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ORIGINAL ARTICLE **OPEN ACCESS**

Formulation and Evaluation of Floating Microspheres of Ranitidine Hydrochloride by using Two Different Polymers in Combination

Barde L.G[1*], Harale M.V[2], Deo S.D [3]
1*TVES's College of Pharmacy Faizpur, 425503.
2 Shri.Vitthal Education & Reaserch Institute College of Pharmacy, Pandharpur, 416521.
3.Dr. Uttamrao Mahajan College of Pharmacy, Chalisgaon.424101
***E-mail- lokeshbarade1234@gmail.com**

ABSTRACT
The aim of this study was to formulate and evaluate floating microspheres of Ranitidine Hydrochloride. This formulation mainly used for inhibition of gastric acid secretion. Floating microspheres of Ranitidine Hydrochloride were prepared by Emulsification Solvent Evaporation Technique using chitosan and Eudragit RL 100 polymers. FTIR and DSC studies showed that Ranitidine Hydrochloride and excipient are compatible. Scanning Electron Microscopic studies shows spherical and smooth surface floating microspheres. The prepared product was subjected to various studies and give values in ranged like particle size 186.80±0.027 – 196.38±0.039 µm, bulk density 0.261±0.001 – 0.467±0.008 gm/cm³, tapped density 0.309±0.001 – 0.532±0.009 gm/cm³, % yields 71.33%±0.01 – 95..23%±0.07, and drug release time (>12 h), floating time (> 12 h) and best results were obtained at the ratio (1:3) using 300 rpm stirring speed. The developed floating microspheres of ranitidine hydrochloride may be used in clinic for prolonged drug release in stomach for at least 12 hrs, thereby improving the bioavailability.
Keywords *Floating microspheres, Ranitidine Hydrochloride, Chitosan, Eudragit RL 100, Emulsification Solvent Evaporation Technique.*

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INTRODUCTION

The new way of patenting the drug is use "Novel Drug Delivery System" i.e. NDDS with improve bioavailability. To formulate a drug or to reformulate it in a form of NDDS is not a Herculean task if one goes methodically and skilfully. This is where the formulation development studies play an important rule [1, 2].

Floating microspheres are gastro-retentive drug delivery system. If System is floating on gastric environment then its increases residence & fluctuation in plasma peak level and the drug is release slowly at the esteem rate. It also reduces chances of striking and dose dumping and produces prolonged therapeutic effect [3].

Ranitidine Hydrochloride is competitive, reversible inhibiter of action histamine at the histamine H_2-receptor found in the gastric parietal cell and the meal-stimulated secretion of acid. It is widely prescribed in gastric ulcers, duodenal ulcers, zollinger-Ellison syndrome and gastro-esophageal reflux disease [4]. Approximately 50% bioavailability orally. The drug has absorbed only initial part of the small intestine [5]. It undergoes first-pass metabolism. Ranitidine is metabolised to the N-oxide, S-oxide, and N-demethyl metabolites, accounting for approximately 45, 1%, AND 1% of the dose, respectively. The principle route of excretion is the urine. Approximately 30% orally administered dose collected in the urine as unchanged drug in 24 hrs [6].

MATERIAL AND METHODS

Materials

Ranitidine Hydrochloride was obtained as a gift sample from Orchev Pharma Pvt Ltd., (Rajkot, Gujrat). Chitosan was received from Sisco Research Laboratories Pvt Ltd., Eudragit RL 100 was received from Vishal Chem, (Mumbai, India). Ethanol was obtained from RFCL Ltd., (Surajkund), Dichloromethane was obtained from Research Lab Ltd., (Poona). Heavy Liquid Paraffin was obtained from Research Lab Ltd.,

(Poona), Tween 80 was obtained from Vishal Chem., Mumbai (India), n- hexane was obtained from RFCL Ltd., Surajkund.

Preparation of Floating microspheres

Floating microspheres containing Ranitidine Hydrochloride were prepared by using emulsification solvent evaporation technique.

In this technique, floating microspheres prepared by taking drug and polymers ratio as 1:1,1;1.5,1:2,1:2.5,1:3with same drug and two different polymers. Drug and polymers in different proportions were weighted and codissolved at room temperature into a mixture of ethanol, dichloromethane (1:1% v/v) etc. with vigorous agitation to form uniform drug–polymer dispersion. This was slowly poured into dispersion medium consisting of heavy liquid paraffin (100 ml) containing 0.1 % Tween 80. The system was stirred using overhead propeller agitator 300 rpm at room temperature over a period of 2-3 hrs, to ensure complete evaporation of solvent. Liquid paraffin was detected and the microspheres were separated by filtration through a filter paper, washed thrice with 180 ml of n-Hexane and aired dried for 24 hrs [7].

Table No. 2: Formulation of Floating Microspheres of Ranitidine Hydrochloride

Sr. No.	Formulation Code	Ranitidine HCL (mg)	Chitosan: Eudragit RL 100 (mg)	Dichloromethane: Ethanol (1:1)	Heavy Liquid Paraffin (ml)	Tween 80	n-Hexane (ml)
1.	A	300	300	10	100	0.1%	180
2.	B	300	300	10	100	0.1%	180
3.	C	300	450	10	100	0.1%	180
4.	D	300	450	10	100	0.1%	180
5.	E	300	600	10	100	0.1%	180
6.	F	300	600	10	100	0.1%	180
7.	G	300	750	10	100	0.1%	180
8.	H	300	750	10	100	0.1%	180
9.	I	300	750	10	100	0.1%	180

Formulation A, B, C, D, E, F, G, H, I gives speed of rotation in rps as follows such as 300, 500, 300, 500,300, 500, 300, 500, 300.

Evaluation of Floating microspheres

Particle Size Determination [8]

The particle size can be determined by using an optical microscope (Radical Instrument, RXL.5T Amabala Cant, India) under regular polarized light, and mean particle size was calculated by measuring 100particles with the help of a calibrated ocular micrometer.

The average of particle size was determined by using Edmondson's equation,

$$D=\sum nd/\sum n$$

Where, n=Number of microspheres checked; D=Mean of size range.

Angle of Repose [9]

The angle of repose θ of the microspheres, which measures the resistance to particle flow, was calculated as,

$$\tan \theta = 2H/D$$

Where, 2H/D is the surface area of the free standing height of the microspheres heap that is formed after making the microspheres flow from the glass funnel.

Bulk Density [10]

Bulk density can be determined by three tap method, after filling the weighed quantity of microspheres in a graduated cylinder, the volume occupied by microspheres should be determined.

Bulk density = Weight of microspheres in g/Bulk Volume [3]

Tapped Density

The tapping method can be used to calculate tapped densities. The volume of weighed quantity of microspheres was determined after 100 taps as well as1000 taps using tapped density apparatus such as OSC, India.

Tapped density = Mass of microspheres/Volume of microspheres after tapping [11]

Percentage Compressibility Index/Carr's Index [10]

The same tapping method was used to determined percentage compressibility index was calculated according to following formula,

%Compressibility Index = Tapped density-Bulk density/ Tapped density × 100

Hausner's Ratio

Hausner's ratio of microspheres was determined by comparing the tapped density to the bulk density using the equation [10].

Hausner's Ratio = Tapped density/Bulk density

Percentage Yield of Microspheres

The prepared microspheres were collected and weighed. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the microspheres.

% Yield = (Actual weight of product /Total weight of excipients and drug) x 100

Determination of Drug Entrapment Efficiency

To determine the incorporation efficiency, 40 mg of microspheres were taken, thoroughly triturated and suspended in a minimal amount of dichloromethane. The suspension was filtered to separate shell fragments. Drug contents were analysed spectrophotometrically at 313.5 nm [12].

DEE= (Amount of drug actually present/Theoretical drug load expected)× 100

Percentage Drug Content [13]

The prepared microspheres were powdered and passed through sieve no (85/120). The powder retained on the sieve 120 was taken for content uniformity or percentage drug content studies. A weight of powder containing 100 mg of drug was taken in 100 ml standard volumetric flask. To this of 0.1 N NaOH solutions was added and made upto the mark with 0.1 N NAOH solutions and kept overnight. The final solution was filtered using what man filter paper. From this 10 ml was pipetted out into a 100 ml standard volumetric flask and made upto the volume with 0.1 N NaOH solution and estimated the drug content by using Lab India UV visible spectrophotometer, (3000+), Mumbai.

Drug content is calculated according to following equation,

% of Drug Content= Weight of drug in microspheres/Weight of microspheres recovered × 100

Buoyancy Percentage (Floating Ability) [13]

Fifty milligrams of the floating microspheres were placed in 0.1M HCL, 100 ml containing 0.02% v/v Tween 80. The mixture was stirred at 100 rpm in a magnetic stirrer (Remi Lab Stirrer (RQ 121/D, India).After 12hrs, the layer of buoyant microspheres was pipette and separated by filtration. Particles in the sinking particulate layer were separated by filtration. Particles of both types were dried in a desiccator until constant weight.

% Buoyancy= (Qf/Qf+Qs)× 100

Qf+Qs Where, Qf and Qs are the weight of the floating the settled microspheres, respectively.

***In-vitro* Drug Release Studies [13]**

In vitro dissolution of Ranitidine from floating microspheres was determined in a United States Pharmacopeia (USP) XXIV basket type dissolution apparatus in Electro Lab (TDL-08L) Ltd., Mumbai. Drug loaded microspheres (weight equivalent to 50 mg of drug) were introduced into the 900, ml of 0.1 M HCL containing Tween 80 (0.5% v/v). The dissolution fluid was maintained at 37 ± 2^0C at a rotation speed of 100 rpm. Perfect sink conditions prevailed during the drug release study. 5 ml samples were withdrawn at regular intervals for 12 h and analysed under UV-Spectrophotometer at 313.5nm.The initial volume of dissolution fluid was maintained by adding 5 mL of fresh dissolution fluid after each withdrawal. All experiments were run in triplicate.

Surface Morphology Study

The surface topography, morphology, cross-section, particle size, etc., were determined by Scanning Electron Microscopy using JEOL JSM-T330A Scanning Microscopy (Japan). Dry micro particles were places on an electron microscope brass stub and coated with gold in an ion sputter. Picture of micro particles were taken by random scanning [14, 15].

Fourier Transforms Infra-Red Spectroscopy Analysis (FT-IR)

The FT-IR spectra of drug (Ranitidine Hydrochloride), Chitosan, Eudragit RL 100 And Floating Microspheres was recorded using FT-IR Spectrophotometer (Simandu 84005, between ranges 400-4500 cm^{-1}. The samples were gently triturated with small amount of potassium bromide (K Br) powder (300 mg) and compressed into pellets/discs by applying 6000 kg/cm^2 pressure, using a manual hydraulic presser [16].

DSC Study

Assessment of possible incompatibility between an active drug substance and different excipients forms an important part of pre-formulation stage during the development of solid dosage form. Differential scanning Calorimeter (DSC PerkinElmer 4000, USA) allows the fast evaluation of possible incompatibility because it shows changes in the appearance, shift of melting endothermic and exothermic, and/or variations in the corresponding enthalpies of reaction. The DSC thermograms of pure drug, other excipients and optimized film were recorded. The thermal analysis was performed in a nitrogen

atmospheres at a heating rate of 10°C/min over a temperature range of 40°C to 300°C.DSC study was performed for Ranitidine Hydrochloride and physical mixture of all ingredients of microspheres [17-19].

RESULTS AND DISCUSSIONS

Table No. 2: Evaluation parameter Mean Particle Size, Angle of Repose, Bulk Density, Tapped Density, % Compressibility Index for floating microspheres

Formulation Code	Mean Particle Size(µm)	Angle of Repose (^{0})	Bulk Density gm/cm^3	Tapped Density gm/cm^3	% Compressibility Index
A	189.20±0.029	16^0.69±0.28	0.261±0.001	0.309±0.001	15.53±0.01
B	186.80±0.027	17^0.90±0.42	0.280±0.002	0.330±0.003	15.15±0.08
C	193.23±0.038	18^0.61±0.61	0.301±0.003	0.360±0.004	16.38±0.61
D	191.30±0.036	18^0.90±0.60	0.335±0.003	0.391±0.007	14.32±1.22
E	179.46±0.022	19^0.00±0.22	0.429±0.007	0.496±0.009	13.50±0.50
F	176.30±0.038	19^0.42±0.24	0.443±0.009	0.513±0.011	13.64±0.51
G	196.37±0.038	21^0.13±0.4	0.451±0.006	0.509±0.010	11.74±0.35
H	193.93±0.041	21^0.88±0.49	0.462±0.008	0.532±0.009	13.15±0.49
I	196.38±0.039	20^{0}23±0.38	0.467±0.008	0.525±0.008	11.04±1.011

n = 3

Table No. 3: Evaluation parameter Hausner's Ratio, Percentage yield, Drug Entrapment Efficiency, Percentage Drug Content for floating microspheres

Formulation Code	Hausner's Ratio	Percentage yield (%)	Drug Entrapment Efficiency (%)	Percentage Drug Content
A	1.1839±0.019	72.66±0.002	68.3±0.02	92.87±0.02
B	1.1785±0.010	71.33±0.01	65.8±0.01	91.85±0.01
C	1.1960±0.020	79.41±0.03	71.2±0.04	93.90±0.04
D	1.1671±0.007	78.83±0.01	69.00±0.08	93.11±0.04
E	1.1561±0.016	82.4±0.04	78.6±0.01	95.76±0.07
F	1.1580±0.016	81.33±0.04	76.1±0.02	95.09±0.07
G	1.1286±0.013	86.44±0.03	83.9±0.01	97.80±0.08
H	1.1515±0.016	85.5±0.01	82.30±0.04	97.19±0.08
I	1.1241±0.014	95.23±0.07	89.38±0.05	99.91±0.11

n = 3

Buoyancy Percentage (Floating Ability)

The floating test was carried out to investigate the floating ability of the prepared microspheres. Floating microspheres was dispersed in 0.1 N HCL containing Tween 80 (0.02% v/v).

Buoyancy percentage (Floating ability) of different formulations was found to be differed according to polymer ratio. G to I formulations showed best floating ability (76-79 %) in 12 hours. A to E Formulation showed less floating ability (71-74%) in 12 hours.

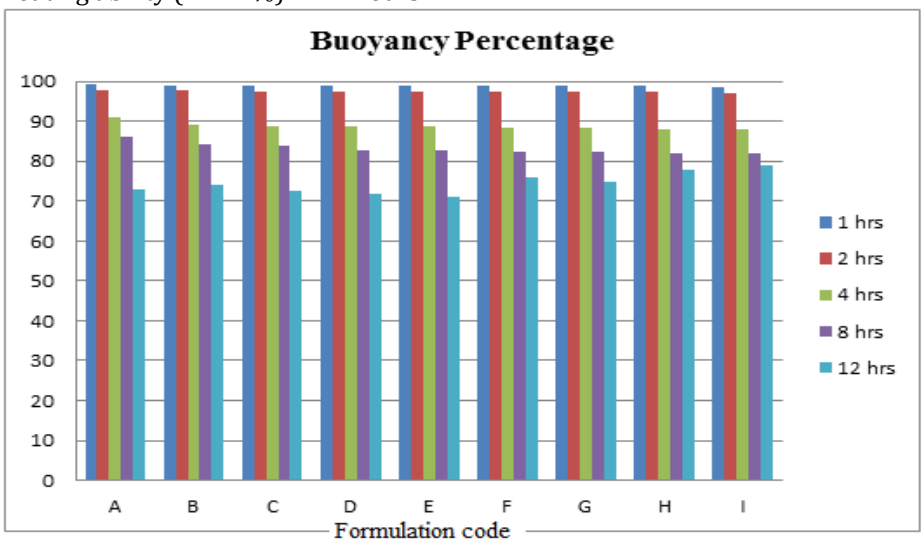

Fig. No. 1 Floating behaviour of formulation A to I

***In-vitro* Drug Release Study**

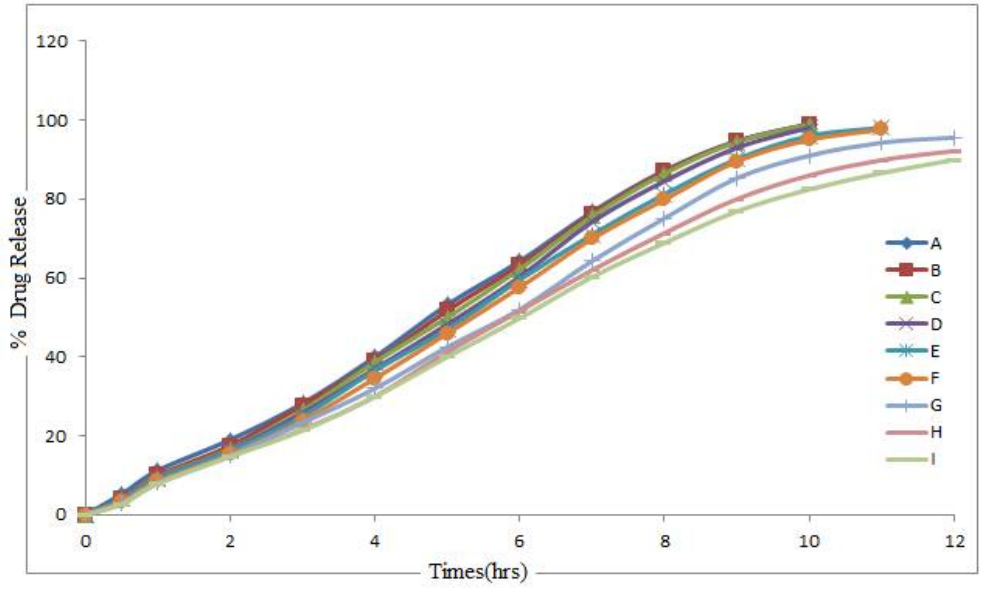

Fig. No. 2 *In-vitro* Drug Release Profile of Formulations A to I in 0.1 N HCL

Release of Ranitidine Hydrochloride from floating microspheres was evaluated in 0.1 N HCL (p^H 1.2). Polymer chitosan is of sparingly soluble in water. Floating microspheres showed sustained released of drug in acidic condition (p^H 1.2) and drug released found approximately linear. Approximately 5.23%±0.52 of drug was released initially. Furthermore, drug released from floating microspheres matrix was controlled by polymer. Eudragit RL 100 is insoluble in water and it does show p^H dependency. As polymer content was increased and drug loading was decreased, the released of drug decreased significantly.

In order to increase the released rate of drug, the ratio of drug and polymer is decreased and increased respectively. Formulation (I) showed best approximately balance between buoyancy and drug release rate.

Surface Morphology Study

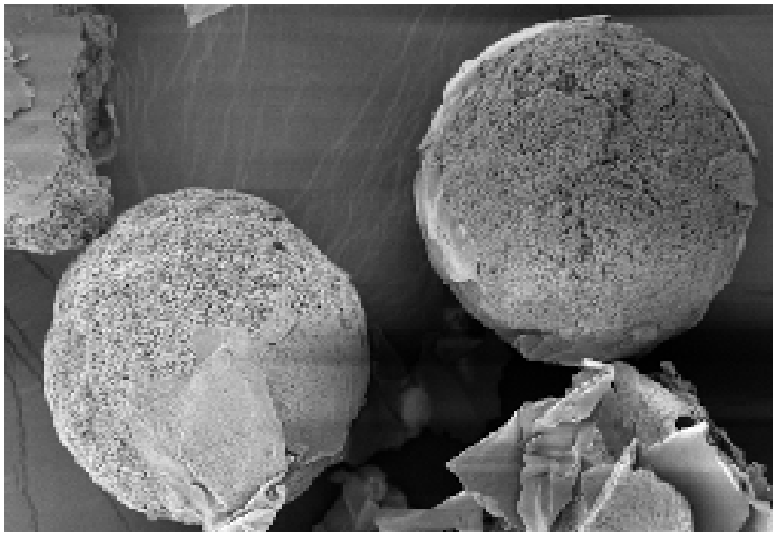

Fig.No.3 Surface Morphology Study of Formulation I at 500 X

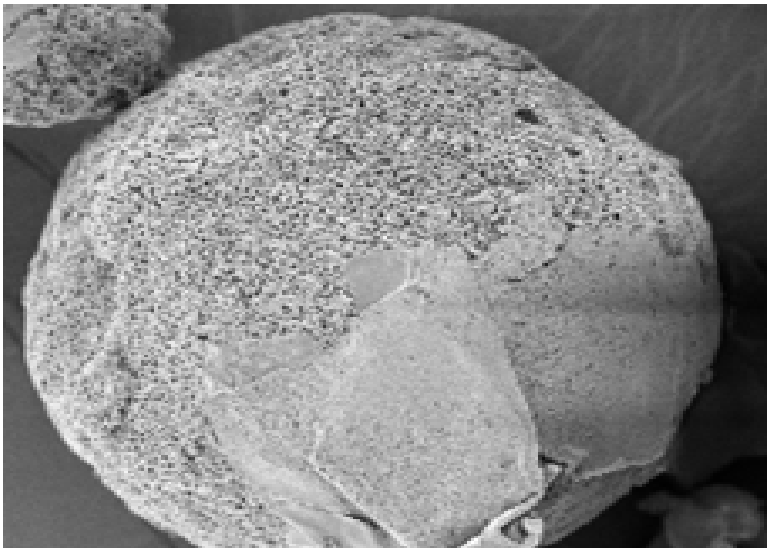

Fig.No.4 Surface Morphology Study of Formulation I at 3.00 K X

The floating microspheres were examined by Surface Morphology study as shown in figures. These figure (Figure no.3-4) illustrating the microscopy formulation I at lower and higher magnification. The floating microspheres were porous, smooth, spherical with no visible major surface irregularity. The surface topography reveals that the microspheres were small porous due to rapid escape of volatile solvents during formulation. Inward dents were seen on the surface, probably due to collapse of the walls of the microspheres during in-situ drying process. The Surface morphology of (I) formulation was examined at higher magnification (500 X) Figure no.3 which is illustrates porous, smooth, spherical surface of floating microspheres, probably arising as trace of solvent evaporation.

Fourier Transforms Infrared Spectroscopy (FTIR) analysis

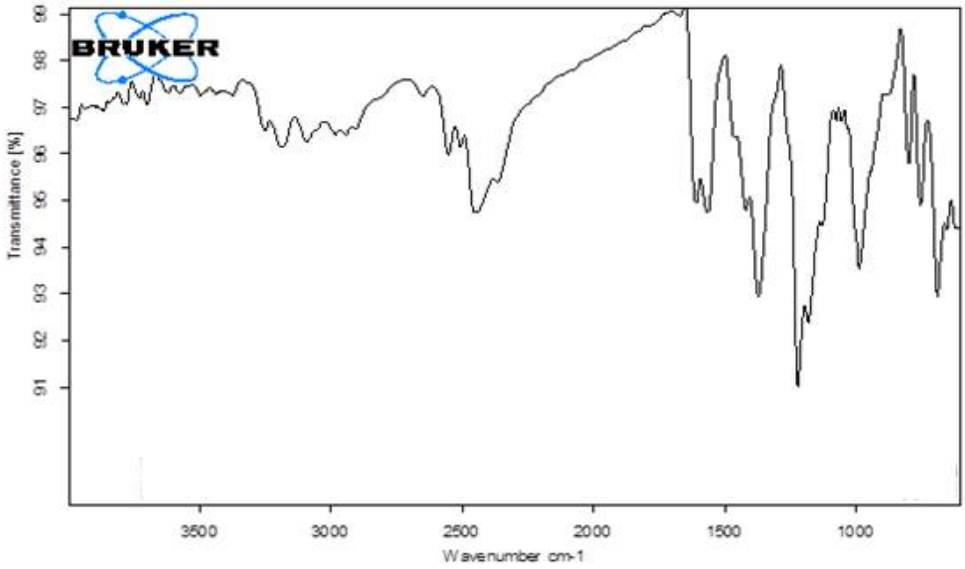

Fig. No. 5 FT-IR spectrum of Ranitidine Hydrochloride

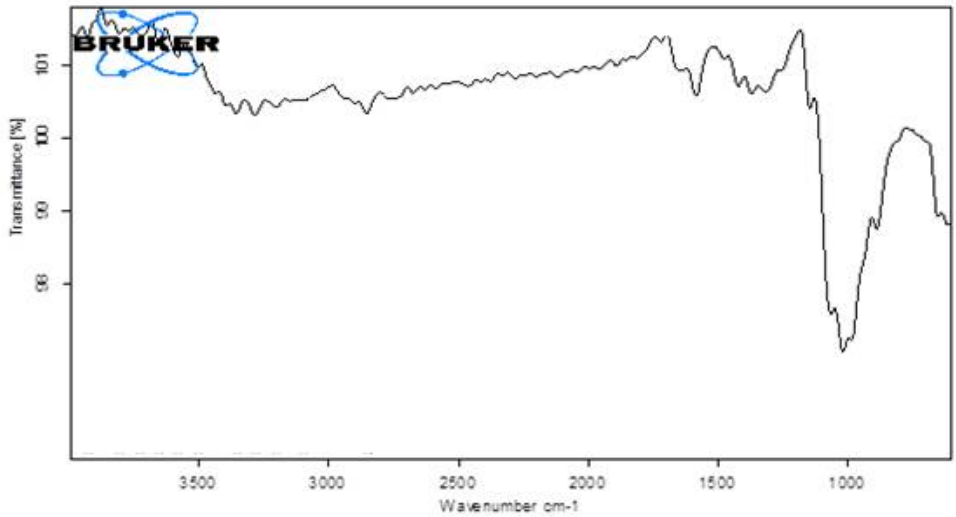

Fig.No. 6 FT-IR spectrum of Chitosan

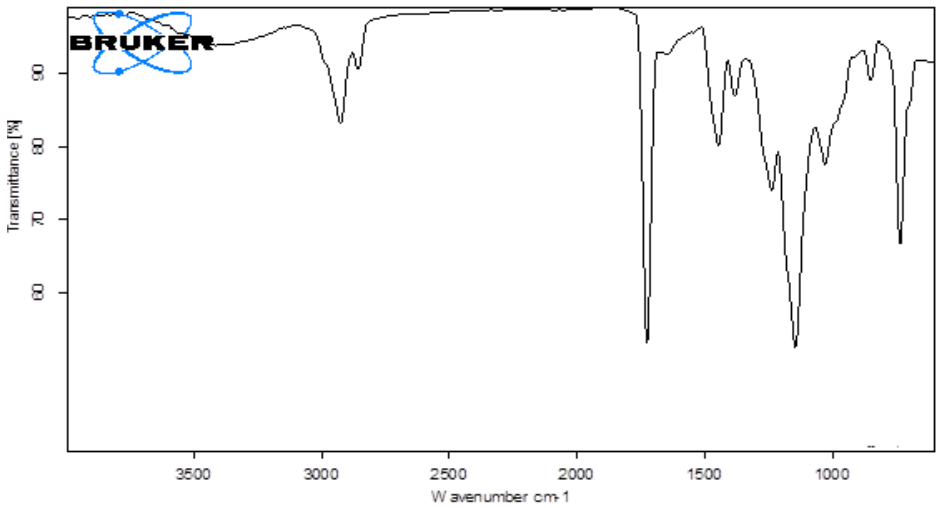

Fig. No.7 FT-IR Spectrum of Eudragit RL 100

The FT-IR spectra of the pure drug-polymers were recorded to check interaction between drug and polymers. The characteristic peak of Ranitidine Hydrochloride, Chitosan, Eudragit RL 100 were appeared in the spectra of physical mixture without any makeable change in the position. It indicates that there was no chemical interaction between Ranitidine Hydrochloride and polymers.

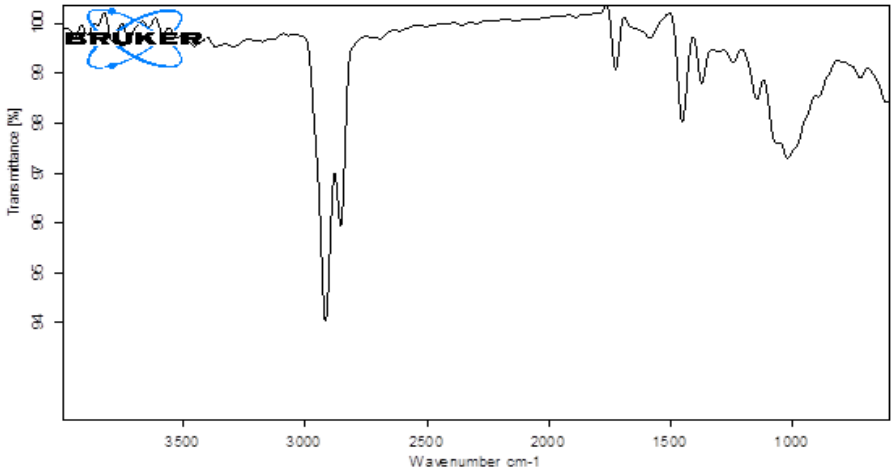

Fig. No.8 FT-IR Spectrum of Optimized Formulation I

The IR spectrum did not show any additional pecks for new functional groups indicating no chemical interaction between drug and excipients and in formulation.

Differential Scanning Calorimetry (DSC) Analysis

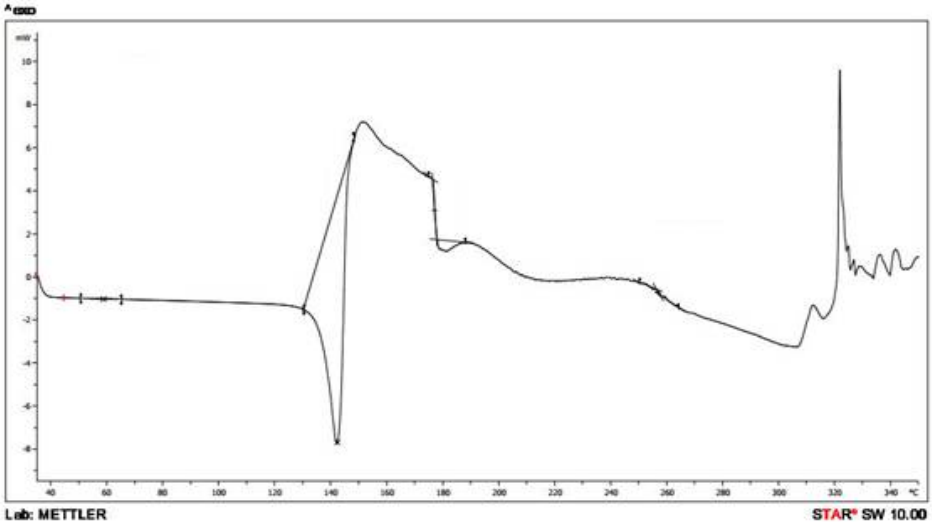

Fig. No.9 DSC of Ranitidine Hydrochloride

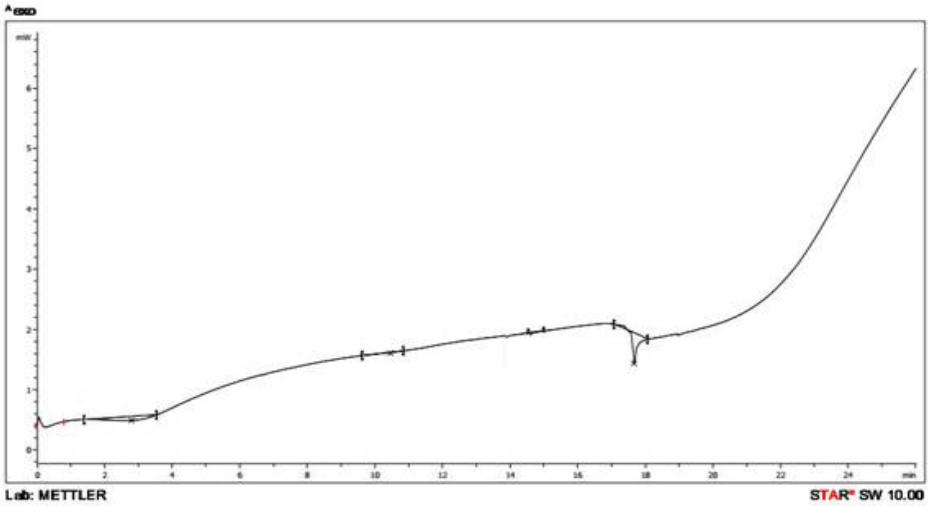

Fig. No.10 DSC of Chitosan

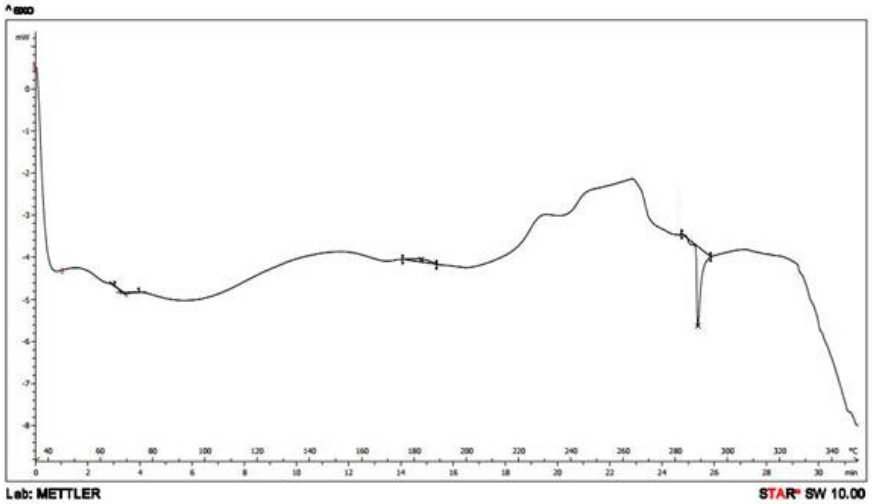

Fig. No. 11 DSC of Eudragit RL 100

The pre-formulation study were performed by Differential Scanning Calorimetry (DSC) and found that there was no any interaction between Ranitidine Hydrochloride and polymers. By the Differential Scanning Calorimetry conclude that Ranitidine Hydrochloride gives peak at 58.63^{0}C which has its Melting point peck which is correspond with formulation Melting point peck.

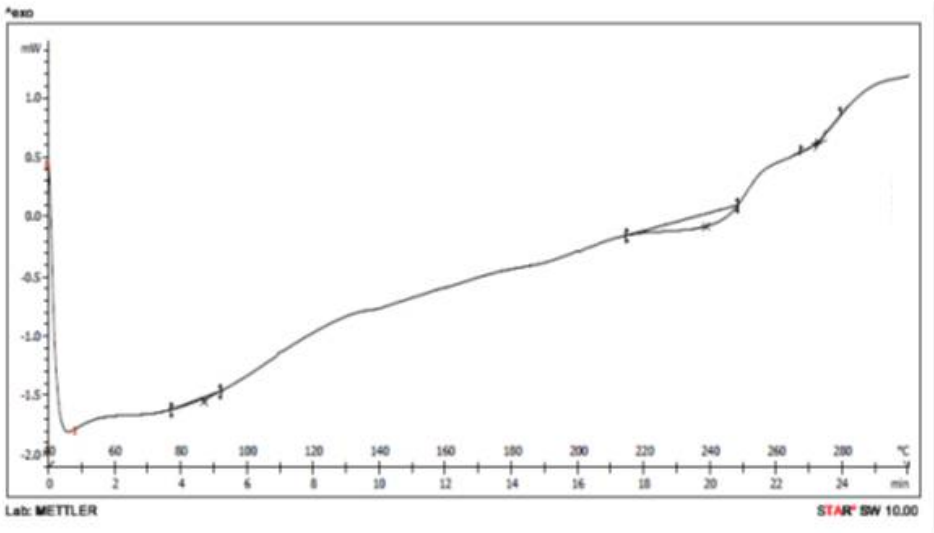

Fig. No.12 DSC of Optimized Formulation I

DSC of optimized formulation gives peak was not shifted to endothermic to exothermic or exothermic to endothermic. The big and small due to presence of water the DSC thermograph confirmed that there was no interaction between Drug and polymers.

CONCLUSION

The prepared floating microspheres by using Emulsification Solvent Evaporation Method showed acceptable drug entrapment and floating behaviour with drug release upto 12 hrs. The microspheres can be prepared by using this method. The prepared microspheres were able to pass all the evaluation parameters which are necessary for the ideal properties of microspheres.

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