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Formulation Development and Evaluation of Rebamipide Floating Microspheres

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ABSTRACT

The aim of the current study was to formulate and characterize oral floating alginate microspheres of Rebamipide to sustain the gastric residence time and to target gastritis. The floating alginate microspheres were prepared by ionotropic gelation technique. Sodium alginate was used as polymer, sodium bicarbonate as gas generating agent, calcium chloride as cross-linking agent, HPMC K4, HPMC K15 as rate retarding agent. Microspheres were characterized for the Micromeretic properties, entrapment efficiency, buoyancy test, SEM analysis, FTIR, and *in vitro* release studies. The release studies were carried out in 0.1N HCl and the results were applied to various kinetic models. Among the total 14 formulations F12 was optimized. The % yield of F12 formulation was found to be 93.73%. On the basis of optical microscopy, the particle size was 79.45±0.09µm. The % buoyancy, % entrapment efficiency and swelling index of F12 formulation was 94.2%, 95.5% and 96.16, respectively. The Cumulative % drug release of F12 formulation was 96.12±0.22% in 12h when compared with marketed product 95.15±0.23 in 1h. SEM studies showed the particles were in spherical shape. Based on obtained results, floating alginate microspheres were of good candidate for targeting to GIT in the efficient management of gastritis.

Keywords: Rebamipide, Floating microspheres, gastritis, buoyancy, SEM studies,

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INTRODUCTION

Conventional oral dosage forms include tablets and capsules promised an immediate drug release, but they fail to sustain the concentration of drug within the therapeutic range for a required time period[1]. To retain successful drug concentration in plasma, these dosage forms should be administered repeatedly. Currently, there is need to overcome the problems associated with the conventional oral dosage forms[2]. Principally, controlled drug delivery systems (CDDS) consist of a reservoir of drug from which released the drug in GIT, in a programmed rate to sustain the drug absorption[3]. Drugs used in oral CDDS showed uniform absorption in the entire gastrointestinal tract. The drug absorption of oral controlled drug delivery varied the entire GIT and depends on several factors such as dissolution, solubility, pH, enzymes and microbial flora hence to localize the drug absorption one of the approach is floating drug delivery system. The Floating drug delivery system is also best approach to improve the bioavailability of those drugs, which are poorly absorbed from the intestine[4].

Rebamipide is an amino acid derivative used for the treatment of gastritis and also reduces the recurrence of gastric ulcers[5]. Nowadays, Rebamipide is commercially delivered in solid dosage form (tablets, capsules). Rebamipide in oral administration will significantly metabolize into its inactive metabolite within liver and colonic environment so the efficacy would be reduced as well. One approach to this problem would be control the Rebamipide release in upper GIT portion and avoid the formation of its inactive metabolite hence increases the bioavailability at insitu level. Sustained release formulation of Rebamipide microspheres via oral route will reduce the frequency of administration, as well as dose and dose-dependent side-effects during the management of gastritis[6].

Polymeric drug delivery system displays several advantages over the conventional dosage forms and it includes enhanced efficacy, patient compliance, reduced toxicity, and also to control the encapsulated drug release[7]. Sodium alginate is an anionic natural polysaccharide, prepared by mixture of D-mannuronic acid and L-glucuronic acid. Sodium alginate is extensively used as carrier for drug delivery due to its biocompatibility and low toxicity. Ionic gelation technique offers several advantages such as simple method of preparation no need to use of organic solvent, and, also easier to control. Sodium alginate could form gel in the presence of multivalent cations such as Ca2+, Zn2+, Ba2+ and Al3+ etc... by ionic cross-linking to form microspheres, it has been widely used in sustained drug release[8]. Hence in this study calcium chloride is selected as cross-linking agent and because of its nontoxic and biocompatibility[9]. HPMC K4 and HPMC K15 are

the commonly used polymers for the floating microspheres preparation by ionic gelation technique and sodium bicarbonate used as gas generating agent[10].

The objective of present work was Rebamipide loaded alginate floating microspheres were developed for GIT specific drug delivery. The prepared microspheres were characterized by incorporation efficiency, buoyancy, particle size, differential scanning calorimetry (DSC), Fourier-transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM) and *in vitro* release studies.

MATERIALS AND METHOD

Materials:

Rebamipide was procured as sample of gift from Daewoong Pharmaceutical Co. Ltd, Hyderabad, India. Sodium alginate and Sodium bicarbonate was used as polymer obtained from Pruthvi Chemicals, Mumbai. Calcium chloride was purchased from SD fine chemicals Mumbai, India. HPMC K4M and HPME K15M were purchased from Rubicon Labs, Mumbai, India. All other chemicals used were of analytical grade.

Formulation of Rebamipide Floating microspheres – Formulation design:

Sodium alginate as Microsphere core forming agent, Sodium bicarbonate as Gas generating agent, Calcium chloride as Cross-linking agent and HPMC K4, HPMC K15 as Rate controlling agent were used for the formulation of Rebamipide Microspheres.

Floating microspheres Preparation:

Microspheres containing anti-gastric ulcer drug as a core material were formulated by ionotropic gelation technique depicted in Table 1. Sodium alginate dissolved in distilled water at a concentration ranges from 1% to 2.2% w/v then solution was stirred thoroughly by magnetically. On complete solution, weighed quantities of Rebamipide followed by HPMC K4, HPMC K15 and sodium bicarbonate of different weights were added to the above dispersion. Then to form homogeneous dispersions the above mixture was stirred at 500rpm, maintained room temperature. The mixture was sonicated for 30min to eliminate air bubbles that may have been formed during the stirring process. The homogenous alginate solution was extruded using a 20 G needle fitted with a 10ml syringe into 100ml of 1% calcium chloride solution, being stirred at 100rpm for 10min into the gelation medium. The gel microspheres formed were left in the solution with gentle stirring for 10min at room temperature to be cured. After preparation of microspheres were collected, washed with distilled water and oven-dried subsequently (60°C) [11, 12].

Table 1: Formulation trials of Rebamipide Floating microspheres using HPMCK4 and HPMCK15:

Formulation code	Rebamipide (mg)	Sodium alginate	HPMCK4 (mg)	Sodium bi carbonate(mg)	Calcium chloride
F1	100	1%	50	25	1%
F2	100	1. 2%	75	50	1%
F3	100	1.4 %	100	75	1%
F4	100	1.6%	150	100	1%
F5	100	1.8 %	175	125	1%
F6	100	2.%	200	150	1%
F7	100	2.2%	200	175	1%
Formulation code	**Rebamipide (mg)**	**Sodium alginate**	**HPMC K15 (mg)**	**Sodium bi carbonate (mg)**	**Calcium chloride**
F8	100	1%	150	25	1%
F9	100	1. 2%	200	50	1%
F10	100	1.4%	250	75	1%
F11	100	1.6%	300	100	1%
F12	100	1.8%	350	125	1%
F13	100	2%	400	150	1%
F14	100	2.2%	450	175	1%

Evaluation parameters:

Micromeritic properties:

Micromeritic properties were used for the characterization of microspheres, such as particle size distribution, angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio[13].

Determination of swelling index:

For estimating the swelling index, the accurately weighed quantities of microspheres were suspended in simulated gastro intestinal fluids (0.1 N HCl with pH 1.2). The excess moisture of the swollen microspheres was removed by using blotting paper and then weighed it with the help of a microbalance. The swollen microspheres were dried in oven at 60°C for 5h or until showed the constant weight. The change in swelling of microspheres before and after drying was used to calculate the percentage of swelling index[14]. The following equation was used.

Swelling index= (Mass of swollen microspheres - Mass of dry microspheres/mass of dried microspheres) 100.

% yield of microspheres:

The prepared floating microspheres were collected and weighed[15]. The actual weight of obtained microspheres divided by total weight of added drug and polymer was used for the calculation of % yield and mentioned below.

% yield = [Total weight of microspheres / Total weight of drug and polymer] x 100

Entrapment efficiency:

To found out the entrapment efficiency of Rebamipide 10mg of floating microspheres were taken, crushed and dissolved in 50ml of methanol then transferred in to 100ml conical flask. The above solution was agitated to dissolve the drug and polymers and to extract the drug. Then solution was filtered using membrane filter (0.45µm) to separate shell fragments. The drug was estimated at the λmax of 227nm by using a double – beam spectrophotometer (Shimadzu, UV-1800). The incorporation efficiency was determined using the following equation.

% Drug entrapment = Calculated drug concentration / Theoretical drug concentration X 100

Test for buoyancy:

100mg of the microspheres were transferred to a USP type II dissolution test apparatus containing 900ml of simulated gastric fluid (0.1N HCl) and 0.02% of tween 20 was maintained at 37°C. The content of the beakers was stirred at 100rpm. The floating and non-floating microspheres were separated at different time intervals and dried until a constant weight obtained. Then the microspheres were weighed and percentage of buoyancy[16]. is calculated by using following equation.

Buoyancy (%) = Weight of floating microspheres/Initial weight of floating microspheres X 100

In vitro drug release:

In vitro drug release studies were conducted in 900ml of 0.1N HCl (pH 1.2) at 37 ±0.5°C by using USP dissolution apparatus II (Paddle type) for floating alginate microspheres. Accurately weighed quantity of floating microspheres were equivalent to 100mg of drug transferred into 900 ml of 0.1 N HCl (pH 1.2) medium maintained at 37±0.5°C and stirring at 100rpm. Aliquots of samples were withdrawn at specified time intervals, filtered and diluted with similar medium finally assayed at 227nm using UV-Visible spectrophotometer. The samples withdrawn were replaced with same dissolution medium at predetermined time intervals. All the samples were analyzed in triplicate[17].

Release order kinetics:

Drug release data of optimized floating microspheres formulation were fitted to various models to disclose the mechanism of drug release from the microspheres. Those include Zero order (% cumulative drug release vs. time), first order (log % drug release vs. time), Higuchi model (% cumulative drug release vs. square root of time) and Korsmeyer-Peppas exponential equation (log % drug release vs. log time). All curve fitting, and plotting procedure was carried out using Microsoft excel software and r^2 values were calculated[18].

Drug - excipient compatibility studies:

Fourier Transform Infrared Spectroscopy (FTIR):

The FTIR technique can be used to identify the functional groups in the pure drug and drug-excipient compatibility. Pure Rebamipide FTIR spectra, physical mixtures and optimized formulation were recorded by using FTIR (SHIMADZU). Weighed quantity of KBr and excipients were taken in the ratio 100: 1 and mixed by mortar. The samples were made into pellet by the application of pressure[19]. Then the FTIR spectra were recorded between 4000 and 400 cm^{-1}

SEM studies:

Surface nature of microspheres includes size and shape was examined with the help of Scanning Electron Microscope (HITACHI, S-3700N). The microspheres were dried completely prior to analysis and SEM was carried out at different magnifications of 15.0 kv × 7.6mm, 15 kv x 6.6mm, 15Kv x 7.0mm.

Stability studies:

Optimized formulation such as F12 alginate floating microspheres were subjected to stability testing at 40°C ± 2°C/75% RH ± 5% RH for 6months using stability chamber (Thermo Lab, Mumbai). Samples were withdrawn at predetermined intervals 0, 30, 60, 120, and 180 days period according to ICH guidelines. Various in vitro parameters like % yield, entrapment efficiency and *in vitro* release studies were evaluated[20].

RESULTS AND DISCUSSION

Floating microspheres: The prepared floating microspheres were shown in Figure 1.

Figure 1: Rebamipide floating microspheres.

Tables 2 showed the micromeritic properties and physical parameters of various formulations and were found within the limits. From all the above results F12 was found to be best formulation when compared with other formulations. Comparatively, the % buoyancy and particle size was also found to be 94.2% and 79.45±0.09µm, respectively.

Table 2: Micromeretic properties of Rebamipide floating microspheres:

Formulation code	Particle size (µm)	Bulk density g/cc^3	Tapped density g/cc^3	Angle of repose	Carr's index	Buoyancy %
F1	60.05±0.04	0.69±0.13	0.65±0.21	25˚.93±0.33	13.56±0.24	81.2±0.11
F2	60.12±0.08	0.66±0.11	0.59±0.16	24˚.74±0.17	11.34±0.22	84.5±0.18
F3	65.29±0.13	0.74±0.23	0.62±0.38	29˚.67±0.25	10.34±0.16	85.3±0.23
F4	67.43±0.04	0.76±0.32	0.63±0.17	25˚.03±0.16	14.36±0.34	92.1±0.37
F5	73.35±0.04	0.79±0.21	0.73±0.29	29˚.74±0.37	8.12±0.26	88.64±0.15
F6	79.67±0.09	0.87±0.02	0.76±0.26	30˚.15±0.08	7.23±0.15	89.4±0.28
F7	84.45±0.09	0.89±0.31	0.82±0.11	25˚.54±0.22	13.95±0.36	87.1±0.32
F8	55.23±0.14	0.65±0.16	0.63±0.14	22˚.91±0.03	10.32±0.28	72.5±0.17
F9	71.22±0.11	0.67±0.33	0.74±0.22	25˚.70±0.34	11.03±0.19	75.8±0.22
F10	73.34±0.10	0.68±0.24	0.75±0.19	30˚.24±0.21	12.34±0.25	76.4±0.39
F11	78.45±0.21	0.74±0.15	0.82±0.27	24˚.91±0.11	11.90±0.33	85.3±0.13
F12	79.45±0.09	0.57±0.17	0.53±0.33	20˚.60±0.28	9.032±0.29	94.2±0.26
F13	80.23±0.19	0.85±0.34	0.83±0.20	25˚.54±0.35	10.34±0.17	89.4±0.34
F14	81.67±0.13	0.89±0.27	0.74±0.11	25˚.91±0.17	13.94±0.23	92.2±0.19

Entrapment efficiency, Percentage yield and Swelling index:

Among the 14 formulations F12 formulation showed the higher % yield, incorporation efficiency and Swelling index i.e. 93.70%, 95.5% and, 96.1%. The results were shown in Table 3.

Table 3: Percentage yield, incorporation efficiency, swelling index of Rebamipide microspheres:

Formulation code	Percentage Yield (%)	Incorporation Efficiency (%)	Swelling index (%)
F1	80.24±0.12	80.92±0.34	80.13±0.22
F2	85.61±0.23	84.83±0.22	84.21±0.17
F3	86.39±0.35	81.17±0.18	86.72±0.32
F4	87.42±0.27	90.36±0.21	89.17±0.05
F5	89.37±0.10	87.25±0.37	88.62±0.26
F6	90.20±0.21	90.17±0.16	91.86±0.33
F7	84.17±0.34	83.31±0.23	87.92±0.15
F8	81.46±0.26	84.33±0.32	82.81±0.21
F9	86.52±0.19	82.19±0.19	79.57±0.30
F10	89.60±0.34	88.28±0.27	86.42±0.16
F11	90.12±0.17	89.12±0.35	84.30±0.23
F12	93.73±0.23	95.50±0.17	96.16±0.34
F13	82.38±0.33	85.20±0.02	83.54±0.14
F14	83.32±0.18	86.88±0.27	87.61±0.22

In vitro release:

The release of Rebamipide from the developed floating microspheres was studied in 0.1N HCl upto 12h. Since the alginate microspheres insoluble in acidic medium, the microspheres retained their integrity during *in vitro* diffusion studies. The cumulative % drug release for F12 formulation was found to be 96.12±0.22% at the end of 12h. The innovator product showed the drug release 95.15±0.23% with in 1h. The results were shown in Table 4 & 5, Figure 2 & 3.

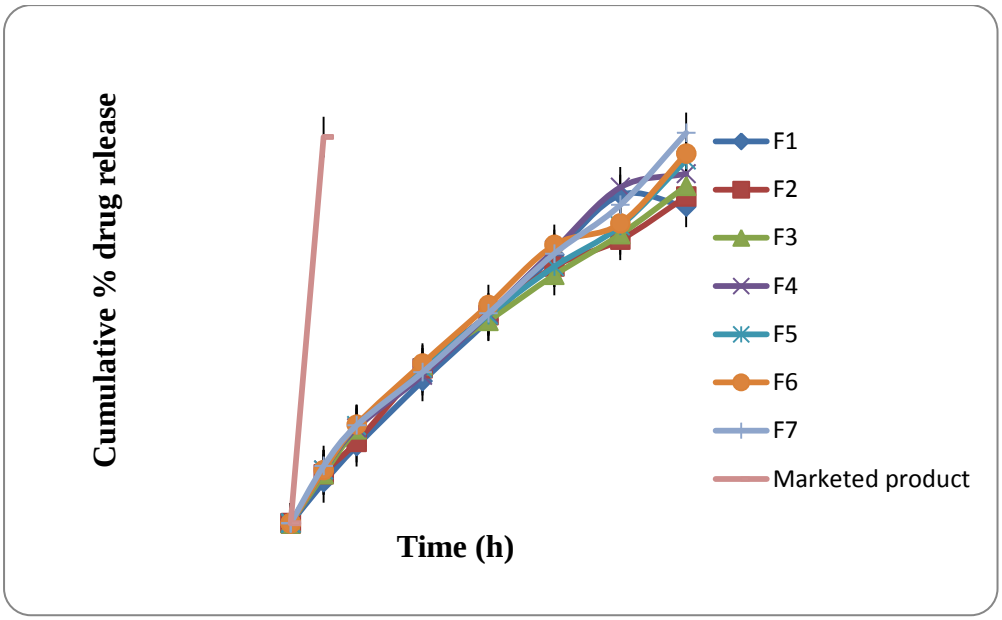

Figure 2: In vitro Cumulative % drug release of Rebamipide floting microspheres F1to F7 and marketed product

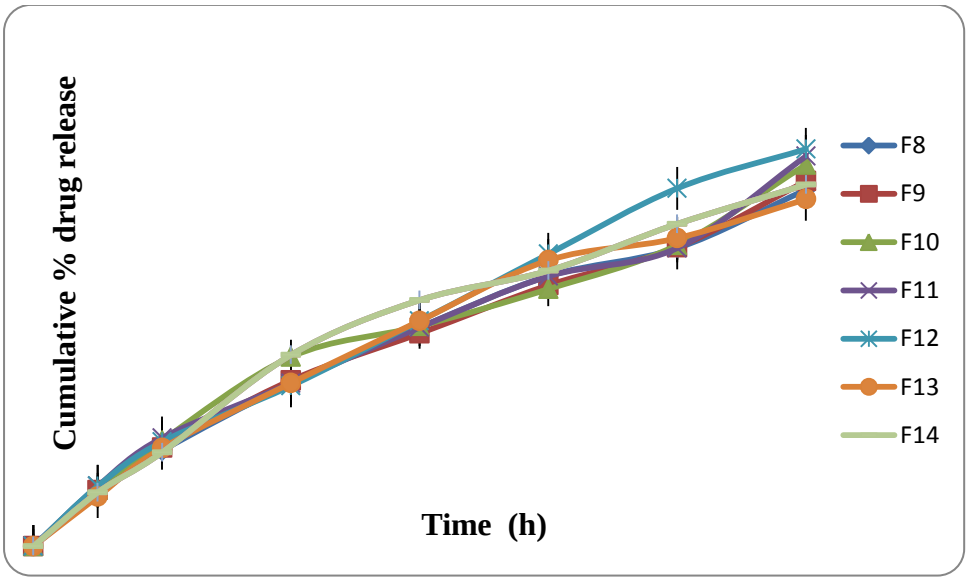

Figure 3: In vitro Cumulative % drug release of Rebamipide floating microspheres formulation F8 to F14

Table 4: In vitro Cumulative % drug release of Rebamipide floting microspheres F1to F7 and marketed product (Rebagen 100mg immediate release)

Time (h)	F1	F2	F3	F4	F5	F6	F7	Marketed product
0	0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0
1	10.45±0.24	12.67±0.16	12.8±0.22	12.10±0.15	13.34±0.22	16.10±0.17	14.31±0.12	95.15±0.23
2	24.5.7±0.15	25.23±0.17	23.41±0.21	20.50±0.15	25.12±0.16	24.30±0.21	21.15±0.21	
4	35.08±0.26	38.20±0.15	38.95±0.24	36.50±0.22	38.28±0.15	39.40±0.11	37.23±0.52	
6	50.92±0.25	51.34±0.23	49.95±0.21	51.60±0.21	51.36±0.12	53.80±0.23	51.73±0.14	
8	66.25±0.24	63.33±0.22	61.26±0.25	67.49±0.24	63.38±0.22	68.60±0.21	66.46±0.22	
10	70.90±0.15	69.99±0.21	71.21±0.12	82.80±0.19	73.39±0.15	73.90±0.24	78.45±0.23	
12	81.03±0.16	85.52±0.25	87.15±0.16	88.17±0.18	89.54±0.16	91.07±0.25	89.23±0.21	

Table 5: In vitro Cumulative % drug release of Rebamipide floating microspheres formulation F8 to F14

Time	F8	F9	F10	F11	F12	F13	F14
0	0±0	0±0	0±0	0±0	0±0	0±0	0±0
1	15.32±0.21	13.43±016	14.55±0.132	15.09±0.11	11.40±0.12	13.62±0.21	12.63±0.21
2	25.45±0.12	23.55±0.18	24.85±0.22	25.48±0.21	21.05±0.21	23.01±0.21	22.01±0.31
4	37.25±0.13	38.89±0.16	44.43±0.17	38.26±0.15	36.66±0.22	38.24±0.13	44.83±022
6	50.33±0.15	49.69±0.18	51.6±0.21	51.13±0.14	51.18±0.24	52.83±0.21	57.47±0.15
8	61.35±0.21	62.24±0.16	60.3±0.24	63.03±0.22	67.58±0.21	67.03±0.15	64.46±0.51
10	67.09±0.16	70.18±0.18	70.06±0.21	72.69±0.21	82.79±0.23	72.22±0.15	75.56±0.24
12	83.56±0.21	85.56±0.18	87.45±0.21	89.42±0.25	96.12±0.22	88.36±0.16	87.17±0.16

Table 6: Release order kinetics of optimized floating microspheres:

Formulation Code	Zero Order	First Order	Higuchi	Korsmeyer-Peppas	
	R^2	R^2	R^2	R^2	n
F12	0.976±0.0217	0.866±0.0116	0.962±0.0183	0.989±0.0205	0.834±0.04

Table 7: Staility studies of optimized floating microspheres:

Retest Time For Optimized formulation (F12)	Percentage yield (%)	Entrapment efficiency (%)	*In-vitro* drug release profile (%)
0 days	93.73±0.137	95.50±0.219	96.12±0.120
30 days	92.66±0.212	94.68±0.161	95.46±0.215
60 days	91.53±0.164	93.17 ±0.122	94.73±0.104
120 days	93.12±0.220	94.43±0.239	93.42±0.259
180 days	92.23±0.348	92.45±0.187	95.18±0.302

Release order kinetic studies:

The drug release of F12 Formulation showed the zero order and Korsmeyer-Peppas model. The optimized formulation n value was 0.834 indicating non fickian (anomalous) transport thus it projected that delivered its active ingredient by coupled diffusion and erosion. The marketed

conventional formulation followed the first order kinetics indicating drug release is directly proportional to the concentration of drug.

Drug - excipient compatibility studies:

Fourier Transform Infrared Spectroscopy (FTIR):

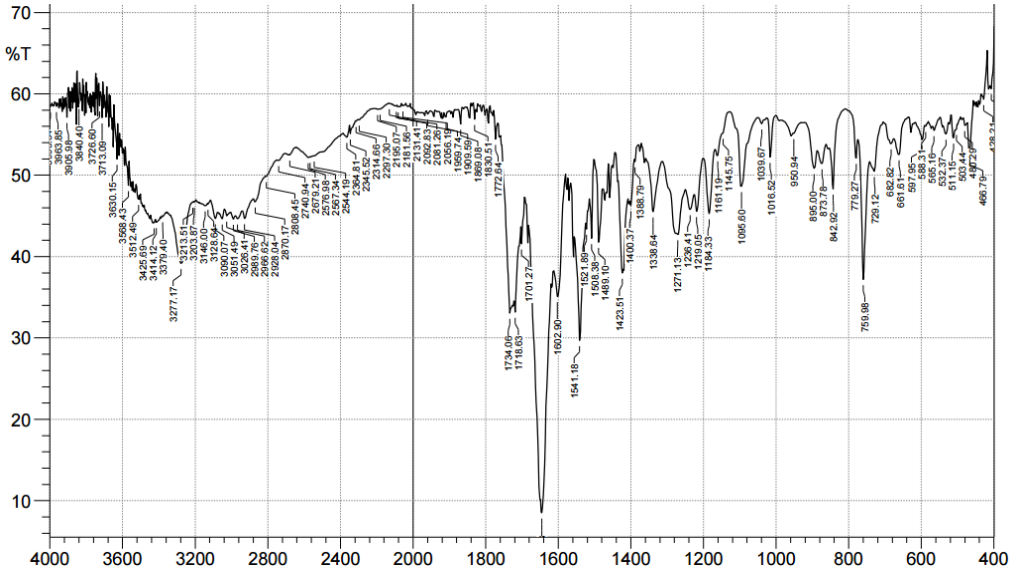

Figure 4: FT-IR spectrum of pure drug Rebamipide

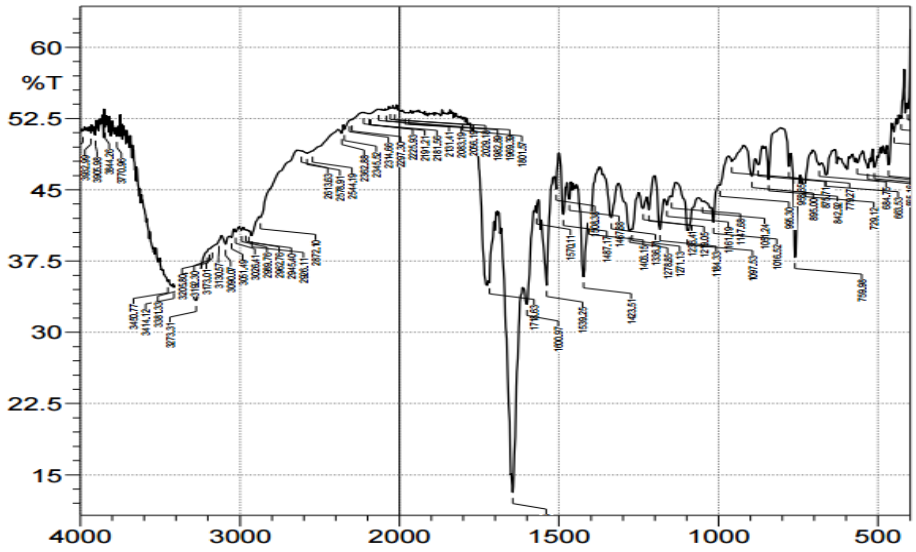

Figure 5: FT-IR spectrum of Rebamipide optimized formulation (F12) of floating microspheres

There were no new significant bands observed in the pure drug of Rebamipide (Figure 4) and optimized formulation (Figure 5), which confirms that no interaction between the drug and the polymers.

SEM studies:

The SEM photomicrographs of the dried floating microspheres were shown in Figure 6. The shape of optimized formulation microspheres seems to be spherical with hollow outer surface.

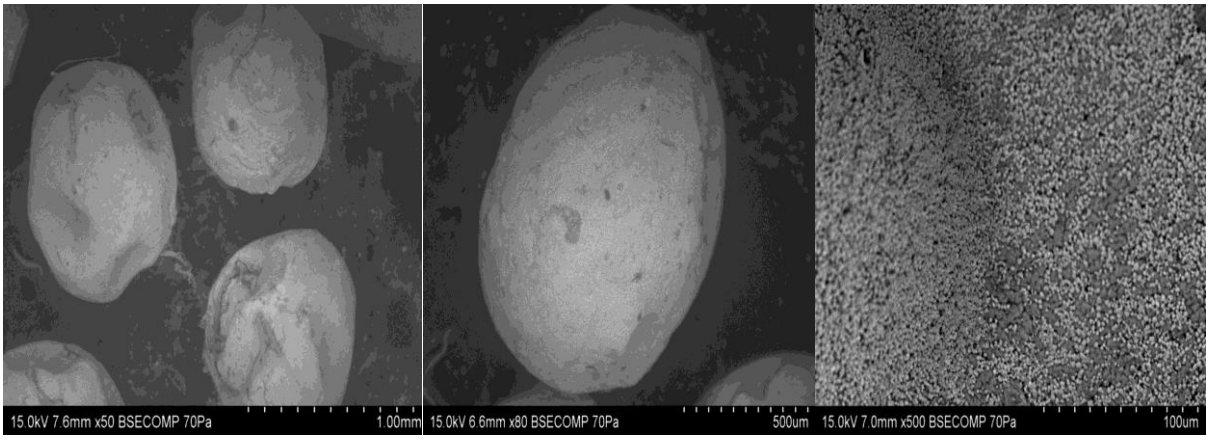

Figure 6: Scanning electron micrographs of optimized floating microspheres

Stability studies:

Table 7 showed the stability of optimized rebamipide microspheres as per ICH guidelines and analysis was carried out for 6months at 40°C ± 2°C/75% RH ± 5% RH. At specified time intervals samples were withdrawn and subjected to % yield, entrapment efficiency and *in vitro* drug release analysis. Finally, observed that there was no significant change in results before and after stability studies hence the optimized formulation found stable.

CONCLUSION

The novel floating microspheres were prepared by ionotropic gelation technique for prolonged as well as stomach specific delivery of Rebamipide, which showed the good floating ability. The formulation of Rebamipide loaded sodium alginate and HPMC K4 and HPMC K15 microspheres were effectively prepared. Various investigations on formulation, characterization, *in-vitro* release study were carried out and performance of the formulation was evaluated. Comparatively, F12 formulation displayed better results than marketed product. Hence it clearly indicated floating microspheres was a successful way to sustained drug release.

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