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FORMULATION AND EVALUATION OF RANOLAZINE HOLLOW MICROSPHERES

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ABSTRACT

The objective of the present work was to formulate floating hollow microspheres of Ranolazine which is soluble and shows better absorption in gastric pH. Microspheres were prepared by emulsion solvent diffusion technique. Using various such as sodium alginate, HPMC, and eudragit polymers. The formulations were evaluated for micromeritic properties, buoyancy, % yield, entrapment efficiency and in vitro studies. They were characterized by FT-IR. FT-IR and studies indicated that there was no interaction between the drug and polymers. SEM photographs showed the outer surface of microspheres was smooth and dense where as internal surface was porous which helped to prolong floating to increase residence time in stomach. The results showed that floating microspheres could be successfully prepared with better yield. Results showed larger the particle size, longer was the floating time. In vitro drug release studies showed controlled release of Ranolazine for over 8 h. From the results it can be concluded that gastric floating hollow microspheres can be successfully used for the delivery of Ranolazine maleate to control blood glucose level.

KEYWORDS: Ranolazine, Polymers, Ionotropic gelation technique, floating time, in vitro drug release studies.

INTRODUCTION

Gastroretentive dosage form can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility of drugs that are less soluble in a high pH environment.[1,2] It is also suitable for local drug delivery to the stomach

and proximal small intestine. Oral route of drug administration is the ideal, convenient and preferred route. Conventional oral drug administration does not generally offer target specificity or rate-controlled release.[3] In controlled release drug delivery systems (CRDDSs), an active therapeutic is incorporated in the network structure of the polymer in such a way that the drug is released in a predefined controlled manner. Prolonging gastric residence time (GRT) is the most important objective of CRDDSs as short GRT is the major hindrance in the development of CRDDSs. The prolonged residence time of the drug in the body is believed to prolong its duration of action.[4] Ranolazine, a drug which is used as antianginal agent and it exhibits short half life, and has good solubility in gastro acidic medium, so has been desired to formulate it with pH dependent binder to sustain the release upto intestinal pH and to extend the action of antianginal effect.[5,6]

MATERIALS AND METHOD

Materials

The chemicals were obtained from different sources. Ranolazine gifted sample from Hetero labs Hyderabad, Sodium alginate, HPMC, Eudragit, Polyethylene glycol and methanol gifted from AR chemicals.

Methodology[7,8,9]

Fourier Transform Infra-red Spectroscopy (FT-IR) Analysis

The Fourier transform infra-red analysis was conducted for the analysis of drug polymer interaction and stability of drug during microencapsulation process. Fourier transform infra-red spectrum of pure Ranolazine, Eudragit RS 100, HPMC and hollow microspheres were recorded.

Preparation and evaluation of Ranolazine hollow microspheres

Formulation table

Table 1: Preparation of ranolazine hollow microspheres.

Ingredients	F1	F2	F3	F4
Drug	100	100	100	100
Sodium alginate	1000	-	-	800
HPMC	-	1000	-	200
Eudradit	-	-	1000	-
Methanol	5 ml	5 ml	5 ml	5 ml
Cacl $_2$	5 gms	5 gms	5 gms	5 gms

Method

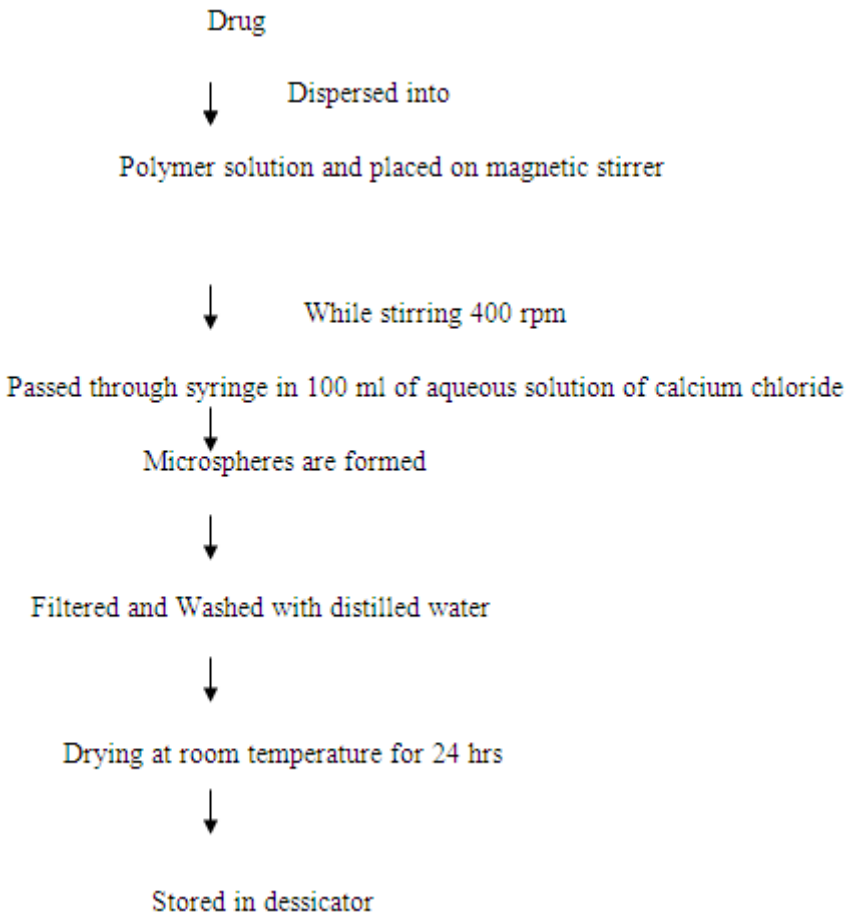

Fig. 1: Schematic representation of preparation of hollow microspheres of Ranolazine.

Evaluation of of hollow microspheres[10,11,12]

Particle size analysis

Particle size analysis plays an important role in determining the release characteristics and floating property. The sizes of hollow microspheres were measured by using a set of standard sieves ranging from 14, 16, 18, 22, 30 and pan. The sieves were arranged in increasing order from top to bottom. The hollow microspheres were passed through the set of sieves and amount retained on each sieve was weighed and calculate the % weight of hollow microspheres retained by each sieve. Mean particle size for all formulation was determined by dividing the total weight size of formulation to % total weight of hollow microspheres.

Floating Property of Hollow microsphere

100 mg of the hollow microsphere were placed in 0.1 N HCI (300 ml) containing 0.02% Tween 20. The mixture was stirred with paddle at 100rpm. The layer of buoyant

microballoons was pipetted and separated by filtration at 1, 2, 4 and 6 hours. The collected microballoons were dried in a desiccator over night.

The percentage of hollow microspheres was calculated by the following equation

$$\% \text{ hollow microsphere} = \frac{\text{Weight of hollow microsphere}}{\text{Initial weight of hollow microsphere}} \times 100$$

Drug Entrapment

An accurately weighed quantity of the floating microspheres equivalent to 20mg of drug was taken for evaluation. The amount of drug entrapped was estimated by crushing the microspheres and extracting with aliquots of phosphate buffer (pH 6.8) repeatedly. The extract was transferred to a 100ml volumetric flask and the volume was made up using phosphate buffer (pH 6.8). The solution was filtered and the absorbance was measured after suitable dilution at 233 nm by using UV-visible spectrophotometer. The drug content was estimated in triplicate using a calibration curve constructed in the same solvent.

The percentage drug entrapment was calculated as follows.

$$\% \text{ Drug entrapment} = \frac{\text{Calculated drug concentration}}{\text{Theoretical drug concentration}} \times 100$$

Percentage Yield

The percentage yield of different formulations was determined by weighing the hollow microspheres after drying. The percentage yield was calculated as follows.

$$\% \text{ Yield} = \frac{\text{Total weight of hollow microspheres}}{\text{Total weight of drug and polymer}} \times 100$$

Shape and Surface Characterization by Scanning Electron Microscopy

From the formulated batches of hollow microspheres, formulation which showed an appropriate balance between the buoyancy and the percentage release were examined for surface morphology and shape using scanning electron microscope Hitachi, Japan. Sample was fixed on carbon tape and fine gold sputtering was applied in a high vacuum evaporator.

The acceleration voltage was set at 20KV during scanning. Microphotographs were taken on different magnification and higher magnification (200X) was used for surface morphology.

In vitro Release Studies

The drug release rate from floating micro spheres was carried out using the franz diffusion cell assembly. A weighed amount of floating micro spheres equivalent to 100 mg drug were dispersed in 900 ml of 6.8 phosphate buffer (pH 6.8) maintained at 37 ± 0.5°C and stirred at 100 rpm. At preselected time intervals one ml sample was withdrawn and replaced with equal amount of 6.8 phosphate buffer. The collected samples were suitably diluted with 6.8 phosphate buffer and analyzed spectrophotometrically at 241 nm to determine the concentration of drug present in the dissolution medium.

Stability Study

From the prepared hollow microspheres which showed appropriate balance between the buoyancy and the percentage release was selected for stability studies. The prepared formulation were placed in borosilicate screw capped glass containers and stored at room temperature (27 ± 2° C), oven temperature (42±2° C) and in refrigerator (5-8° C) for a period of 45 days. The samples were assayed for drug content at regular intervals of two week.

RESULTS AND DISCUSSION

FT-IR Spectrum of Ranolazine

FT-IR Spectra of Ranolazine and F3 formulation were recorded. All these peaks have appeared in formulation and physical mixture, indicating no chemical interaction between Ranolazine and polymer. It also confirmed that the stability of drug during microencapsulation process.

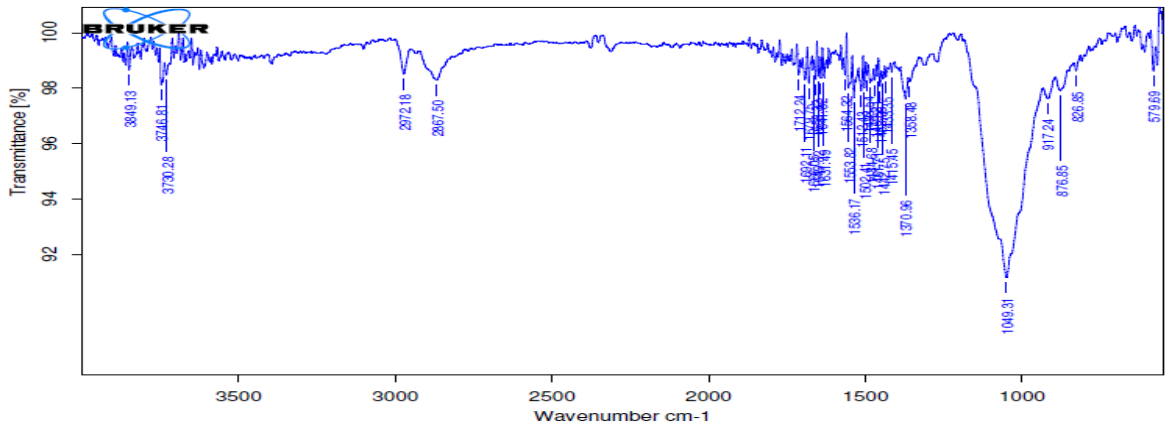

Fig. 2: FTIR Studies of Ranolazine.

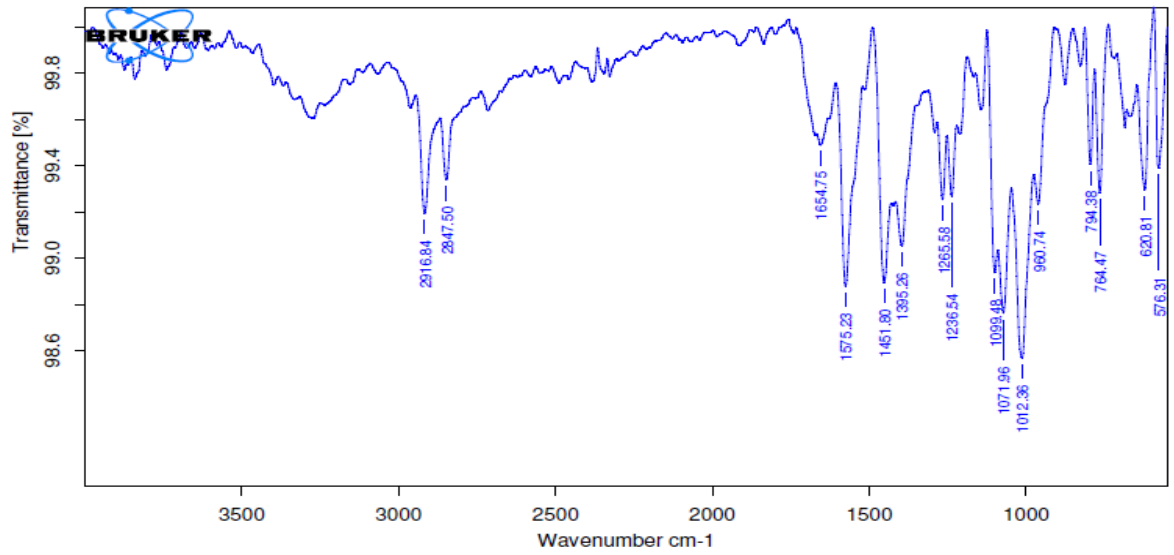

Fig. 3: FTIR Studies of optimized formulation.

Evaluations of hollow microspheres

Particle size analysis

Particle size was determined by sieving method it plays important role in floating ability and release corrected of drug from hollow microspheres. If size of hollow microspheres less than 500 mm so release rate of drug will be high and floating ability will reduce, while microballoons range between 500mm - 1000mm, floating ability will be more and release rate will be in sustained manner. The mean particle size of hollow microsphere was in range 812-838 mm.

Table 2: Particle size of Different Batches of Hollow microsphere.

S. No	Formulation code	Mean particle size* (μm)
1	F1	815
2	F2	829
3	F3	838
4	F4	812

Floating Property of hollow microsphere

Floating ability of different formulation were found to be differed according to polymer ratio.

Table 3: Floating property of Hollow microsphere.

S. No	Formulation code	% of floating
1	F1	79.86
2	F2	81.26
3	F3	82.55
4	F4	79.98

Drug Entrapment

The drug entrapment efficacy of different formulations were in range of 71.60-85.23%. Drug entrapment efficacy increases with increases eudragit content and decreases HPMC ratio in microballoons. This is due to the permeation characteristics of eudragit, that could facilitate the diffusion of part of entrapped drug to surrounding medium during preparation of hollow microspheres.

Table 4: Drug entrapment for different formulation.

Formulation	Drug Entrapment
F1	75.95
F2	71.60
F3	85.23
F4	82.66

Percentage Yield

Percentage yield of different formulation was determined by weighing the hollow microspheres after drying. The percentage yield of different formulation were in range of 79.60 – 80.55% as shown in Table.

Table 5: Percentage yield for different formulation.

Formulation	Percent Yield*(%)
F1	79.90
F2	79.60
F3	80.55
F4	72.85

Scanning Electronic Microscopy

Shape and surface characteristic of hollow microspheres examine by Scanning Electronic Microscopy analysis as shown in Fig. Surface morphology of F3 formulation examine at different magnification 40X and 200X, which illustrate the smooth surface of floating microballoons and small hollow cavity present in microsphere which is responsible for floating property.

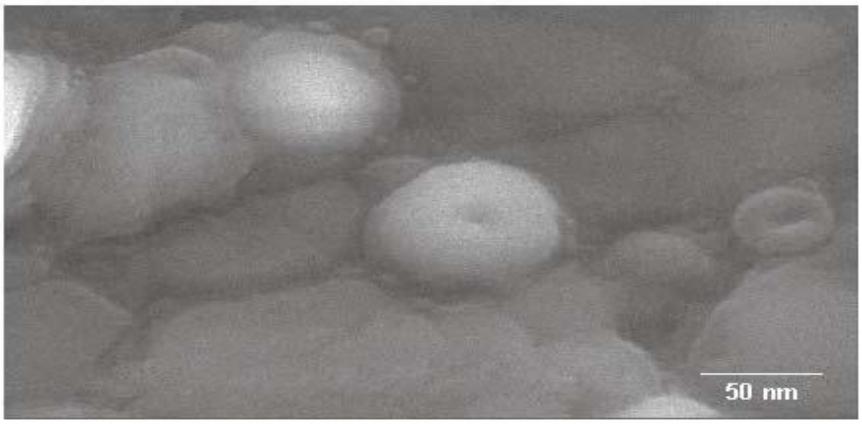

Fig. 4: Micro Photographs of Formulation F3.

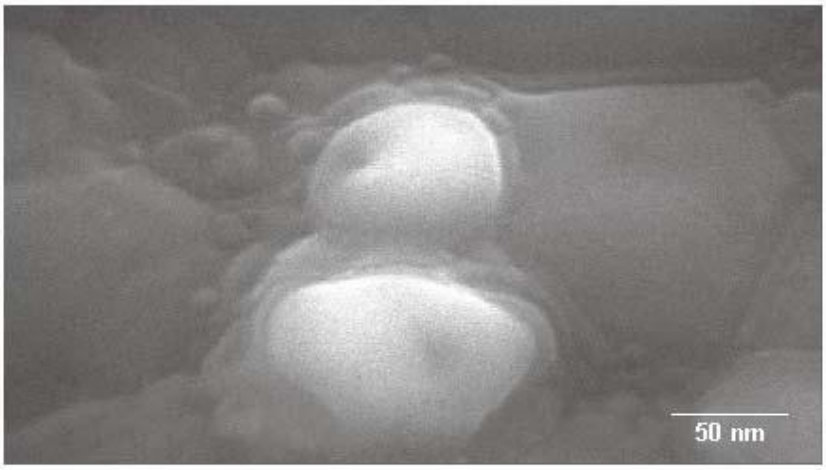

Fig. 5: Cross Section.

***IN-VITRO* Drug release study**

In-vitro drug release study of hollow microspheres was evaluated in phosphate buffer pH 6.8. Eudragit RS100 which is present in all formulation, have low permeability in acid medium. F 3 formulation showed best appropriate balance between buoyancy and drug release rate.

Table 6: *In-Vitro* Drug Release Profile for Formulation in 6.8 phosphate buffer.

S. No	Time (hrs)	F1	F2	F3	F4
1	**0**	0	0	0	0
2	**1**	14.21	15.50	18.96	16.55
3	**2**	27.18	29.56	28.92	27.90
4	**3**	34.22	36.45	37.55	38.45
5	**4**	45.10	49.25	51.44	48.20
6	**5**	53.81	55.90	58.55	52.15
7	**6**	69.46	71.65	73.56	70.22
8	**7**	79.90	80.15	81.72	80.25
9	**8**	90.88	93.55	95.80	91.55

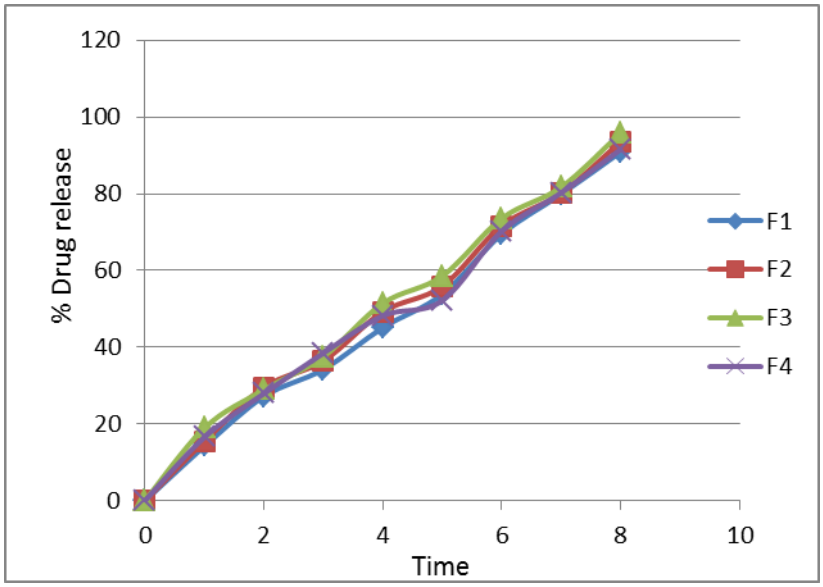

Fig. 6: In-Vitro Drug Release Profile Of all formulations.

Stability Study

Stability study was carried out for the F3 formulation by exposing it to different temperature for 30 days. The sample was analyzed for drug content at the regular intervals. It was found that no remarkable change in the drug content of F3 formulation. This indicates that F3 was stable for following temperature.

Table 7: Results of stability studies of optimized formulation F-3.

S. No.	Time in days	Physical changes	Mean % drug content ± SD		
			Ranolazine		
			25^0C/60%	30^0C/75%	40^0C/75%
1.	01	No Change	95.80	95.80	95.80
2.	30	No Change	95.76	95.72	95.69

CONCLUSION

Hollow microspheres of Ranolazine were prepared by ionotropic gelation and performances of this formulation were evaluated. It increases the bioavailability of dosage form with prolong effect hence improves the patients compliances. Mean particle size for all formulations were varied, due to change in drug and polymer ratio. Drug entrapment efficiency slightly decreases with increasing the polymer content. Drug release pattern was evaluated in phosphate buffer pH 6.8. Release rate of F1, F2, formulations were found to be slow and incomplete in dissolution medium. In order to increase the release rate of drug the ratio of Eudragit increased respectively. Ideal property of hollow microsphere includes high

buoyancy and sufficient release of drug in pH 6.8. It is necessary to select an appropriate balance between buoyancy and drug release rate from all developing hollow microsphere. F3 formulation showed best appropriate balance between buoyancy and drug release rate, it considered as a bestfit for drug release. The design system F3 might be able to float in the stomach. This phenomenon could prolong the gastric residence time (GRT) consequently, it provides sustained action. In addition, hollow microspheres enabled increased drug absorption rate, as it gradually sank in the stomach and arrived at the absorption site. The developed formulation overcomes the drawbacks and limitations of sustained release preparations. Therefore multiple unit floating system, i.e., hollow microsphere will be possibly beneficial with subject to sustain action.

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