is more efficient sustaining material than calcium pectinate but at the same time, it was also true that this sustaining effect could be obtained only with combination of alginate & pectin and not with alginate only.

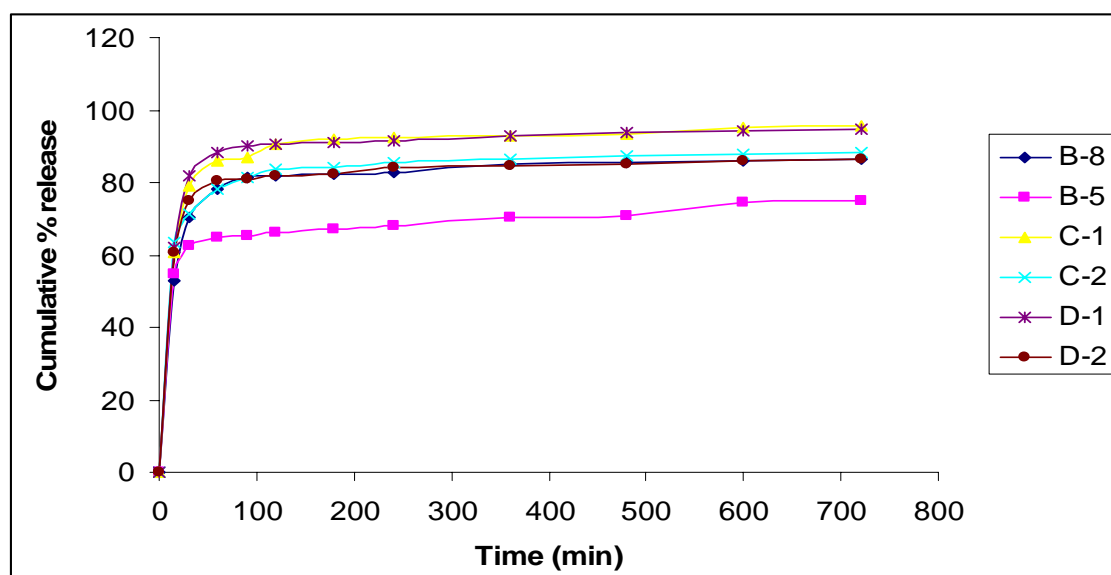
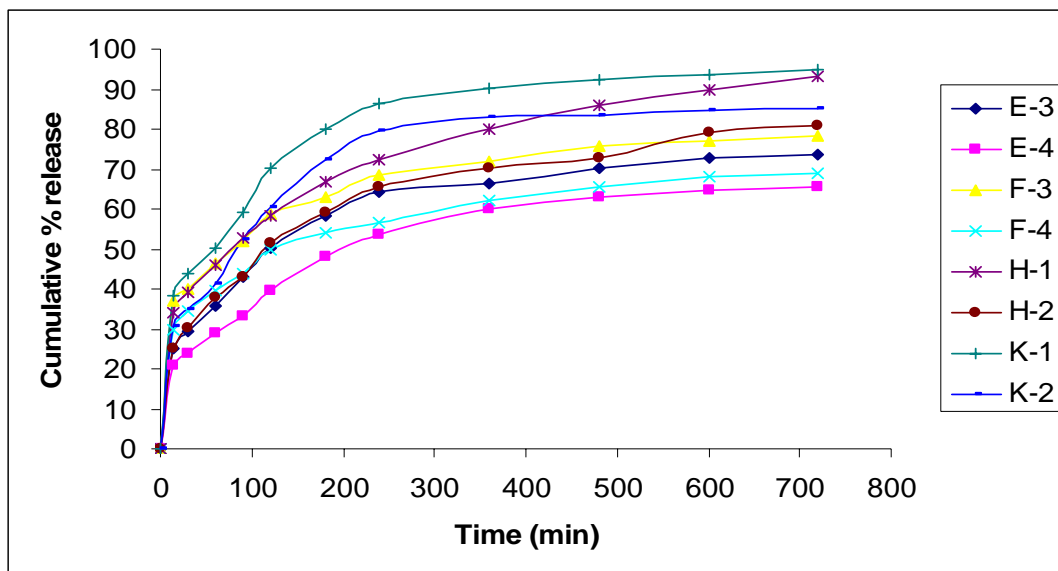


Fig. 5: Release profile of RHCl in pH 1.2 acid buffer from RHCl loaded gel beads of batch B-8(◆), B-5(■), C-1(▲), C-2(×), D-1(\*) & D-2(●).



**Fig. 6: Release profile of RHCl in pH 1.2 buffer from RHCl loaded gel beads of batch E-3(◆),E-4(■), F-3(▲), F-4(✕),H-1(✱), H-2(●), K-1(⊕)& K-2(—)**

The next important parameter, which affected the drug release from different batches, was amount of oil. After analyzing the release pattern of different batches prepared with 15%

& 20% oil, it can be explained that the higher amount of oil forms an additional barrier for the release of drug resulting in slow release of drug from beads.

**Table 5: Study of drug release kinetics of optimized batch H-1**

Batch code	Zero order ( $r^2$ )	First order ( $r^2$ )	Higuchi ( $r^2$ )
H-1	0.8836	0.7937	0.9776

After studying the drug release kinetics for optimized batch i.e. H-1, it can be concluded that Ranitidine hydrochloride was released from the optimized batch prepared with the blend of alginate and pectinate in sustained manner. After studying the different kinetics models, it could be concluded that release of RHCl from batch H-1 followed the Higuchi model i.e. square root kinetics (Table 5). Thus the release from these batches was diffusion controlled.

Thus the floating emulsion gel beads of Ranitidine hydrochloride prepared with sodium alginate and pectin appears to be a promising vehicle for delivering Ranitidine

hydrochloride like drug, which has maximum absorption from gastric region. These beads can entrap even a water soluble drug as Ranitidine hydrochloride in sufficient amount and also can successfully deliver the drug in stomach for a prolong duration of time. Thus without using any organic solvent and any time consuming step in the preparation of these floating beads it is possible to develop an effective, cheap and nontoxic FDDS for Ranitidine hydrochloride.

**ACKNOWLEDGEMENTS**

The authors are grateful to Orchev Pharma Pvt Ltd, Rajkot, Gujarat, India for providing gift sample of Ranitidine hydrochloride. The

authors wish to thank The Management, Department of Pharmacy, Raj Kumar Goyal Institute of Technology, Delhi-Meerut Road, Ghaziabad (India) for providing facilities to carry out this research.

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