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Original Article

Design and Development of Rebamipide Solid Dispersion-Loaded Floating Beads for Ameliorated Therapeutics

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ABSTRACT

Objectives: Rebamipide, a gastroprotective drug, is used for preventing and treating ulcers but it has low aqueous solubility leading to poor bioavailability (10%). It acts both locally and systemically to provide gastroprotection and ulcer healing effects. The therapeutics of Rebamipide can be improved by enhancing its aqueous solubility and by sustaining its release in the stomach. **Materials and Methods:** The above objective was fulfilled by preparing solid dispersion of Rebamipide by solvent evaporation method for aqueous solubility enhancement which was incorporated in floating beads by emulsion gelation method using different concentrations of sodium alginate and olive oil for prolonged gastroretention. The beads were characterized for size, swelling, entrapment efficiency, floating lag time, floating time and *in-vitro* drug release. **Results and Discussion:** The solubility of rebamipide in solid dispersion was found to be 18.66 mg/mL which was much greater than its normal value (1.3 µg/mL). The size of beads varied between 2.03 mm-2.52 mm. The swelling index was found to be 12-28%. Entrapment efficiency was 90.1-96.9% proving excellent entrapment of drug by the method chosen. Floating lag time of optimized formulation (F6) was 3 sec with 90.2% drug release at 12 hr showing adequate sustenance of drug release. **Conclusion:** The solid dispersion loaded floating beads would prove effective in preventing and treating stomach ulcers because of enhanced aqueous solubility of drug in solid dispersion form resulting in higher drug concentration in gastric fluid, sustained release of drug and greater gastroretention time, giving improved therapeutics both locally and systemically.

Keywords: Peptic Ulcer, Rebamipide, Poloxamer 407, Solid Dispersion, Floating Beads.

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INTRODUCTION

Gastroretentive drug delivery is a method of extending the time a medication remains in the stomach, allowing it to achieve site-specific drug delivery in the proximal Gastrointestinal Tract (GIT) for local or systemic effects.[1] It is also used for drugs with an absorption window in the stomach or proximal part of the small intestine or for pharmaceuticals that are poorly soluble or undergo deterioration in intestinal fluid. A Floating Drug Delivery System (FDDS) can be an approach for prolonging gastroretentive time. The considerable fluctuation of the GI transit time of single-unit tablets or capsules limits their usage making multiple-unit dosage forms a suitable choice because they decrease inter- and intra-subject variability in drug absorption and also the possibility of dose dumping.

Gastroretentive Drug Delivery Systems (GRDDS) are especially useful for treating ulcers which are caused by inflammation in the gastric mucosa resulting in a local defect or excavation in it.[2] Ulcers are a result of an imbalance between aggressive (acid, pepsin, H. pylori, and NSAIDs) and defensive factors (mucus bicarbonate, blood flow and prostaglandins).[3] The control of gastric acid secretion is regarded as a prime therapeutic target in ulcer management in addition to the use of cytoprotective agents, H2 blockers and proton pump inhibitors.

Rebamipide, a gastroprotective drug, belongs to BCS class IV (low solubility, low permeability), possessing poor aqueous solubility and low oral bioavailability (less than 10%). It is usually given in the dosage of 100 mg, thrice daily. This medication acts by cell preservation and tissue replacement and increases prostaglandin production in the gastric mucosa, which improves the quality of ulcer healing. It also shields the gastric mucosa from noxious and ulcerogenic factors.[4]

Rebamipide stimulates tissue regeneration by increasing the expression of EGF and its receptors which promote angiogenesis,

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formation of granulation tissue, and epithelialization of ulcer.[5,6] It enhances mucosal defense against gastric acid and also possesses an inhibitory effect on gastric cancer growth. Thus, Rebapimide can be considered a relatively safe drug for long-term treatments sans the more serious side effects (like increased risk of *Clostridium difficile* infection, pneumonia, gastric cancer, bone fractures, and cognitive impairment) associated with proton pump inhibitors and H2 receptor antagonists, and was therefore the drug of choice for the present study. It is a weakly acidic drug showing pH-dependent solubility resulting in low solubility in the acidic gastric medium. It has both systemic and local action and acts in the gastrin mucin and mucosa for providing gastroprotection and ulcer healing. Therefore, increasing the local concentration of the drug in the stomach and prolonging its gastric retention would improve the therapeutics of the drug not only locally but systemically as prolonged high concentration would augment local effect as well as systemic absorption.

Several approaches have been investigated for overcoming the challenge of poor bioavailability of Rebamipide in the treatment of gastric ulcers like formulation of mucoadhesive tablets, floating tablets, mucoadhesive alginate based beads, mucoadhesive microspheres, floating microspheres, Solid Lipid Nanoparticles (SLN), but they presented one or the other drawbacks viz use of specialized, sophisticated, expensive equipment or polymers (SLN), difficult to attain size (microspheres and SLN), use of organic solvents (SLN), variability in gastrointestinal transit time and risk of dose-dumpimg (floating and mucoadhesive tablets).[7-12] This investigation attempts to overcome these shortcomings by formulating Rebamipide solid dispersion loaded alginate based floating beads. The novelty of the present work lies in the use of simple, inexpensive and easily available equipment, use of biocompatible economical polymer and absence of organic solvents. Being a multi particulate system, there would be minimum inter and intra subject variability in drug absorption and gastrointestinal transit time and reduction in the likelihood of dose dumping.

In the current study, the challenge of low aqueous solubility was overcome by preparing solid dispersion of rebamipide with a suitable polymer as solid dispersions have been widely used for solubility enhancement because of their amorphous nature.[13] Further the solid dispersion of drug with enhanced solubility was incorporated in floating multiple unit system, beads, to prolong gastric retention so as to augment local action and to provide sustained release for decreased dosing frequency. This would result in high local concentration of drug in stomach and prolonged and sustained action, also decreasing the frequency of dosing. Multiple unit floating drug delivery system was preferred over single unit ones to minimize the fluctuation in GI transit time associated with them.

Thus, the study was undertaken with the objective of enhancing solubility of rebamipide by formation of solid dispersion and incorporation of solid dispersion of drug in floating beads for prolonged gastric residence time.[14]

MATERIALS AND METHODS

The drug rebamipide was purchased from BLD Pharmatech (India) Pvt. Ltd., Poloxamer 407, HPMC E 15 LV were purchased from Yarrow chemical Products. Methanol, hydrochloric acid, and Sodium alginate were purchased from Rankem; Olive oil was purchased from Aceites Del Sur-color, S.A.Seville-Spain. Calcium chloride was procured from Fisher Scientific.

Methods

Solubility of Rebamipide

The determination of solubility of Rebamipide was conducted in 0.1 NHCl by employing the equilibrium solubility method. The drug, in excess was added to the volumetric flask containing the solvent. The flask was kept in an incubator shaker maintained at 37°C and shaken for 72 hr at 300 rpm.[15] Filtration of the obtained sample was done through Whatman filter paper and the resulting filtrate was diluted (if necessary) and analyzed using UV-visible spectrophotometer at a λ_{max} of 244 nm. The amount of drug dissolved in the acid was calculated using the regression equation obtained from the previously prepared calibration curve in 0.1 N Hydrochloric acids.

Preparation and Characterization of Rebamipide Solid Dispersion

Rebamipide has low solubility leading to poor bioavailability (10%). Solid dispersion of Rebamipide was prepared using solvent evaporation method. Rebamipide and Poloxamer 407 were weighed in the ratio 1:1, 1:3, 1:5, 1:7, 1:9. Methanol (50 mL) was added to dissolve Rebamipide and Poloxamer407. The solvent was dried in a rotary evaporator at 45-48°C and the semi-solid residue obtained was further dried in a vacuum oven. The resulting samples were pulverized in mortar and pestle and the solid dispersions of rebamipide were placed in desiccators until further use.[16]

Fourier Transform Infra-Red Spectroscopy (FTIR)

FTIR study was performed to determine the authenticity of the drug sample and to ascertain its compatibility with the excipients. The FTIR spectrum of sample was obtained using ATR FTIR Spectrophotometer (Make: Agilent technologies; Model: Carry 600 series). 10 mg of drug was directly placed on the sample compartment (made up of selenium coated diamond) and the spectrum was obtained in the range of 4000-650 cm^{-1} at a resolution of 8 cm^{-1} for the characterization of chemical functional groups.

Differential Scanning Calorimetry (DSC)

A differential scanning calorimeter (TA Instrument USAQ10) was used for determining the drug form before and after formation of solid dispersion. 3 mg samples were accurately weighed and placed in standard aluminium pans with lids. The sample's phase transition was studied at 10°C/min heating rate from 5°C to 350°C with a nitrogen purge rate of 20 mL/min.

X-ray Powder Diffraction (XRD)

XRD was performed to establish the crystalline or amorphous characteristics of the drug. The XRD of samples was done using an X-ray diffractometer (Xpert Pro, PANanalytical, The Netherlands) using Nickel-beta filter, copper Kα radiation, at a voltage of 45kV and a current of 40mA. The diffraction pattern was recorded in a step scan model over an angle range of 3°<2q<45°, with a step size of 0.02°.

Preparation of Floating Beads of Solid Dispersion of Rebamipide

The floating beads were formulated by emulsion gelation method using olive oil. Accurately weighed hydroxypropyl methyl cellulose was transferred to a beaker having distilled water for soaking it overnight. Sodium alginate was added to this dispersion with stirring. Prepared solid dispersion of drug was added to the polymer solution with continuous stirring. The required quantity of olive oil was also added to it with constant agitation. The emulsion so formed was added drop-by-drop through a 16 gauge needle into the calcium chloride solution (4% w/v) at 100 rpm agitation until all the emulsion was added. The formed beads were allowed to remain in the solution for 10 min for curing before separation and washing with distilled water. The collected beads were allowed to dry at room temperature and stored in desiccators till further investigation. Nine batches of beads were formulated by altering the concentration of sodium alginate and olive oil[17] (Table 1).

The concentration of calcium chloride for cross linking was optimized at 4% w/v level for use during emulsion gelation method.

Characterization and Optimization of Floating Beads of Rebamipide

Optical microscopy study

The size of drug-loaded beads was assessed by using an optical microscope equipped with a calibrated ocular and stage micrometer. Fifty particles from nine different formulations were studied and average calculated for 50 beads was reported as mean±SD.[18]

Percentage yield

The weight of the batch of beads was determined. The observed weight was divided by the sum of all non-volatile components used in the bead preparation.[19]

$$Percentage\ yield = \frac{Total\ weight\ of\ dried\ beads}{Total\ weight\ of\ raw\ material} \times 100 \quad \text{---- eq. 1}$$

Entrapment Efficiency of Beads

Beads containing drug equivalent to 100 mg were used for testing. The quantity of entrapped drug was calculated by crushing the beads and extracting the solid dispersion with aliquots of 0.1 N HCl. The extract was transferred to a 100 mL volumetric flask and diluted with 0.1N HCl. Filtration of the solution was done and its absorbance measured at λ_{max} of 244 nm against blank. The following formula was used to calculate the amount of drug entrapped in the beads.[20]

$$Entrapment\ efficiency = \frac{Practical\ drug\ content}{Theoratical\ drug\ content} \times 100 \quad \text{---- eq. 2}$$

In vitro Buoyancy Study

The formulated beads were studied for buoyancy and floating time using USP dissolution apparatus type II having 900 mL of 0.1 N HCl. 100 beads of each formulation were added to the medium which was agitated with a paddle at 50 rpm. The beads' floating and settled portion was segregated and counted separately. The percentage buoyancy was calculated as the ratio of the number of the floating beads to the total number of beads.[21]

$$F(\%) = \frac{N_F}{N_T} \times 100 \quad \text{---- eq.3}$$

Where,

F =floating percent.

N_F=the number of floating beads.

N_T=the number of total beads.

Buoyancy Lag Time

The buoyancy lag time were measured in 100 mL beaker containing 0.1 NHCl solution. The method given by Adeibisi *et al.* was used with some modification. Hundred beads were added to the beaker and the time taken by beads to come up to the surface and float was considered as buoyancy lag time.[22]

Swelling Index

The swelling characteristics of beads were studied in 0.1 NHCl. 250 mg beads were taken in a dissolution basket. The basket along with the beads was immersed in a dissolution flask containing 900 mL of 0.1 NHCl maintained at 37°C. After 12 hr beads were removed and weighed after blotting for removal of excess moisture.[23]

$$Swelling\ index = \frac{Final\ weight\ of\ beads - Initial\ weight\ of\ beads}{Initial\ weight\ of\ beads} \times 100 \quad \text{.....eq.4}$$

Table 1: Composition of Rebamipide floating beads.

Sl. No.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Sodium alginate (%)	1	1	1	2	2	2	3	3	3
2	HPMC (mg)	100	100	100	100	100	100	100	100	100
3	Solid dispersion of Drug (mg)	200	200	200	200	200	200	200	200	200
4	Olive oil (%)	7.5	10	12.5	7.5	10	12.5	7.5	10	12.5
5	Water (mL)	100	100	100	100	100	100	100	100	100

In vitro Drug Release Study of Floating Beads

The study of *in vitro* drug release for beads was performed in 900 mL of 0.1 N HCl taken as dissolution medium (pH-1.2) at 50 rpm and 37°C in a USP dissolution apparatus Type II. 5 mL sample was taken every hour for 12 hr, similar volume of fresh medium was replenished to maintain sink conditions. Samples were analyzed spectrophotometrically at a wavelength of 244 nm and an appropriate regression equation was used to calculate the release of drug with respect to time. The drug release calculated was plotted against time to obtain the dissolution profile.[21]

Drug Release Kinetics

The *in vitro* drug release data was subjected to kinetic study to ascertain the drug release mechanism. The drug release data was fitted into Zero order (cumulative % drug release vs. time), first order (log % drug release vs. time), Higuchi (cumulative % drug release vs. square root of time) and Korsmeyer-Peppas models (log% drug release vs. log of time) to find the mechanism of drug release.[23] The model giving the highest R^2 value was accepted as the best fit model.

Scanning Electron Microscopy (SEM)

Surface morphological analysis of optimized batch of beads was performed using a SEM (JSM-690 V Jeol Japan) equipped with a secondary detector at a 15.0 kV accelerated voltage. In a vacuum evaporator, gold coating was done on the sample to a thickness of about 30 nm for SEM analysis.

Accelerated Stability Study

Optimized formulation of floating beads underwent stability testing at 40°C±2°C/75% RH±5% RH for a period of 3 months. The samples at different time intervals were assessed for physical appearance, size, *in vitro* buoyancy, buoyancy lag time, % entrapment efficiency.[24]

RESULTS AND DISCUSSION

Solubility of Rebamipide

In 0.1NHCl, the solubility of rebamipide was found to be 1.3 µg/mL, which corroborates with the value reported in literature. Being a weakly acidic drug, its solubility is pH dependent.

Table 2: Solubility of solid dispersion of Rebamipide.

Sl. No.	Drug: polymer	Solubility in 0.1 NHCl*±SD (mg/mL)
1	1:1	18.66±0.4
2	1:3	5.16±0.5
3	1:5	1.604±0.5
4	1:7	1.132±0.6
5	1:9	1.745±0.1

Value represents, mean±SD, where n*=3.

As reported in literature, it is practically insoluble in aqueous medium at acidic pH but as the pH is increased it becomes slightly soluble. A calibration curve of the drug was prepared in 0.1 N hydrochloric acid and the regression equation used for determination of solubility was

$$y=0.0525x+0.0404$$

with an R^2 of 0.998.

Preparation and Characterization of Solid Dispersion of Rebamipide

Rebamipide and Poloxamer407 were used in the ratio of 1:1, 1:3 1:5, 1:7, and 1:9 for preparing solid dispersion by solvent evaporation method. This method was selected as it was easily applicable and simple and the drug was not subjected to high temperature or pressure.

Solubility of Solid Dispersion of Rebamipide

Solubility data obtained for solid dispersion of Rebamipide in 0.1 NHCl is shown in the Table 2. At all ratios, increase in solubility of the drug was exhibited. The drug: polymer ratio 1:1 possesses highest solubility (18.66 mg/mL) as compared to other ratios. This could be because of change in drug to amorphous form from crystalline because of interaction with the carrier polymer. So, drug: polymer ratio of 1:1 was chosen for formulation of beads.

Differential Scanning Calorimeter (DSC)

DSC thermogram of Rebamipide shows a sharp endothermic peak at 291.63°C indicating the crystalline nature and the melting

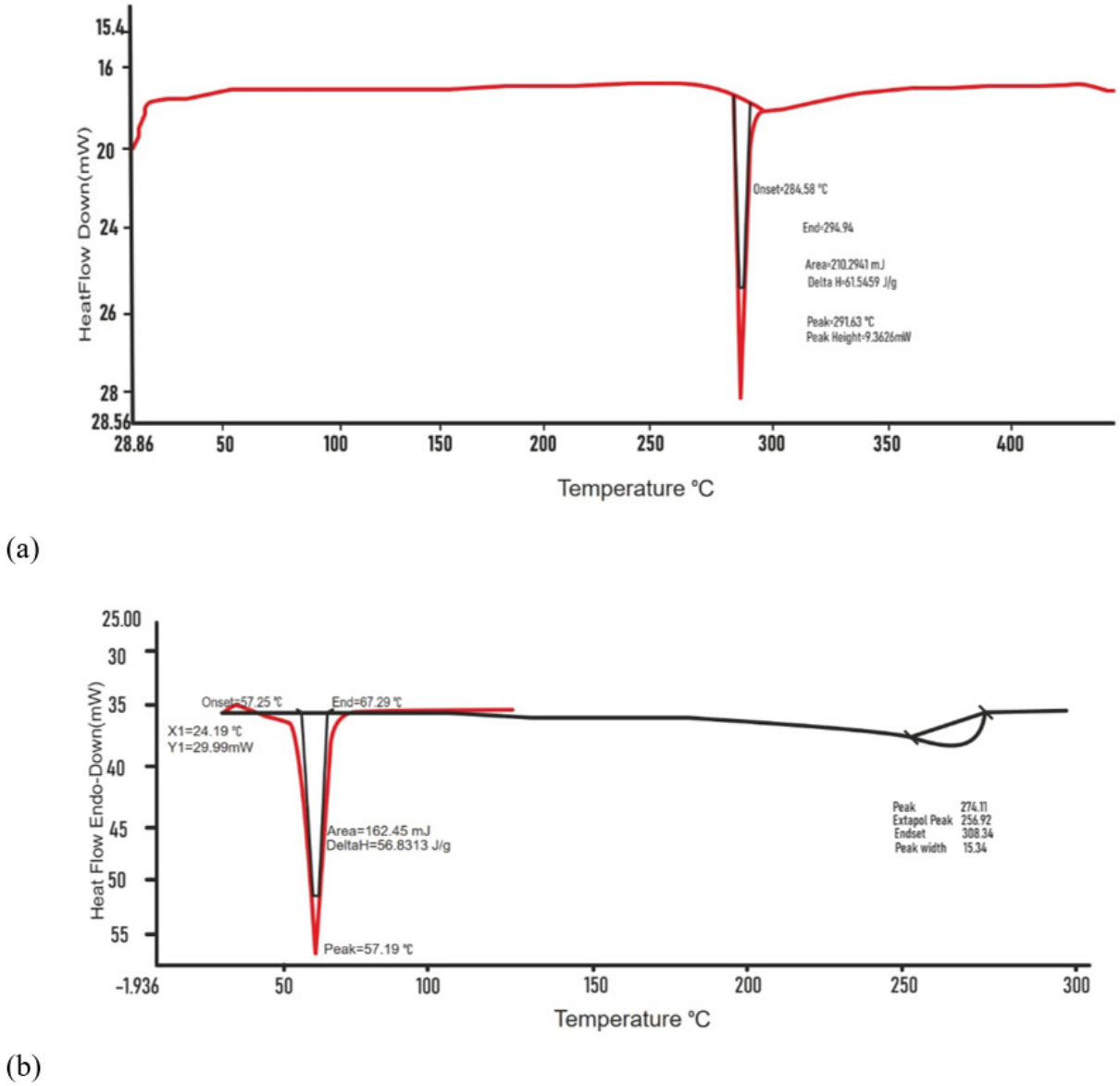

Figure 1: DSC thermogram of a) Rebamipide b) Solid dispersion of Rebamipide.

point of rebamipide. Thermogram of solid dispersion of drug and polymer shows an endothermic peak at 57.19°C which is the melting point of Poloxamer 407 and shows a rounded peak at 274.11°C, which is around the melting point of rebamipide. Change in the shape of drug peak to a round one and its shifting towards lower temperature indicates that the drug has changed its form from crystalline to amorphous in the solid dispersion with decreased melting point which has resulted in enhancement of solubility (Figure 1).

X-ray Diffraction

XRD of pure drug Rebamipide shows high intensity sharp peaks at 4.20, 8.41, 11.1, 12.7, 15.3, 1 19.7, 20.6, 21.5, 22.8, 24.8, 25.5, 26.8, 28.8, 29.9, and 33.7 indicating crystalline nature of the drug (Figure 2). Diffractogram of solid dispersion of drug and polymer shows disappearance of some high intensity peaks and reduction in intensity of others indicating partial alteration in form of drug from crystalline to amorphous.[25]

Fourier Transform-Infra-Red (FTIR) Spectroscopy

The infrared absorption spectrum of Rebamipide and its solid dispersion (Figure 3) was recorded from 4000 to 450 cm^{-1} by using Fourier Transform Infra- Red spectrophotometer (Shimadzu Corpn, Japan, IR-Prestige 21). FTIR spectra were obtained and analyzed to check authenticity of drug sample and confirm compatibility of drug and polymer. The FTIR spectrum of rebamipide showed peaks around 3270.98 cm^{-1}, 3049.79 cm^{-1} due to N-H and CH_2 stretching vibration, peak at 2984 cm^{-1}, 2880 cm^{-1} due to alkane stretching, peak at 2543 cm^{-1} due to CH_2 vibration, at 150 9 cm^{-1} due to COOH stretching, at 1642 cm^{-1},

1600 cm^{-1} due to C=O-NH secondary amine, peak at 1538 cm^{-1}, 1509 cm^{-1} due to primary amine, 1423 cm^{-1} due to C=O stretching vibration, peak around 1338 cm^{-1}, 1183 cm^{-1} due to C-O stretching respectively (Figure 4). The drug spectrum obtained was compared with the spectrum previously reported in literature and was found to conform with it, establishing the authenticity of the sample of drug.[26] The FTIR spectrum of solid dispersion of rebamipide and Poloxamer 407 showed all important peaks of the drug with only minor shifts confirming the compatibility of drug and polymer.

Similar spectrum was also obtained for optimized formulation (F6) (Figure 3c) which shows that all peaks of drug are retained with minimal shifting and changes in the intensity of major peaks which is considered acceptable, indicating no interaction between drug and excipients.

Formulation of Floating Beads of Solid Dispersion of Rebamipide

The beads of Rebamipide were formulated by emulsion gelation method. In this method the oil droplets are encapsulated during crosslinking of the polymer, sodium alginate, by divalent cations of calcium. This method is economical, requiring less equipment and time. The olive oil used helps to provide buoyancy to the beads after entrapment. HPMC used maintained swelling of beads for a longer time. The swollen surface of beads was able to control the release of drug effectively.

Characterization of Rebamipide Beads

Percentage Yield

All formulations' percentage yield was in the range of 68.3-77.3%. This showed that the method of preparation of beads is quite efficient. The percentage yield was found to be highest in F6 and F7 batches although all batches had similar yields as shown in the Table 3.

Particle Size

The mean particle size of formulated beads fell in the range of 2.05±0.1 to 2.78±0.05mm as shown in Table 3.The size of the beads is found to augment with elevation in oil concentration for the same concentration of sodium alginate. This might be due to an increase in medium viscosity and due to availability of more oil for entrapment. With increment in the polymer concentration the size of beads is also seen to increase probably due to increase in micro viscosity of polymeric dispersion.

Flow Properties

The values of angle of repose, carr's index, bulk density, tapped density and Hausner ratio of the all the nine formulations were assessed after drying of beads. The values of carrs index was excellent for all the formulations except for F1, F4, F7. Hausner ratio also revealed that all the nine formulations had good flow. The values of angle of repose for formulations F3 and F6 were excellent, and other formulations had fair to passive flow. The

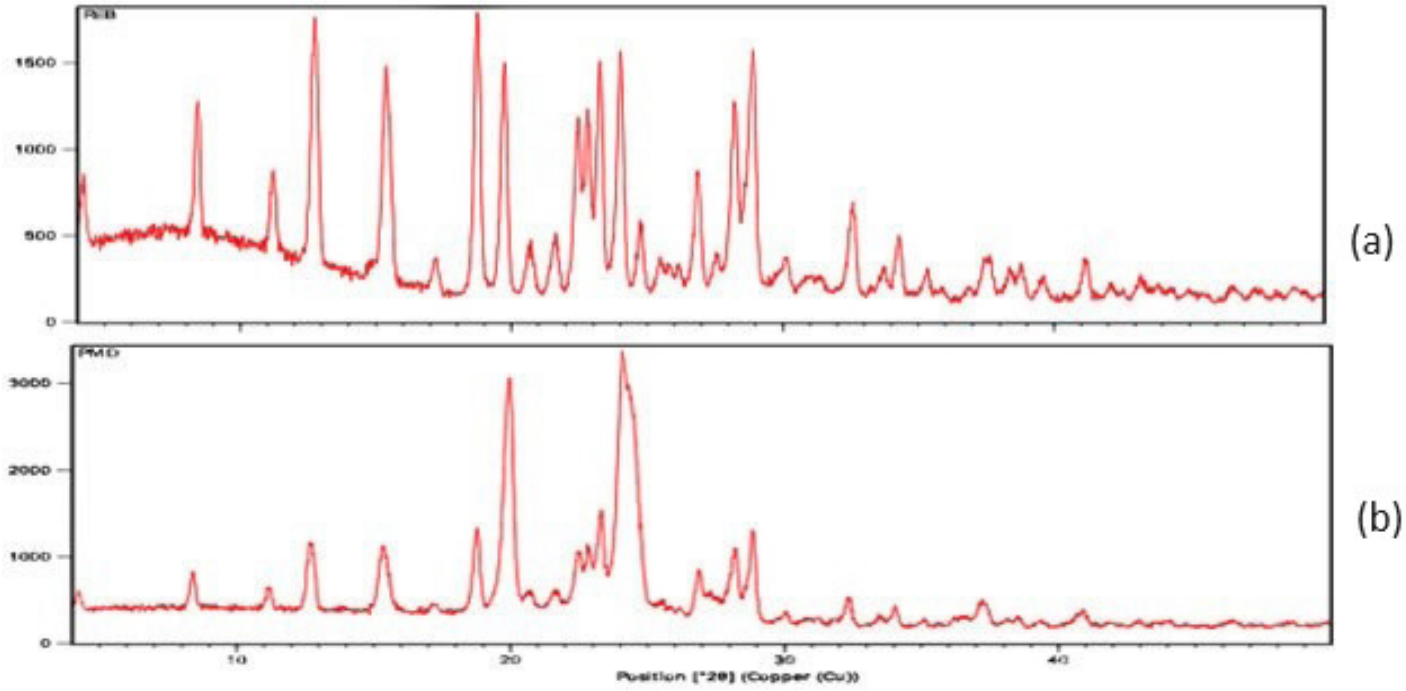

Figure 2: XRD of a) Rebamipide b) solid dispersion of Rebamipide.

good flow property of almost of all batches of beads also gives evidence about their near spherical shape.

Buoyancy of Beads

All the formulations exhibited buoyancy for more than 12 hr except F5, F7, and F8. This could be due to lesser symmetry in shape. The beads with higher concentration of oil can be seen to have better buoyancy as compared to beads with low concentration of oil because of reduced density. The percentage of beads showing buoyancy ranged from 43-95% for different batches (Table 3) which was found to be highest for F3 batch. An interplay of polymer concentration (sodium alginate) and oil concentration led to these results. Higher sodium alginate concentration added to the weight of beads thus decreasing their buoyancy percentage whereas greater oil concentration produced less dense beads elevating the percentage of floating beads.

Buoyancy Lag Time

All the formulations demonstrated floating lag time between 3-13 sec (Table 3). The beads with higher concentration of oil have less buoyancy lag time because of reduced density. Increase in concentration of polymer demonstrated longer lag time because of formation of heavier beads.

Swelling Index

The swelling characteristics of sodium alginate are an essential factor for controlling the release of drug from the beads. The swelling index lies in the range of 12%±0.31-28%±0.42 for all the batches of formulation as shown in the Table 3. Swelling index studies revealed that it was dependent on the concentration of the polymer. From the study of results it was found that increased oil concentration decreased the swelling index of beads, although no regular trend can be seen.

Entrapment Efficiency

All batches of beads were evaluated for entrapment efficiency. The entrapment efficiency lies between 88.7 to 96.9% (Table 3). All formulations show good entrapment of drug and there was no major difference in the entrapment efficiency of all formulation batches still a trend can be seen of increase in entrapment with elevation of sodium alginate concentration and with increase in concentration of oil at the same level of polymer. This can be explained on the basis of formation of a more rigid

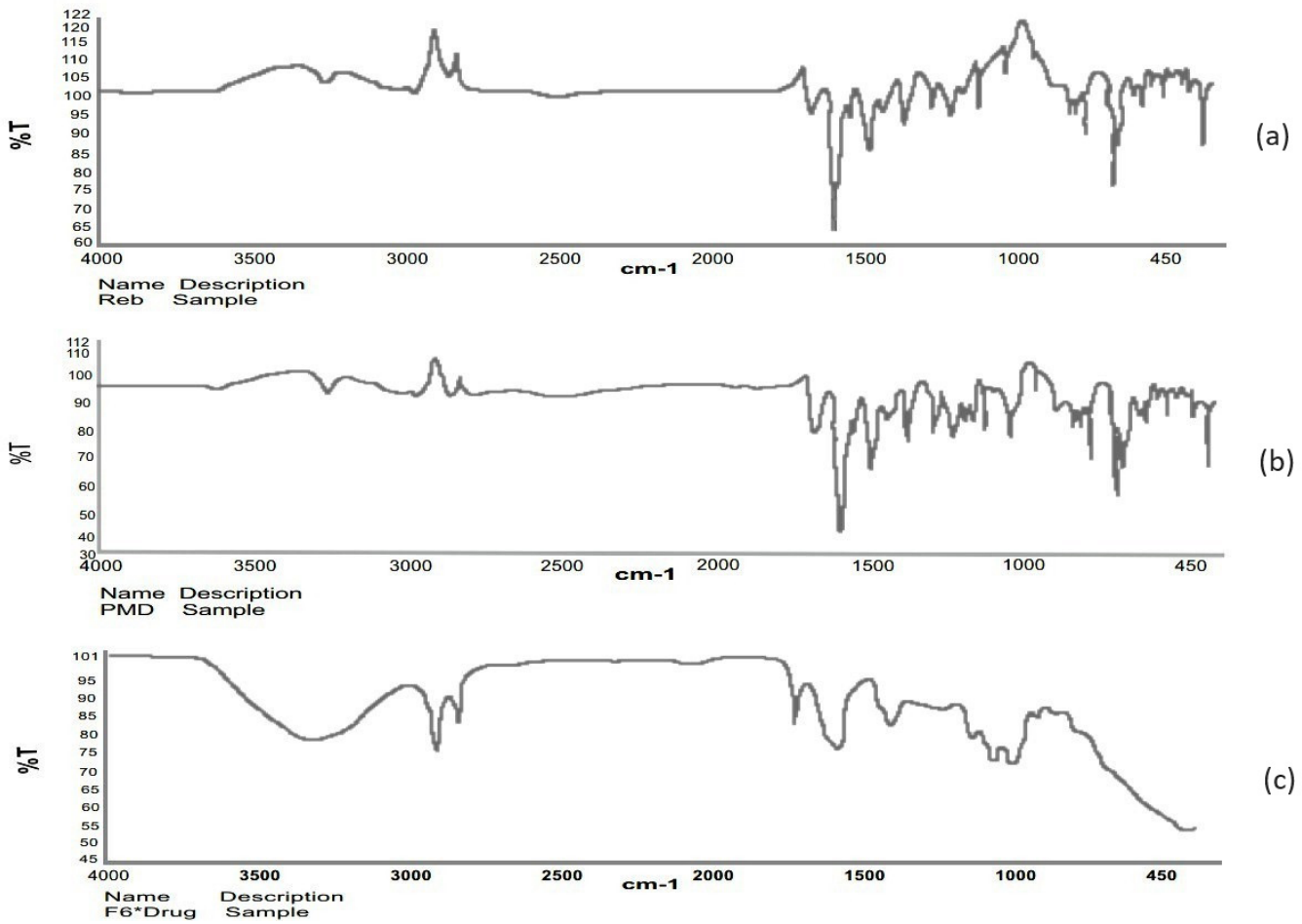

Figure 3: FTIR spectrum of a) Rebamipide b) Solid dispersion of Rebamipide c) Optimized batch of floating beads of Rebamipide.

structure with availability of increased polymer amount by crosslinking preventing the leakage of drug. Also, increment in oil concentration poses a barrier to the diffusion of drug outside resulting in better entrapment of the drug.[27] An anomaly is observed for F9 batch.

In vitro Drug Release

The *in vitro* drug release study of floating beads was carried out in 0.1 NHCl. The drug release profile of all formulations is illustrated in Figure 4. The drug release rate and extent lies in following order- F1>F2>F3>F4>F5>F6>F7>F8>F9. This trend shows that the release rate of rebamipide from floating beads decreased with increase in the concentration of sodium alginate and olive oil. Formulation F4 showed 91.76% drug release within 12 hr at pH 1.2 and formulation F6 showed 90.26% drug release within 12 hr. The slow and sustained release of drug is due to the formation of drug oil dispersion system. At high concentration of

Table 3: Characterization of Rebamipide beads.

Formulation code	Percentage yield* (%)±SD	Mean Particle size**±SD (mm)	Shape**	Buoyancy*±SD (%)	Buoyancy lag time (sec)	Swelling index*±SD (%)	Entrapment efficiency*±SD (%)
F1	68.3±0.7	2.05±0.05	Spherical with tailing	72±1.7	8	15±0.21	88. 7±1.03
F2	70.3±0.1	2.14±0.1	Spherical	90±1.1	6	19±0.25	90.1±0.86
F3	72.5±0.4	2.19±0.05	Spherical with tailing	95±0.5	4	14±0.11	90.4±0.52
F4	75.8±0.6	2.15±0.05	Spherical	67±1.1	11	28±0.42	91.8±1.22
F5	71.7±0.6	2. 26±0.05	Spherical with tailing	74±1.2	7	20±0.29	92.4±1.51
F6	77.2±0.4	2.36±0.4	Spherical	94±1.5	3	13±0.10	96.9±0.44
F7	76.5±0.8	2.53±0.05	Spherical with tailing	43±1.9	13	17±0.29	92.4±0.76
F8	74.1±0.4	2.67±0.05	Spherical with tailing	58±1.1	8	12±0.31	92.8±1.76
F9	75.2±0.6	2.78±0.05	Spherical	75±0.5	5	15±0.35	93.5±0.57

Value represents, mean±SD, where n^*=3, n^{**}=50.

Table 4: *In vitro* drug release kinetic modeling data for optimized formulation F6.

Formulation F6	Zero order		First order		Higuchi		Kors-peppas	
	R^2	K_0	R^2	K_1	R^2	K_H	R^2	K_P
R^2	0.889	5.68	0.473	0.097	0.987	22.49	0.585	0.861
								n=1.09

Table 5: Stability studies of optimized F6 floating beads.

Stability Conditions	Sampling intervals	Color	Particle size± S.D (mm)	Buoyancy ±S.D (%)	Buoyancy lag time (sec)	Entrapment efficiency ±SD (%)
40± 2°C/75± 5% RH	0	No change	2.36±0.41	99±1.5	3	96.9±0.1
	1	No change	2.34±0.39	98±0.5	2	95.2±0.5
	3	No change	2.30±0.57	99±0.1	3	94.6±0.1

Value represents, mean±SD, where n^*=3, n^{**}=50.

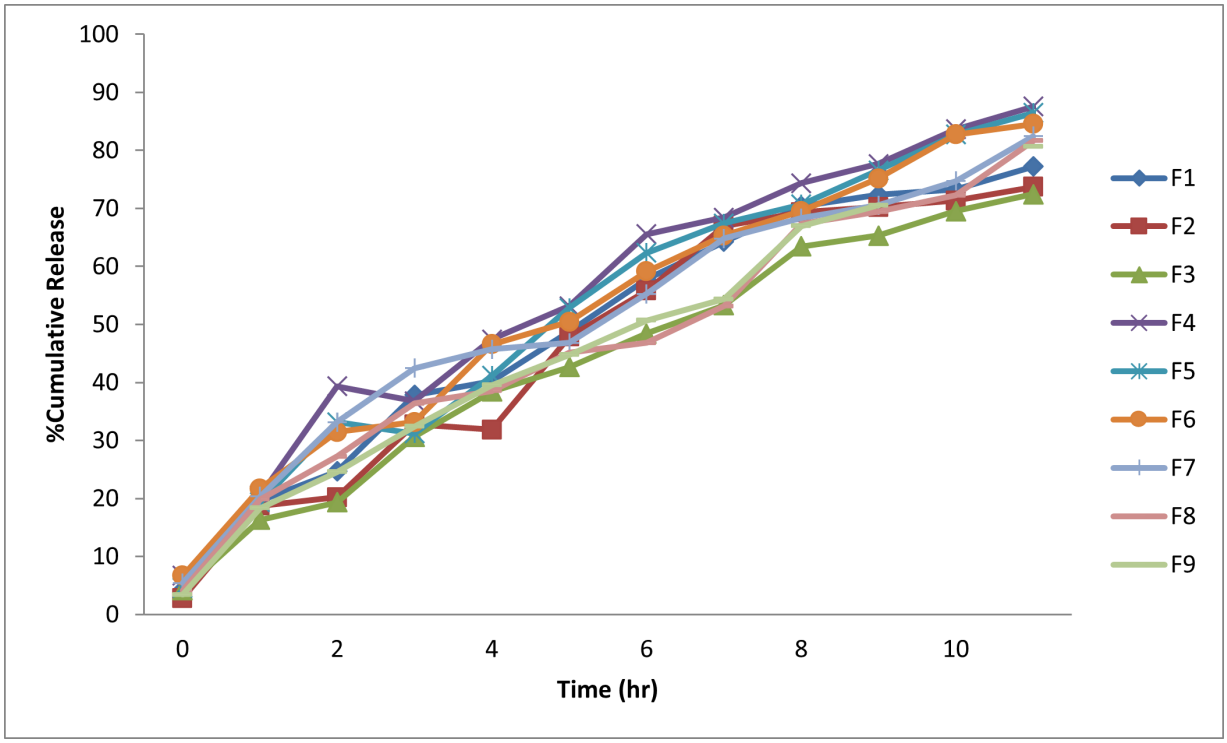

Figure 4: Dissolution profile of various batches of floating beads of Rebamipide. Error bars represent standard deviation for *n*=3.

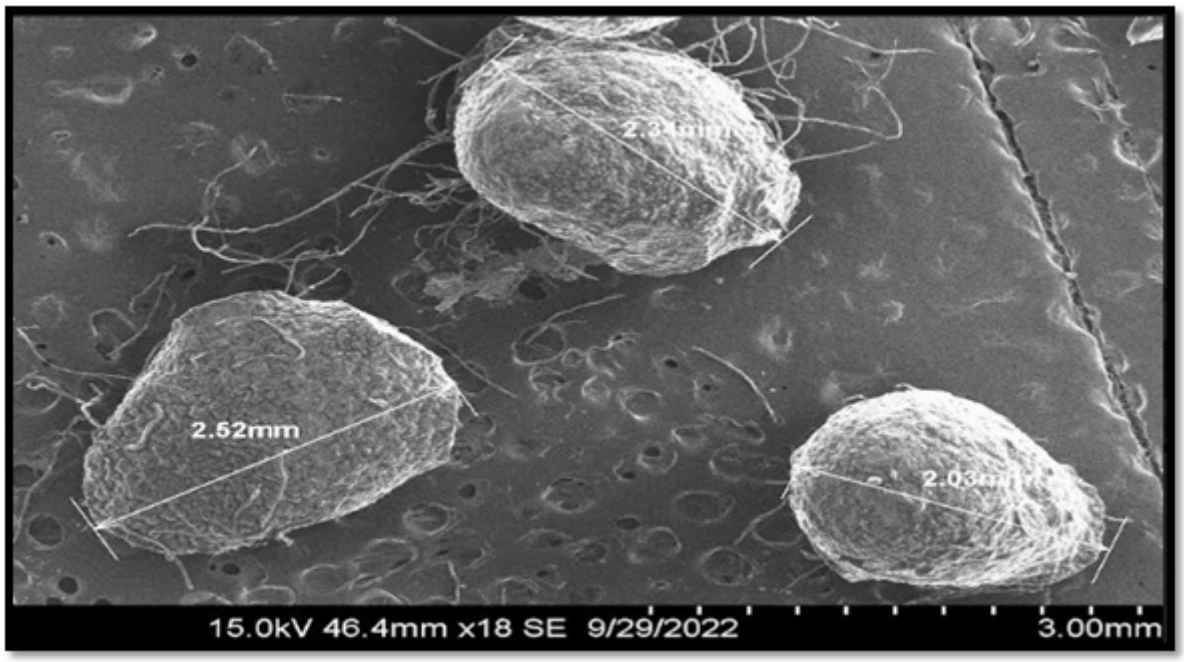

Figure 5: SEM of Floating beads of Rebamipide.

oil and polymer, strong beads with thicker walls are formed with an additional diffusional layer of oil, impeding the drug release.[27]

Selection of Optimized Batch

Optimized batch was selected on the basis of % yield, buoyancy, buoyancy lag time, entrapment efficiency and *in vitro* drug release. Formulation F6 shows maximum buoyancy (94±1.5%), %yield (77.2±0.4%), entrapment efficiency (96.9±0.76%), optimum *in vitro* drug release (90.26%) and less buoyancy lag time (3 sec) as compared to other formulations. Therefore, formulation F6 was selected as optimized formulation for further SEM analysis, accelerated stability study. The *in vitro* drug release data of F6 batch was subjected to kinetic modeling to understand the mechanism of drug release from beads.

Kinetic Modeling of Optimized Formulation F6

Table 4 shows the R^2 and release constant (K_0, K_1, K_H, K_P) for various kinetic models for *in vitro* drug release data of formulation F6. It can be seen that highest R^2 (0.987) has been obtained for Higuchi model making it the best fit model for release kinetics and giving evidence of sustained diffusion controlled drug release. The Higuchi model describes the release of drug from a polymeric system via the diffusion mechanism. Furthermore, the 'n' value acquired from the Korsmeyer Peppas plot, 1.09 indicates it to be following supercase II transport, suggesting that Rebamipide floating beads release drug both by swelling and polymer erosion.[28,29]

Accelerated Stability Studies

Stability study is conducted with objective of predicting the shelf life of a product by accelerating the rate of decomposition, preferably by elevating the temperature and RH. The optimized formulation F6 was put to stability study as per ICH guidelines by storing 40±2°C/75±5% RH for 3 months.[30] Analysis of the samples was done for assessing changes in physical appearance, size, buoyancy, buoyancy lag time entrapment efficiency at fixed intervals.

Table 5 shows the stability of optimized (F6) rebamipide beads as per ICH guidelines. The tested formulation was observed to be stable after exposure to elevated humidity and temperature for a period of 3 months. No discernible changes were seen in results of stability studies giving evidence about the stability of the formulation.

Surface Electron Microscopy

SEM of the floating beads formulation F6 was performed under the magnification of 600 x and energy range 15.0 kV and it observed that the size range of beads was 2.03 mm to 2.52 mm. SEM image of F6 optimized formulation shown in the Figure 5 reveals that beads were spherical in shape with slightly rough surface.

CONCLUSION

The present investigation was designed with the objective of formulating floating beads of solid dispersion of Rebamipide for sustained release and improved therapeutics by prolonging the gastric residence time of the drug. Solid dispersion technique was used to enhance the aqueous solubility of poorly soluble drug by the use of a hydrophilic carrier. Solid dispersion of rebamipide was prepared by using Poloxamer 407 as the polymer by solvent evaporation method. Solubility of Rebamipide enhanced to a great extent by formation of solid dispersion which would lead to improved bioavailability and therapeutics. DSC and XRD of solid dispersion manifested the conversion of drug from crystalline to amorphous form leading to higher solubility as has been reported by several researchers. FTIR technique was used to confirm drug-excipient compatibility. Floating beads of Rebamipide were successfully prepared by using ionotropic gelation method which proved to be a simple, efficient and a fast method. The resulting beads possessed optimum characteristics with respect to size, morphology, entrapment efficiency, floating time, floating lag time and *in vitro* release for effective drug delivery. The *in vitro* drug release studies established Higuchi kinetic model to be followed and the "*n*" value obtained from Korsmeyer-Peppas plot revealed the drug release mechanism to be supercase II transport suggesting drug release by both polymer swelling and erosion. 3 month stability study demonstrated the beads to be stable under accelerated conditions. Thus, the incorporation of solid dispersion of Rebamipide in floating beads resulted in sustaining the drug release and increasing the gastric retention time. This would enhance the local and systemic effect of drug, although further studies on animals are required to prove its enhancement.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

GIT: Gastrointestinal tract; **FDDS:** Floating drug delivery system; **GRDDS:** Gastroretentive drug delivery system; **BCS:** Biopharmaceutics classification system; **EGF:** Epidermal growth factor; **SLN:** Solid lipid nanoparticles; **HPMC:** Hydroxy propyl methyl cellulose; **FT-IR:** Fourier transform Infra-red; **DSC:** Differential scanning calorimetry; **XRD:** X-ray diffraction; **SD:** Standard deviation; **SEM:** Scanning electron microscopy; **ICH:** Internation council for Harmonization.

SUMMARY

The study was undertaken with the objective of improving the therapeutics of Rebamipide, a gastroprotective drug possessing ulcer healing activity. Rebamipide possesses poor aqueous solubility leading to poor bioavailability. It shows both systemic and local action in the stomach. Thus, improvement in solubility as well as prolonged retention of the drug in the stomach would lead to improvement in therapeutics of the drug. The drug's solubility was enhanced by preparing its solid dispersion with the polymer, Poloxamer 407 by solvent evaporation method which was encapsulated in floating alginate beads to sustain the release and presence of drug in the stomach. Nine different batches of sodium alginate beads were formulated by varying the concentration of sodium alginate and olive oil by emulsion gelation method. Drug excipient compatibility was checked by FTIR and the change in form of drug from crystalline to

amorphous was determined by DSC and XRD techniques. The solubility of drug in solid dispersion increased to 18.66 mg/ml from 1.3 µg/ml when the ratio of drug to polymer was 1:1. On evaluation of the floating beads , the size was determined to be between 2.05-2.78 mm with mostly spherical shape for all batches, total buoyancy time was greater than 12 hr for almost all the batches except F5, F7 and F8 and buoyancy lag time was less than 13 s in all the cases. Swelling index ranged from 12-28% and entrapment efficiency was found to be in the range of 88-97% demonstrating good entrapment of drug. The in vitro drug release study of floating beads showed the release to be in the given order - F1 > F2 >F3>F4>F5>F6>F7>F8>F9. F6 was selected as the optimized batch based on the evaluation carried out. It showed approximately 90% drug release at the end of 12 h and was found to follow Higuchi release kinetics model with supercase II transport. The optimized batch was found to be stable under accelerated stability study.

Thus, it can be concluded from the study that solid dispersion of Rebamipide incorporated in floating beads can be an alternative for improving the therapeutics of the drug by increasing the solubility of drug and by prolonging its presence in the stomach.

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