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Design & *In Vitro* Evaluation of Floating Microspheres Using Roxatidine Acetate HCl

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ABSTRACT

The purpose of the research was to prepare and evaluate Roxatidine acetate HCl floating microspheres by ionotropic gelation method. Fourteen formulations were prepared, among all the formulations F13 was selected as optimized formulation based on the micromeretic and evaluation parameters including drug release studies. In the *in vitro* release study of formulation, F13 showed 95.65% drug release after 12 h in a controlled manner, which is desired for disease like peptic ulcer. *In vitro* release profiles from optimized formulation F13 were applied on various kinetic models. The best fit with the highest correlation coefficient was observed in zero order and Higuchi model, indicating diffusion controlled principle. The innovator Rotane 150 mg conventional tablet showed the drug release of 96.45% within 1 h. FT-IR and DSC analyses confirmed the absence of drug-polymer interaction. The results obtained from evaluation and performance study of different types of Roxatidine microspheres showed that system may be useful to achieve a controlled drug release profile, reduce the dose of drug, dosing frequency and improve patient compliance when compared with marketed product.

Key words: Roxatidine, buoyancy, HPMC, gum olibanum, microspheres.

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INTRODUCTION

Since the last three decades many drug molecules formulated as Gastroretentive Drug Delivery System (GRDDS) have been patented keeping in view its commercial success. Oral controlled release (CR) dosage forms have been extensively used to improve therapy of many important medications. The bioavailability of drugs with an absorption window in the upper small intestine is generally limited with conventional pharmaceutical dosage forms. The residence time of such systems and thus, of their drug release into the stomach and upper intestine is often short. To overcome this restriction and to increase the bioavailability of these drugs, controlled drug delivery systems with a prolonged residence time in the stomach can be used[1].

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms[2]. Several approaches are currently used to prolong gastric retention time. These include floating drug delivery systems, also known as hydrodynamically balanced systems, swelling and expanding systems, polymeric bioadhesive systems, modified-shape systems, high-density systems and other delayed gastric emptying devices[3].

Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach[4].Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms[5].

Floating drug delivery system (FDDS) promises to be a potential approach for gastric retention. Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach[6]. Floating microspheres have emerged as an efficient means of enhancing the bioavailability and controlled delivery of many drugs. The increasing sophistication of delivery technology will ensure the development of increasing number of gastro-retentive drug delivery systems to optimize the delivery of molecules that exhibit absorption window, low bioavailability, and extensive first pass metabolism[7].

Peptic ulcer disease, also known as a peptic ulcer or stomach ulcer, is a break in the lining of the stomach, first part of the small intestine, or occasionally the lower esophagus[8].

Roxatidine acetate is a specific and competitive histamine H_2 receptor antagonist, which is used to treat gastric ulcers, Zollinger–Ellison syndrome, erosive esophagitis, gastro-oesophageal reflux disease and gastritis. Roxatidine has less bioavailability (80%) and lesser half life of 5 hrs[9]. The

aim of present work is to design and *in vitro* evaluation of Roxatidine acetate HCl floating microspheres to enhance its bioavailability and prolonged residence time in stomach.

MATERIALS AND METHODS

Floating microspheres

Formulation of Roxatidine acetate HCl Floating microspheres:

Roxatidine acetate HCl floating microspheres were prepared using polymers Sodium alginate, Calcium chloride, HPMC K4M, HPMCK15M, Xanthan gum, Guar gum, Gum kondagogu, Gum olibanum and sodium bicarbonate by Ionotropic gelation method.

Table 1: Formulation of Roxatidine acetate HCl Floating microspheres

Formulation code	Roxatidine acetate HCl (mg)	Sodium alginate	HPMC K4M (mg)	Sodium bi carbonate(mg)	Calcium chloride	Guar gum	Gum Kondagogu
F1	1500	1%	50	25	1%	1%	0.75%
F2	1500	1. 2%	75	50	1%	1.2%	0.75%
F3	1500	1.4 %	100	75	1%	1.4%	0.75%
F4	1500	1.6%	150	100	1%	1.6%	0.75%
F5	1500	1.8 %	175	125	1%	1.8%	0.75%
F6	1500	2.%	200	150	1%	2%	0.75%
F7	1500	2.2%	200	175	1%	2.2%	0.75%
Formulation code	**Roxatidine acetate HCl (mg)**	**Sodium alginate**	**HPMC K15M (mg)**	**Sodium bi carbonate (mg)**	**Calcium chloride**	**Xanthan gum**	**Gum Olibanum**
F8	1500	1%	150	25	1%	1%	0.75%
F9	1500	1. 2%	200	50	1%	1.2%	0.75%
F10	1500	1.4%	250	75	1%	1.4%	0.75%
F11	1500	1.6%	300	100	1%	1.6%	0.75%
F12	1500	1.8%	350	125	1%	1.8%	0.75%
F13	1500	2%	400	150	1%	2%	0.75%
F14	1500	2.2%	450	175	1%	2.2%	0.75%

Procedure:

Floating microspheres of Roxatidine acetate HCl were prepared by ionic gelation technique using different proportion of polymers as shown in table 1. A solution of sodium alginate solution is prepared, weighed quantity of drug and HPMC K4 or HPMC K15 and other polymers were added and triturated to form fine powder, and then added to above solution. Sodium bicarbonate, a gas forming agent was added to this mixture. Resultant solution was extruded drop wise with the help of syringe and needle into 100 ml aqueous calcium chloride solution and stirred at 100 rpm. After stirring for 10 minutes the obtained microspheres were washed with water and dried at 60 degrees -2 hrs in a hot air oven and stored in descicator[10].

Evaluation of Roxatidine acetate HCl floating microspheres:

Micromeretic properties like particle size, angle of repose, bulk density, Tapped density, Compressibility index, Hausner's ratio and evaluation parameters like Swelling index, Drug entrapment efficiency and % yield, *In vitro* dissolution studies and percentage buoyancy studies were performed.

***In vitro* drug release studies:**

In vitro drug release studies for developed Roxatidine acetate HCl microspheres were carried out by using dissolution apparatus II paddle type (Electrolab TDL-08L). The drug release profile was studied in 900 ml of 0.1 N HCl at 37± 0.5^0C temperature at 100 rpm. The amount of drug release was determined at different time intervals of 0, 1, 2, 3, 4, 6, 8, 10 & 12 hrs by UV visible spectrophotometer (Shimadzu UV 1800) at 280 nm.

Percentage buoyancy of Roxatidine acetate HCl floating microspheres:

In vitro floating ability can be determined by calculating percentage buoyancy and performed in USP type II dissolution test apparatus by spreading the floating microspheres in 0.1 N HCl containing the surfactant. The media is stirred at 100 revolutions per minute (rpm) at 37± 0.5°C. After specific intervals of time, both the fraction of microspheres (floating and settled microspheres) is collected and buoyancy of the floating microspheres is determined by using formula.

% Floating Microspheres = Weight of floating microspheres X 100/ Initial weight of floating microspheres

Kinetic modeling of drug release:

In order to understand the kinetics and mechanism of drug release, the result of the *in vitro* dissolution study of floating microspheres were fitted with various kinetic equations like Zero order as cumulative percentage released Vs. time, First order as log percentage of drug remaining to be released Vs. time, Higuchi's model cumulative percentage drug released Vs. square root of time. R^2 and K values were calculated for the linear curves obtained by regression analysis of the above plots. To analyze the mechanism of drug release from the microspheres, the *in vitro* dissolution data was fitted to zero order, first order, Higuchi's release model and Korsmeyer – Peppas model.

Drug excipient compatibility studies

The drug excipient compatibility studies like Fourier Transmission Infrared Spectroscopy (FTIR), Differential Scanning Colorimetry (DSC) method and SEM were performed.

Stability studies

The stability study of the optimized formulation was carried out under different conditions according to ICH guidelines. The optimized microspheres were stored in a stability chamber for stability studies (REMI make). Accelerated Stability studies were carried out at 40 ^{0}C / 75 % RH for the best formulations for 6 months. The microspheres were characterized for the percentage yield, entrapment efficiency and cumulative % drug released during the stability study period.

RESULTS AND DISCUSSION

Floating microspheres:

Figure 1: Roxatidine acetate HCl floating microspheres

All the formulations were evaluated for their various physical parameters like particle size, bulk density, tapped density, angle of repose, Carr's index and % buoyancy and found to be within the limits. The formulation F13 showed best results like particle size 67.23±0.19µm, bulk density of 0.65 g/cc, angle of repose 24˚.47, compressibility index 10.34% and % buoyancy of 96.40%.

Table 2: Micromeretic properties of Roxatidine acetate HCl floating microspheres:

Formulation code	Particle size (µm)	Bulk density (g/cc)	Tapped density (g/cc)	Angle of repose	Carr's index	Buoyancy%
F1	60.45±0.04	0.59	0.55	28˚.93	13.56%	91.20%
F2	60.12±0.08	0.66	0.59	26˚.74	11.34%	84.50%
F3	65.29±0.13	0.74	0.62	29˚.67	12.34%	83.30%
F4	73.43±0.04	0.76	0.73	28˚.03	14.36%	92.10%
F5	77.35±0.04	0.79	0.75	29˚.74	15.12%	81.64%
F6	79.67±0.09	0.81	0.83	31˚.15	14.23%	89.40%
F7	85.45±0.04	0.85	0.82	26˚.54	13.95%	93.10%
F8	55.23±0.14	0.86	0.63	26˚.91	12.32%	72.50%
F9	61.22±0.11	0.69	0.65	29˚.70	14.03%	75.80%
F10	73.34±0.10	0.71	0.74	30˚.24	12.34%	76.40%
F11	78.45±0.21	0.75	0.76	28˚.91	12.90%	85.30%
F12	85.45±0.09	0.79	0.79	28˚.02	13.90%	92.50%
F13	67.23±0.19	0.65	0.63	24˚.47	10.34%	96.40%
F14	81.67±0.13	0.82	0.84	27˚.91	13.94%	92.20%

The results of Percentage yield, entrapment efficiency and swelling index of floating microspheres of all formulations were within the limits as shown in Table 2. The Percentage yield, entrapment efficiency and swelling index of F13 was found to be 94.30%, 95.80% and 96.89% respectively.

Table 3: Percentage yield, entrapment efficiency and swelling index of Roxatidine acetate HCl microspheres

Formulation code	Percentage Yield	Entrapment efficiency	Swelling index
F1	78.09%	77.09%	76.76%
F2	81.12%	82.23%	79.78%
F3	83.23%	84.56%	83.34%
F4	86.87%	87.30%	85.23%
F5	89.30%	90.20%	88.34%
F6	90.30%	91.10%	89.78%
F7	96.10%	96.30%	95.12%
F8	86.42%	84.30%	82.23%
F9	81.56%	84.89%	84.34%
F10	89.76%	88.78%	88.45%
F11	92.78%	92.78%	89.89%
F12	84.50%	92.56%	91.10%
F13	94.30%	95.80%	96.89%
F14	85.30%	84.88%	87.90%

Table 4: *In vitro* cumulative % drug release of Roxatidine acetate HCl floating microspheres

Time (h)	F1	F2	F3	F4	F5	F6	F7	Innovator (Rotane 150mg)
0	0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0
1	17.21±0.12	12.67±0.98	16.26±0.77	10.74±0.23	10.21±0.43	8.28±0.44	7.07±0.17	96.45±0.44
2	35.86±0.16	27.84±0.35	34.39±0.56	18.29±0.23	15.52±0.16	12.56±0.67	12.61±0.32	
4	53.91±0.23	42.04±0.45	45.52±0.52	32.66±0.65	28.73±0.45	20.73±0.16	20.77±0.15	
6	72.59±0.16	58.12±0.24	57.38±0.43	47.52±0.56	42.82±0.54	28.85±0.45	31.23±0.65	
8	84.16±0.40	70.13±0.85	71.27±0.34	63.58±0.45	50.25±0.23	39.53±0.16	49.92±0.45	
10	93.68±0.22	82.13±0.77	93.17±0.32	80.46±0.44	68.61±0.15	51.17±0.32	67.19±0.16	
12	90.94±0.16	91.04±0.76	91.95±0.11	94.03±0.15	76.18±0.45	67.76±0.45	79.93±0.44	

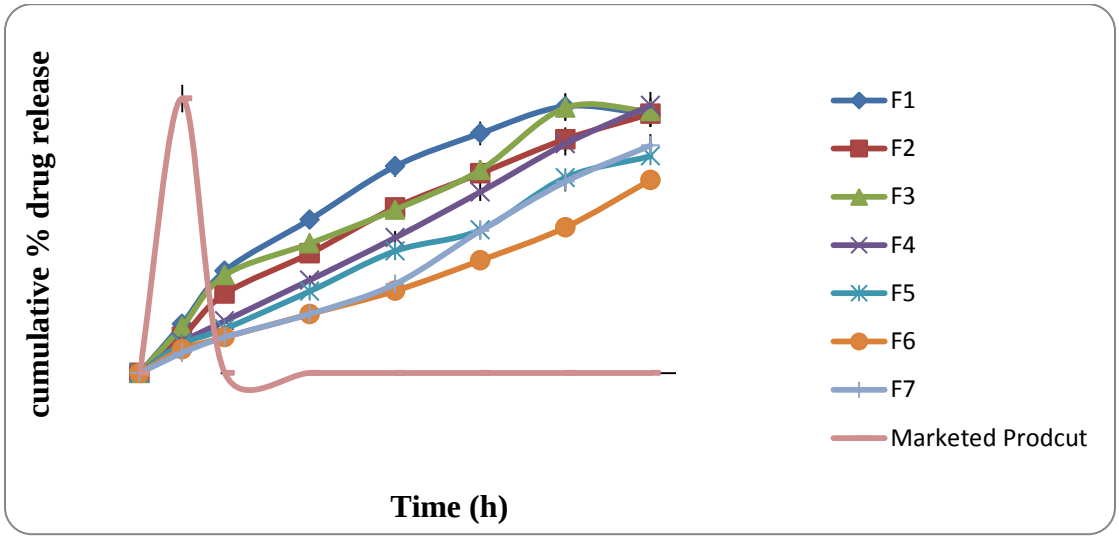

Figure 2: *In vitro* cumulative % drug release of Roxatidine acetate HCl floating microspheres

Table 5: *In vitro* cumulative % drug release of Roxatidine acetate HCl floating microspheres formulations

Time (h)	F8	F9	F10	F11	F12	F13	F14
0	0±0	0±0	0±0	0±0	0±0	0±0	0±0
1	7.27±0.55	9.03±0.34	8.79±0.89	8.55±0.88	9.31±0.65	8.89±0.87	10.83±0.15
2	9.96±0.54	16.49±0.16	13.02±0.15	14.98±0.19	13.08±0.32	13.08±0.65	19.14±0.55
4	18.57±0.32	25.41±0.67	23.25±0.65	25.09±0.18	25.93±0.33	25.68±0.45	29.61±0.16
6	32.13±0.56	33.95±0.45	35.77±0.54	37.59±0.98	39.41±0.15	40.23±0.22	43.05±0.32
8	42.37±0.45	44.08±0.45	48.86±0.34	47.5±0.78	50.21±0.56	51.35±0.12	52.63±0.15
10	54.34±0.56	56.91±0.13	64.48±0.53	62.05±0.88	64.62±0.56	62.05±0.87	69.76±0.11
12	62.76±0.32	63.79±0.45	78.82±0.13	75.85±0.16	76.88±0.87	95.65±0.32	78.940.34±

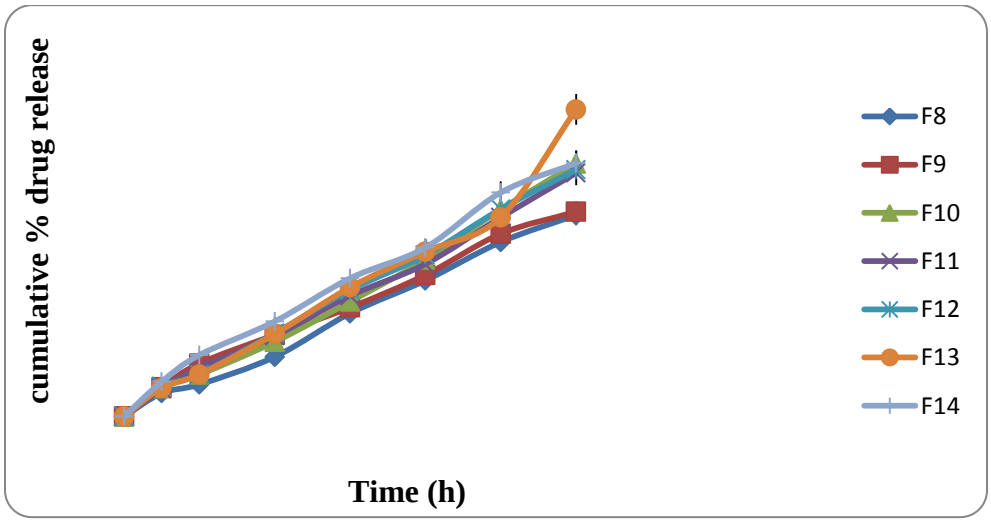

Figure 3: *In vitro* cumulative % drug release of Roxatidine acetate HCl floating microspheres

Release order kinetics of Roxatidine floating optimized formulation (F13)

Table 6: Release order kinetics of optimized formulation of floating microspheres

Formula	Zero Order		First Order		Higuchi		Korsmeyer	
Code	R^2	K	R^2	K	R^2	K	R^2	N
F13	0.995	7.753	0.879	0.089	0.931	27.79	0.997	1.008

From the above results, it is apparent that the regression coefficient value closer to unity in case of zero order plot i.e. 0.995 indicates that the drug release follows a zero order mechanism. Further, the translation of the data from the dissolution studies suggested possibility of understanding the mechanism of drug release by configuring the data in to various mathematical modeling such as Higuchi and Korsmeyer plots. The mass transfer with respect to square root of the time has been plotted, revealed a linear graph with regression value close to one i.e. 0.931 starting that the release from the matrix was through diffusion. Further the n value obtained from the Korsmeyer plots i.e. 1.008 suggest that the drug release from floating tablet was anomalous Non fickian diffusion.

Drug excipient compatibility studies:

Fourier Transform Infrared Spectroscopy (FTIR)

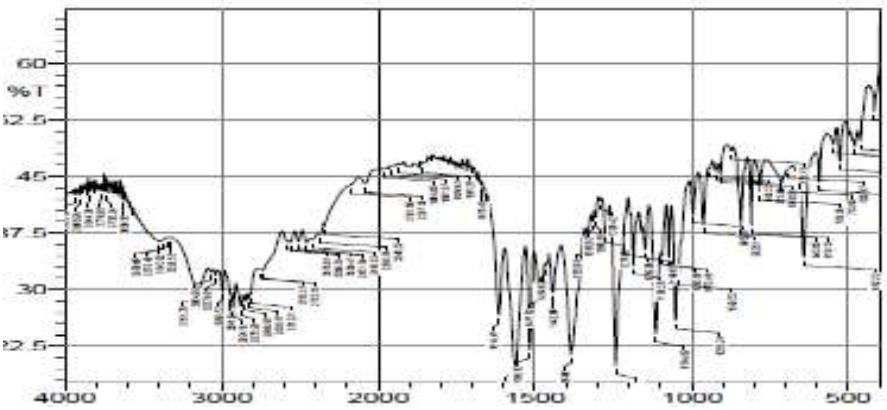

Figure 4: FT-IR spectrum of pure drug Roxatidine acetate HCl

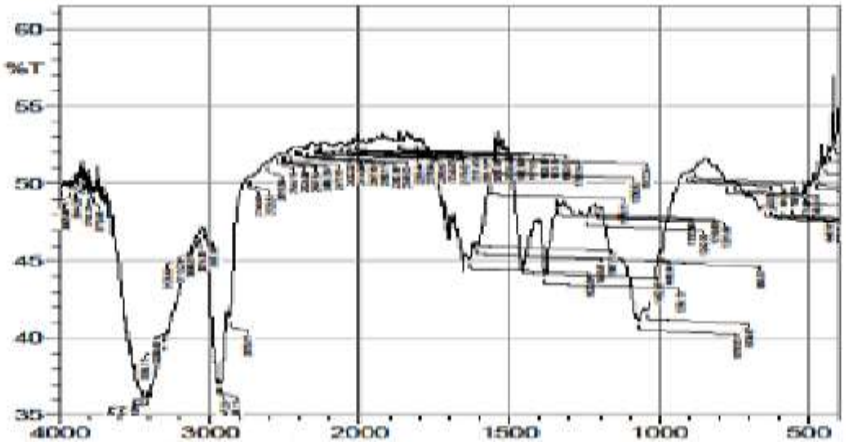

Figure 5: FTIR spectrum of Gum Olibanum

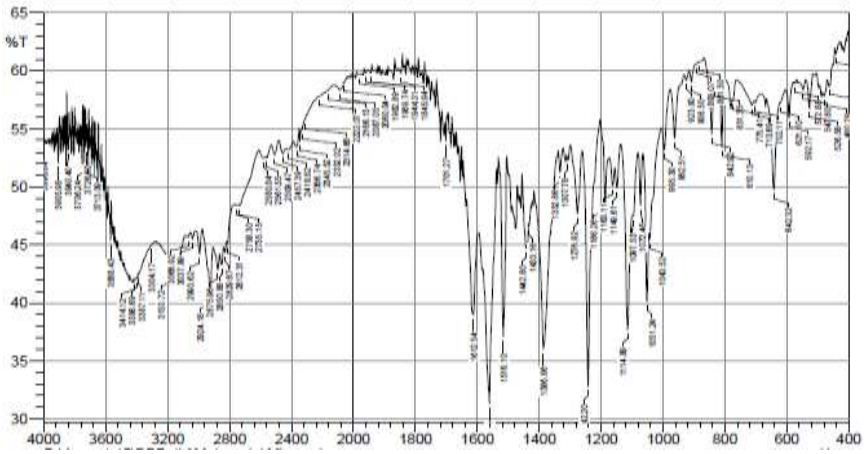

Figure 6: FT-IR spectrum of physical mixture

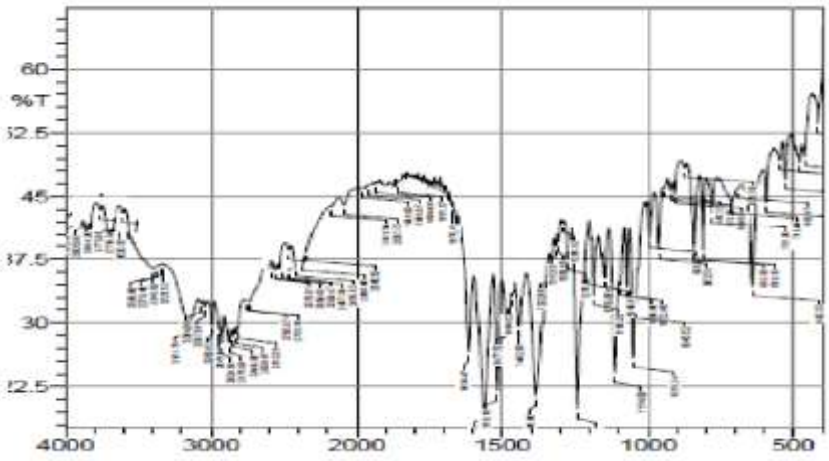

Figure 7: FT-IR spectrum of Roxatidine optimized formulation F13

FTIR was carried out to check the drug excipient interaction. The FTIR peak of Roxatidine acetate HCl is almost similar to that of the peak obtained with excipient and all the peaks of the functional group is in proper range. Hence, it can be concluded that the drug Roxatidine acetate HCl was found to be compatible with the excipient used in the designed formulation.

DSC Studies:

DSC was used to detect interaction between Roxatidine acetate HCl and excipients. The thermogram of pure Roxatidine acetate HCl **(**Figure 8) exhibited a sharp endotherm melting point at 147^{o}C. The thermogram of optimized microspheres loaded with Roxatidine acetate HCl (R9) exhibited a sharp endotherm melting point at150^{o}C (Figure 9). The DSC thermogram of microspheres loaded with Roxatidine acetate HCl retained properties of pure Roxatidine acetate HCl. There is no considerable change observed in melting endotherm of drug in optimized formulation. It indicates that there is no interaction between drug & excipients used in the formulation.

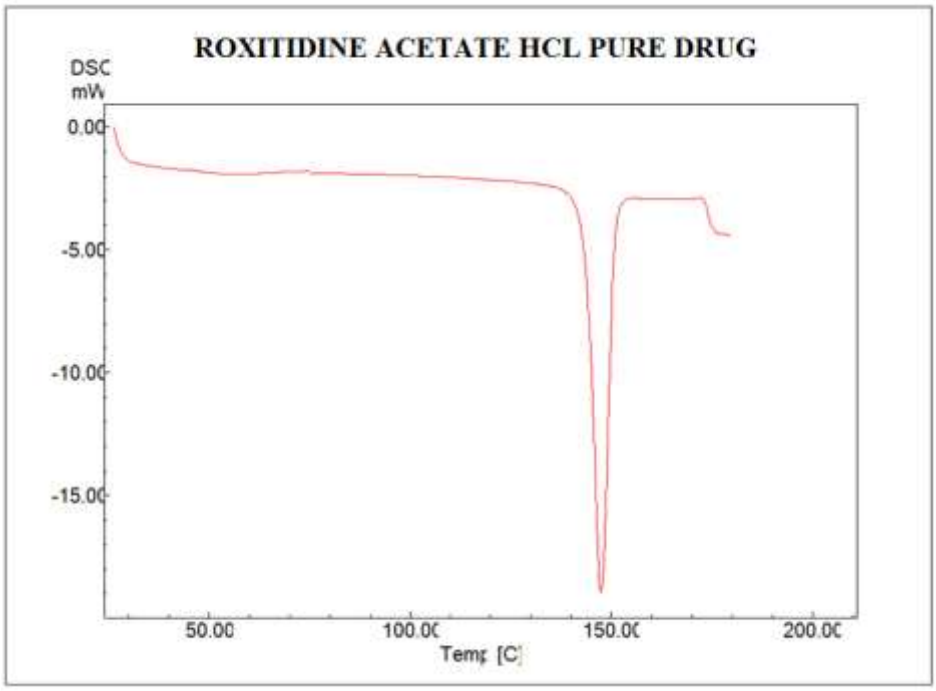

Figure 8: DSC thermogram of Roxatidine acetate HCl pure drug

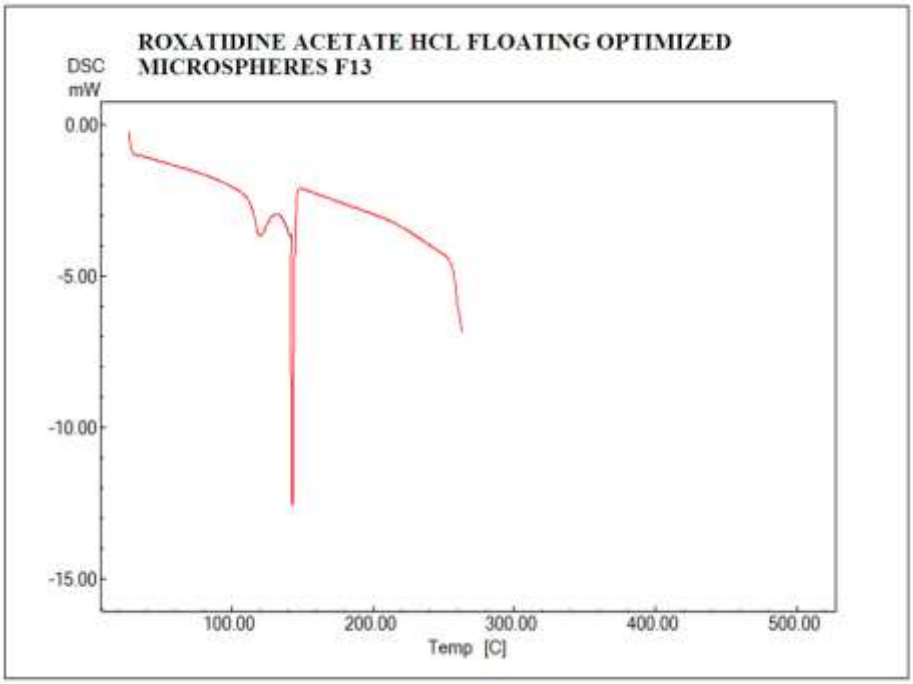

Figure 9: DSC thermogram of Roxatidine acetate HCl mucoadhesive optimized microspheres (M13)

Scanning electron microscopy studies:

SEM of Roxatidine acetate HCl Floating microspheres

The external and internal morphology of controlled release microspheres were studied by Scanning Electron Microscopy.

Roxatidine acetate HCl Floating microspheres:

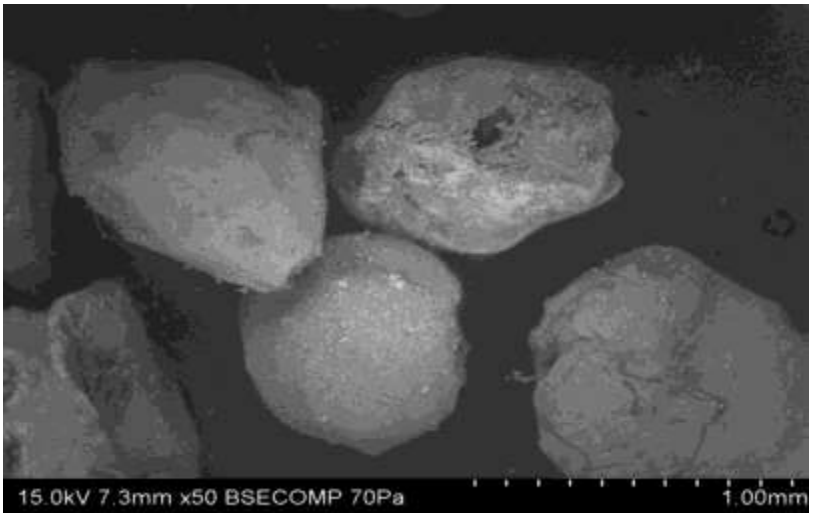

Figure 9: Scanning electron micrograph of Roxatidine acetate HCl floating microspheres

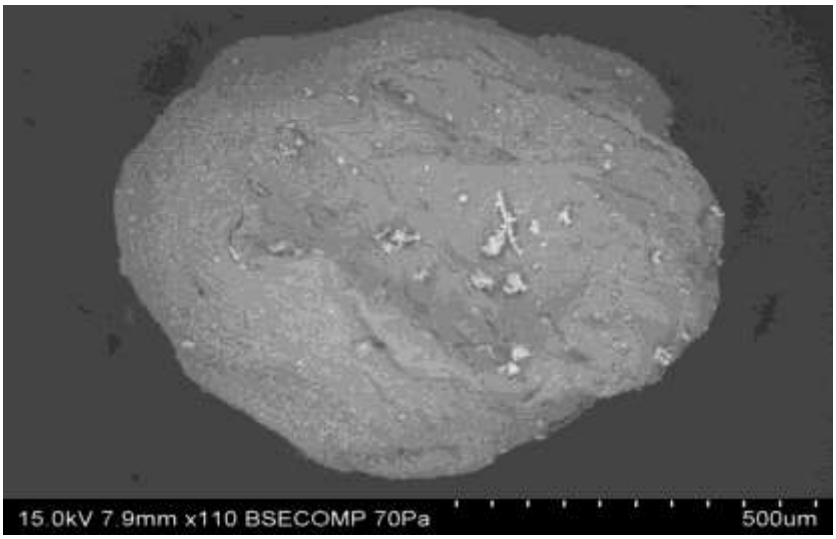

Figure 10: Scanning electron micrograph of Roxatidine acetate HCl floating microspheres

Morphology of the various formulations of Roxatidine acetate HCl microspheres prepared was found to be discrete and spherical in shape (Figure 9 & 10). The surface of the optimized floating Roxatidine acetate HCl microspheres (F13) was rough due to higher concentration of drug uniformly dispersed at the molecular level in the sodium alginate matrices. There are no crystals on surface which states that the drug is uniformly distributed.

Stability studies:

Optimized formulation (F13) was selected for stability studies on the basis of high cumulative % drug release. Stability studies were conducted by performing Percentage yield, % Entrapment efficiency and *In-vitro* drug release profile for 6 months according to ICH guidelines. From these

results it was concluded that, optimized formulation is stable and retained their original properties with minor differences.

CONCLUSION:

In the present study, an attempt was made to prepare different types of Roxatidine floating microspheres, which were characterized for particle size, scanning electron microscopy, FT-IR study, DSC, percentage yield, % drug entrapment, stability studies and found to be within the limits. Among all the formulations, F13 were selected as optimized formulation. *In vitro* release study of formulation F13 showed 95.65% after 12 hrs in a controlled manner. The *in vitro* release profiles from optimized formulation were applied on various kinetic models. The best fit with the highest correlation coefficient was observed in Higuchi model, indicating diffusion controlled principle. The innovator Rotane 150 mg conventional tablet showed the drug release of 96.45% within 1 hrs. FT-IR and DSC analyses confirmed the absence of drug-polymer interaction. From the results it can be concluded that the drug release from the floating microspheres was controlled by the polymer proportion. Prepared Roxatidine floating formulation showed best appropriate balance between buoyancy and drug release rate.

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