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Formulation and evaluation of gastroretentive floating tablets of rebamipide

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ABSTRACT

The present study outlines a systematic approach for design and evaluate of Rebamipide floating tablets to enhance the bioavailability and therapeutic efficacy of the drug. It was prepared based on wet granulation technique for sustained delivery of active agent. Quick GI transit could result in incomplete drug release from the drug delivery system above the absorption zone leading to decreased efficacy of the administered dose and thus less patient compliance. Gastroretentive floating tablets, which was designed to provide the desired sustained and complete release of drug for prolonged period of time. Gastroretentive floating tablets of Rebamipide were prepared by wet granulation technique using different concentrations of Gellan Gum, Fenugreek Gum and Karaya Gum. The optimized formulation (RF22) exhibited 99.17% drug release in 12 hrs, while the buoyancy lag time was 38 sec. In-vitro drug release kinetics was found to follow both the Zero order and the possible mechanism of Rebamipide release from the optimized formulation might be attributed to super case II transport mechanism. The Optimized formulation (RF22) showed no significant change in physical appearance, drug content, floating lag time, *in vitro* dissolution studies after 75% ± 5 % RH at 40s ± 2^0C relative humidity for 6 months.

Keyword: Rebamipide, Floating lag Time, Gastroretentive.

INTRODUCTION

Rebamipide is a gastrocolic guarding vehicle in which basic blocks of it chemical structure constituted by analogs of amino acids (2(1H)-quinoline). Many investigational studies reported the gastrocolic guarding activity of Rebamipide for curing gastric ulcers [1, 2].

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability [3].

One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa. Thus, small intestinal transit time is an important parameter for drugs that are incompletely absorbed. Controlled-release drug delivery systems (CRDDS) provide drug release at a predetermined, predictable, and controlled rate [4].

Controlled-release drug delivery system is capable of achieving the benefits like maintenance of optimum therapeutic drug concentration in blood with predictable and reproducible release rates for extended time period; enhancement of activity of duration for short half-life drugs; elimination of side effects; reducing frequency of dosing and wastage of drugs; optimized therapy and better patient compliances . Several approaches are currently utilized in the prolongation of the gastric residence times (GRT) , including floating drug delivery systems (FDDS), lowdensity systems raft systems incorporating alginate gels, bioadhesive or mucoadhesive systems, high-density systems, superporous hydro gels and magnetic systems [5-7].

MATERIALS AND METHODS

Materials:

The Rebamipide was obtained as a gift sample from splendid laboratories, Pune. Gellan Gum, Fenugreek Gum and Karaya Gum were obtained from Girijan Co-operative corp. Ltd, Hyderabad. Sodium bicarbonate, Citric acid, PVP-K30 was gifted from MSN Labs Ltd, Hyderabad. All other chemicals used were of analytical grade.

Methods

Wet Granulation Method [8]

Gastroretentive floating tablets of Rebamipide were prepared by wet granulation technique using different concentrations of Gellan Gum, Fenugreek Gum and Karaya Gum. All the ingredients were passed through sieve no 85# and were mixed uniformly. Granulation was carried out with sufficient quantity of binder solution (PVP K 30 - 5% in isopropyl alcohol). The wet mass was passed through sieve no 12# and dried at 45^0C for 2 hr. Dried granules were sized by sieve no.18# add magnesium stearate and talc. Granules obtained were compressed with 8 mm flat punch (Cadmach, Ahmedabad, India).

Table 1: Formulation trials of floating tablets of Rebamipide using Fenugreek Gum

Ingredients	RF1	RF2	RF3	RF4	RF5	RF6	RF7	RF8
Drug	100	100	100	100	100	100	100	100
Fenugreek Gum	80	90	100	110	80	90	100	110
Sodium Bicarbonate	30	30	30	30	45	45	45	45
Citric acid	10	10	10	10	10	10	10	10
MCC	110	100	90	80	95	85	75	65
PVP K-30	10	10	10	10	10	10	10	10
Mg stearate	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5
Total weight	**350**	**350**	**350**	**350**	**350**	**350**	**350**	**350**

Table 2 : Formulation trials of floating tablets of Rebamipide using Karaya Gum

Ingredients	RF9	RF10	RF11	RF12	RF13	RF14	RF15	RF16
Drug	100	100	100	100	100	100	100	100

Karaya Gum	75	85	95	105	75	85	95	105
Sodium Bicarbonate	30	30	30	30	45	45	45	45
Citric acid	10	10	10	10	10	10	10	10
MCC	115	105	95	85	100	90	80	70
PVP K-30	10	10	10	10	10	10	10	10
Mg stearate	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5
Total weight	**350**	**350**	**350**	**350**	**350**	**350**	**350**	**350**

Table 3: Formulation trials of floating tablets of Rebamipide using Gellan Gum

Ingredients	**RF17**	**RF18**	**RF19**	**RF20**	**RF21**	**RF22**	**RF23**	**RF24**
Drug	100	100	100	100	100	100	100	100
Gellan Gum	90	100	110	120	100	110	90	120
Sodium Bicarbonate	30	30	30	30	45	45	45	45
Citric acid	10	10	10	10	10	10	10	10
MCC	100	90	80	70	75	65	55	45
PVP K-30	10	10	10	10	10	10	10	10
Mg stearate	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5
Total weight	**350**	**350**	**350**	**350**	**350**	**350**	**350**	**350**

MCC: Microcrystalline Cellulose **PVP K-30:** Polyvinyl Pyrolidone K-30.

Evaluation Parameters

Precompression parameters [9]

Prior to the compression, the formulation powder blends were evaluated for their bulk and tapped density and from these values compressibility index and Hausner's ratio were calculated. While the flow properties of the powder bled were accessed from the angle of repose [4].

Evaluation of Floating Tablets [10, 11]

Post compression parameters

The prepared tablets were evaluated for quality control tests like weight variation, hardness, thickness, friability and content uniformity.

Weight variation

Ten tablets were selected randomly from each batch and weighed individually, calculating the average weight and comparing the individual tablet weight to the average. From this; percentage weight difference was calculated and then checked for USP specifications.

Hardness and friability

Hardness of tablet was determined by Monsanto hardness Tester. Ten tablets were randomly picked from each batch and analyzed for hardness. The mean and standard deviation were also calculated. Friability test was done by Roche friabilator. Ten tablets were weighed and were subjected to the combined effect of attrition and shock by utilizing a plastic chamber that revolve at 25 rpm dropping the tablets at distance of 6 in. with each revolution. Operated for 100 revolutions, the tablets were de-dusted and reweighed. The percentage friability was calculated.

In vitro buoyancy studies

The in vitro buoyancy was determined floating lag time, as per the method described by Rosa et

al. The tablets were placed in a 250 ml beaker, containing 200 ml of 0.1 N HCl. The time required for the tablet to rise to the surface and float was determined as Floating Lag Time (FLT) and the time period up which the tablet remained buoyant is determined as Total Floating Time (TFT).

In vitro Dissolution Studies

The In vitro dissolution study was performed by using a United States Pharmacopeia (USP) type II (paddle) apparatus at a rotational speed of 100 rpm. Exactly 900 ml of 0.1 N HCl was used as the dissolution medium and the temperature was maintained at $37^{o}C \pm 0.5^{o}C$. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus at specified time interval for 12 hrs and the same volume was replaced with pre -warmed fresh dissolution media. The samples were filtered through a whatman filter paper and diluted to a suitable concentration with 0.1 N HCl. Absorbance of these solutions was measured at 227 nm using a UV spectrophotometer.

Stability studies

The optimized formulation of Rebamipide were packed in strips of 0.04 mm thick aluminum foil laminated with poly vinyl chloride by strip packing and these packed formulations were stored in ICH certified stability chambers (Thermo labs, Mumbai) maintained at 40 ^{0}C and 75% RH for 6 months. The samples were withdrawn periodically and evaluated for their floating lag time, content uniformity and for in vitro drug release [12].

RESULTS AND DISCUSSION

In the present work, Rebamipide used in the treatment of ulcer has been utilized as an active drug and considered to be good candidate for reducing dose frequency, for solid oral sustained release formulation as well as more compliance in ulcers. The present it in the form of gastroretentive floating tablets to provide the desired sustained and complete release for prolonged period of time.

Precompression Parameters

The results of precompression evaluation parameters are shown in (Table 4). All the recompression evaluation parameters were within the USP Pharmacopoeia limits.

Postcompression Parameters

The results of post compression evaluation parameters are shown in (Table 5). The Weight variation of all formulations witnessed to be in the limit allowed that is ± 5% of total tablet weight. The suitable hardness for compressed tablets is considered as a vital function for the end user. The deliberated crushing strength of fabricated tablets of formulations RF1-RF24 trended between 4.0-5.0kg/cm^2. The thickness of all the formulations ranges from 5.0-5.5 mm. The friability of all prepared formulation between 0.51-0.79 %, the friability properties limits are in between 0-1%. The drug content of all formulation is in between 95.11-99.34%, drug content depends on the angle of repose since the angle of repose indicates uniform flow nature of powder blend which makes the drug to evenly distribute in all the formulation and to maintain content uniformity in all batches. Tablets of all batches had floating lag time below 60 seconds regardless of viscosity and content of polymers because of evolution of CO_2 resulting from the interaction between sodium bicarbonate and dissolution medium, entrapment of gas inside the hydrated polymeric matrices enables the dosage form to float by lowering the density of the matrices. Total Floating time for the natural polymers formulations were more than 12 hrs.

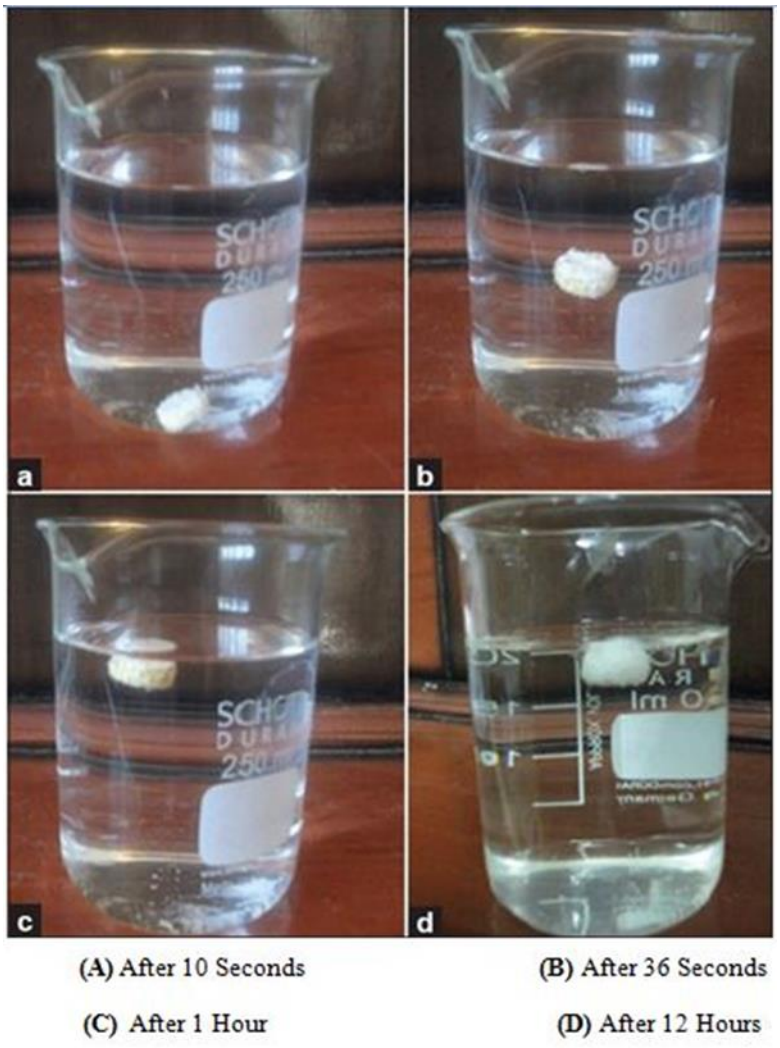

Fig 1: Rebamipide floating lag Time

Table 4: Physical properties of prepared powder blends of the floating tablet

Formulation code	Bulk density (g/cc)	Tapped density (g/cc)	Angle of repose (θ)	Carr's index (%)	Hausner ratio
RF1	0.54±0.19	0.52±0.15	24.34±0.44	09.23±1.12	1.13±0.24
RF2	0.57±0.16	0.58±0.17	22.67±0.31	08.23±1.42	1.11±0.10
RF3	0.57±0.17	0.64±0.21	26.54±0.41	10.12±0.8	1.13±0.20
RF4	0.59±0.25	0.68±0.25	25.89±0.55	11.34±0.6	1.14±0.24
RF5	0.57±0.18	0.59±0.18	22.56±0.0.57	12.23±0.12	1.11±0.32
RF6	0.58±0.20	0.66±0.20	25.30±0.30	11.23±0.25	1.12±0.30
RF7	0.51±0.14	0.64±0.16	22.56±0.57	10.34±0.31	1.14±0.20
RF8	0.54±0.16	0.68±0.17	23.67±0.60	09.11±0.24	1.12±0.25

RF9	0.65±0.18	0.61±0.19	25.56±0.44	09.45±1.15	1.13±0.70
RF10	0.66±0.25	0.67±0.18	21.66±0.31	13.45±1.3	1.15±0.20
RF11	0.51±0.17	0.68±0.16	22.34±0.37	14.23±1.5	1.13±0.16
RF12	0.55±0.16	0.64±0.20	25.99±0.70	11.34±1.25	1.12±0.12
RF13	0.55±0.12	0.68±0.14	22.14±0.21	11.23±1.57	1.12±0.17
RF14	0.52±0.13	0.66±0.17	22.09±0.57	10.23±1.55	1.14±0.15
RF15	0.51±0.18	0.63±0.16	24.78±0.77	10.45±1.5	1.15±0.15
RF16	0.52±0.13	0.61±0.15	23.45±0.80	09.681.3	1.18±0.18
RF17	0.58±0.13	0.68±0.19	25.09±0.86	13.47±1.09	1.12±0.15
RF18	0.56±0.16	0.67±0.20	23.05±0.75	14.99±1.20	1.14±0.15
RF19	0.54±0.18	0.61±0.16	26.06±0.67	12.45±1.45	1.13±0.15
RF20	0.58±0.17	0.64±0.17	23.78±0.57	13.12±1.45	1.15±0.17
RF21	0.59±0.13	0.63±0.18	25.34±0.70	11.09±1.07	1.16±0.20
RF22	**0.56±0.19**	**0.66±0.18**	**20.14±0.50**	**09.67±1.55**	**1.09±0.14**
RF23	0.55±0.14	0.64±0.21	26.45±0.37	10.67±1.25	1.14±0.35
RF24	0.54±0.16	0.64±0.12	25.56±0.31	09.68±1.35	1.14±0.15

Table 5: Physico-chemical parameters of Rebamipide Floating tablets

Formulation	*Weight variation (mg)	#Thickness (mm)	#Hardness (Kg/Cm^2)	#Friability (%)	#Content uniformity (%)	Floating lag time (sec)	Total floating time (hrs)
RF1	350.12±0.20	5.1±104	4.1±0.13	0.51±0.08	97.23±1.23	54	>12
RF2	349.23±0.24	5.01.16	4.0±0.33	0.54±0.09	98.04±1.03	57	>12
RF3	348.08±0.15	5.1±1.05	4.3±0.13	0.63±0.07	96.56±0.94	53	>12
RF4	351.09±0.70	5.2±1.09	4.2±0.10	0.56±0.05	98.11±0.63	49	>12
RF5	351.89±0.50	5.1±1.37	4.1±0.10	0.61±0.07	95.23±0.81	54	>12
RF6	350.34±0.20	5.2±1.11	4.2±0.10	0.67±0.09	96.45±0.32	49	>12
RF7	350.23±0.60	5.0±1.61	4.0±0.15	0.54±0.02	95.11±1.17	47	>12
RF8	349.12±0.50	5.2±0.3	4.2±0.15	0.67±0.02	98.23±0.45	53	>12
RF9	350.23±0.48	5.2±0.45	4.2±0.19	0.56±0.02	97.13±1.17	59	>12
RF10	350.24±0.20	5.1±0.25	4.1±0.21	0.77±0.07	96.23±0.49	57	>12
RF11	351.45±0.97	5.1±0.70	4.4±0.10	0.76±0.05	98.97±0.95	54	>12
RF12	352.03±0.54	5.4±0.25	4.6±0.15	0.73±0.08	98.45±0.35	49	>12
RF13	351.04±0.30	5.5±0.60	4.8±0.18	0.52±0.09	98.85±0.24	47	>12
RF14	348.23±0.35	5.1±0.56	4.2±0.10	0.72±0.02	98.98±0.13	55	>12

RF15	349.34±0.25	5.5±0.70	4.6±0.08	0.71±0.20	98.25±1.21	54	>12
RF16	350.12±0.55	5.1±0.40	4.2±0.21	0.78±0.9	97.45±1.30	59	>12
RF17	351.23±0.50	5.5±0.17	4.7±0.04	0.79±0.04	98.34±1.31	57	>12
RF18	351.67±0.30	5.5±0.40	4.6±0.14	0.82±0.03	98.56±1.36	59	>12
RF19	349.13±0.45	5.0±0.17	4.0±0.12	0.84±0.01	99.29±1.31	53	>12
RF20	349.45±0.55	5.3±0.96	4.5±0.10	0.63±0.03	97.18±1.36	48	>12
RF21	348.12±0.70	5.2±0.50	4.3±0.12	0.66±0.03	96.27±1.30	59	>12
RF22	**350.45±0.80**	**5.0±0.63**	**5.0±0.10**	**0.52±0.015**	**99.34±1.16**	**38**	**>12**
RF23	350.23±0.55	5.3±0.78	4.8±0.17	0.76±0.04	98.14±1.46	57	>12
RF24	350.12±0.60	5.4±0.86	4.7±0.14	0.73±0.06	97.16±0.56	53	>12

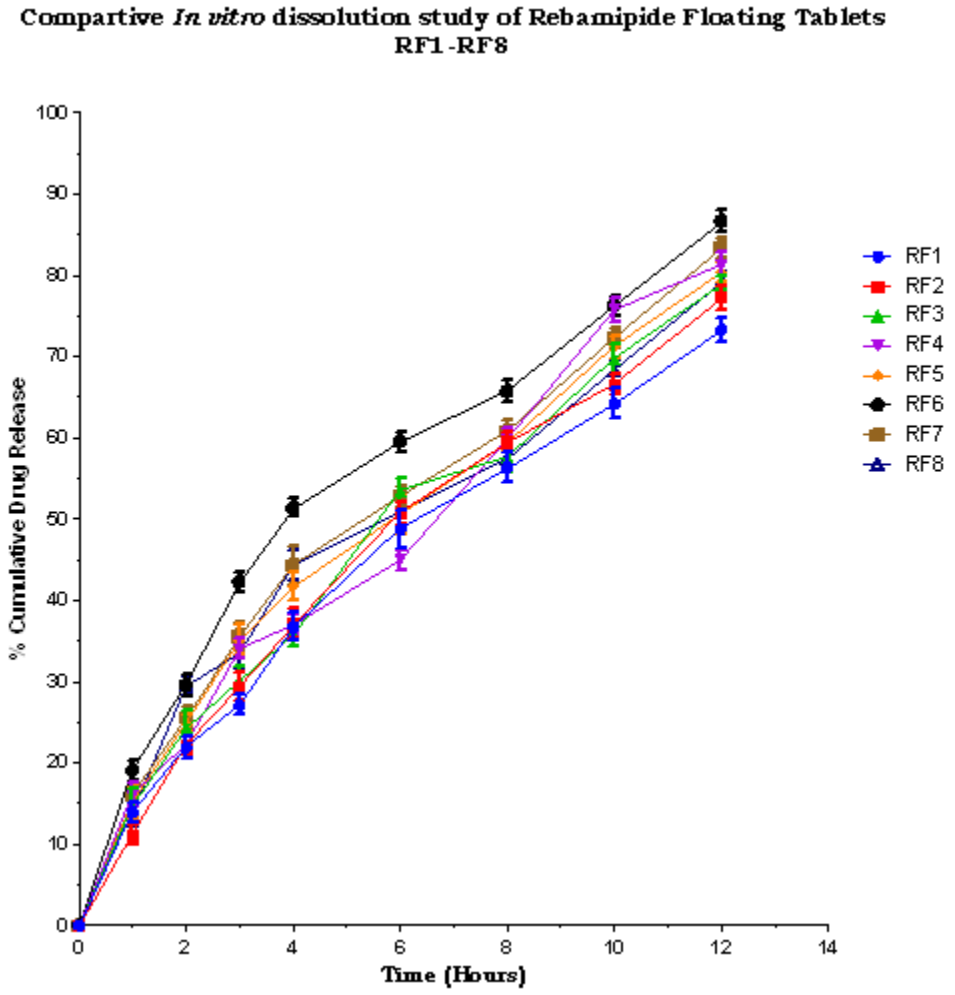

Fig 2: Comparison of *in vitro* Percentage drug release of Rebamipide floating tablet formulations RF1-RF8

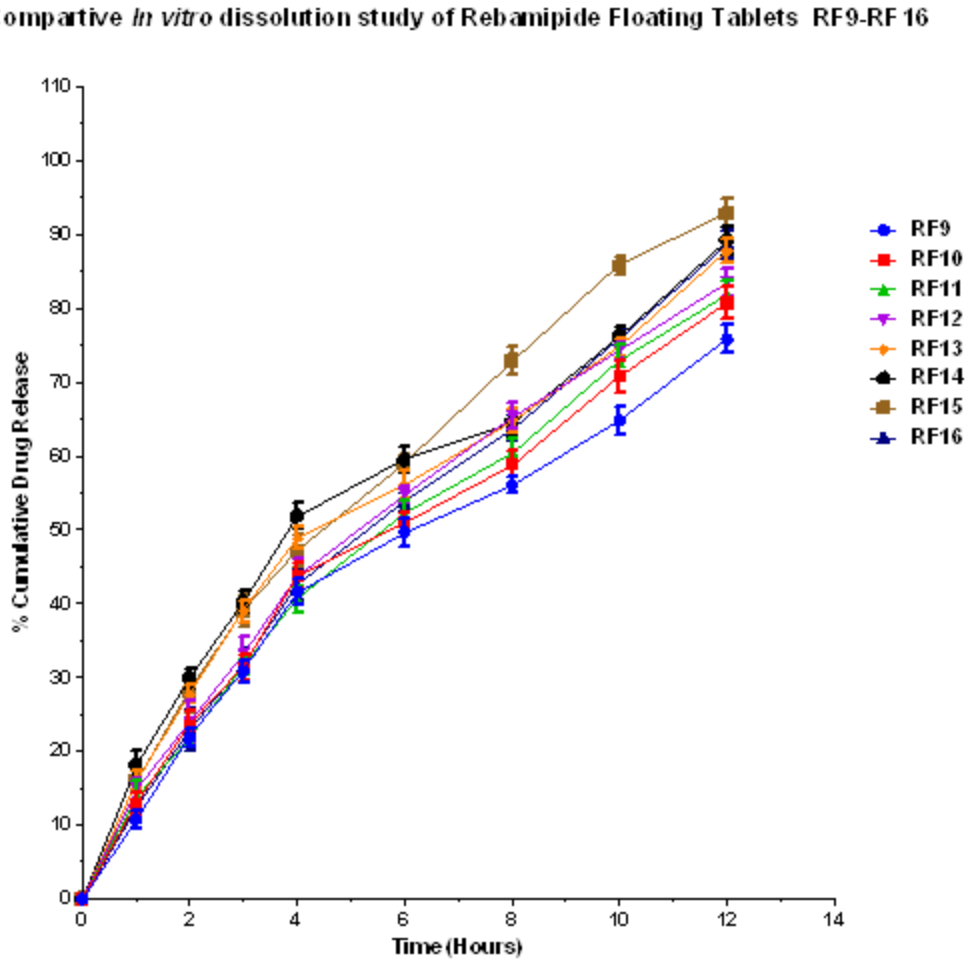

Fig 3: Comparison of *in vitro* Percentage drug release of Rebamipide floating tablet formulations RF9-RF16

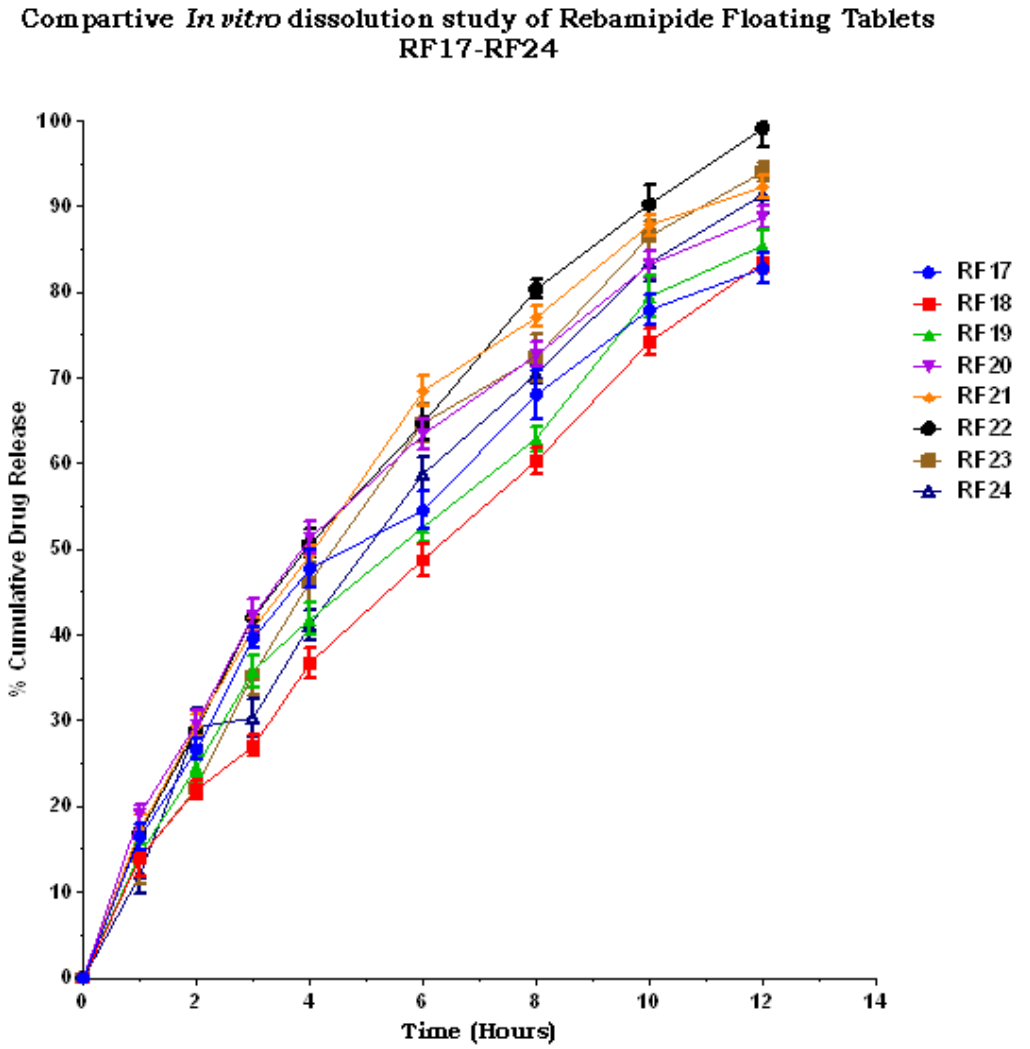

Fig 4: Comparison of *in vitro* Percentage drug release of Rebamipide floating tablet formulations RF17-RF24

From the above figures (**Figure 2, 3 and 4**) it can be observed that the polymer Gellan Gum has sustaining effect on the release of drug from the floating matrix tablet of Rebamipide compared to Fenugreek Gum and Karaya Gum. The difference in the drug release profiles of various formulations was due to the presence of different concentrations of natural polymers. The concentration of polymer was added in increasing order to check its drug release retarding ability and RF22 was considered as best formulation among the all the formulations. RF22 showed good buoyancy properties and sustained the drug release for desired period of time (12hrs). The release profiles from all these formulations followed diffusion controlled release, complying with higher correlation coefficient values of Higuchi and Peppas equations.

Mathematical treatment of optimized formula of Rebamipide floating tablets

In vitro dissolution has been identified as a vital part of drug development. It could be used for assessment of bioequivalence. There are several models to represents the drug dissolution profiles where it is a function of time associated with the amount of drug dissolved in distinction to the dosage form. The quantitative interpretation of the values collected in the dissolution assay is facilitated by the usage of a generic equation that mathematically interprets the dissolution curve in the function of some parameters related to the formulations.

A water soluble drug assimilated in a matrix is mainly liberated by diffusion, while for a low water- soluble drug the self-erosion of the matrix

will be the principal release mechanism. Mathematical modeling of the release kinetics of specific classes of controlled-release systems may be used to predict solute release rates from and solute diffusion behavior through polymers and elucidate the physical mechanisms of solute transport by simply comparing the release data to mathematical models.

In the view of the establishment of the release mechanism and quantitatively interpreting and translate mathematically the dissolution data being plotted.

CONCLUSION

In the present work, it can be concluded that the Rebamipide floating tablets can be an innovative and promising approach for the delivery of Rebamipide for the treatment of gastric ulcers. The optimized formulation **RF22** containing Gellan Gum and a gas-generating agent. In-vitro release profile of Rebamipide and marketed product when compared, the optimized formulation **RF22** showed drug release of 99.17±1.86 % within 12h whereas 95.12±2.28 % of the drug was released from the marketed product within 1h. The major mechanism of drug release follows zero order kinetics and non fickian transport by coupled diffusion and erosion. This means that water diffusion and also the polymer rearrangement have an essential role in the drug release. The release rate constant of optimized formulation **RF22** was low enough prolonging drug delivery. This result is encouraging, because a longer gastric residence time is an important condition for higher bioavailability of the drugs included in the prolonged or sustained release dosage forms.

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