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Design and evaluation of floating microspheres of ranitidine HCL

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Abstract
In recent years oral dosage form for gastric retention (floating drug delivery systems) has drawn increasingly more consideration for their theoretical convenience in permitting control over time and site of drug release. The present study intended to develop floating microspheres of Ranitidine HCL, which belong to the class of Histsamine2 blockers. Floating microspheres Ranitidine HCL was prepared by the emulsion solvent evaporation method using HPMC K15M and ethylcellulose as polymer. Six different formulations were developed. The floating microsphere was assessed for the angle of repose, particle size, percentage yield, in vitro lightness, manifestation efficiency, drug-polymer compatibility (IR-study), scanning electron microscopy, drug release and DSC (Differential Scanning Colorimetry), X-Ray Diffraction (XRD) of the microsphere. The outcome of the experiment shows that as the concentration of polymer influences its result the particle size, percentage yield, in vitro buoyancy and drug release of the microsphere. Formulations produced with HPMC K15M exhibited superb Micromeritic properties, percentage yield, in vitro buoyancy, manifestation efficiency, and percentage drug release when contrasted with ethylcellulose polymer. Consequences of our present study propose that the floating microsphere of Ranitidine HCL can be effectively intended to develop controlled drug delivery which can lessen dosing recurrence thus this formulation can be considered as an alternative to conventional dosage forms.

Keywords: Floating drug delivery systems, ranitidine HCL, incorporation efficiency, dosing frequency

Introduction
The genuine challenge in the development of controlled drug delivery system isn't simply to sustain the drug release but also to prolong the release of a drug over an all-encompassing timeframe. The oral route is contemplated as the most encouraging route of drug delivery. The traditional drug delivery system attains as well as continue the drug concentration inside the therapeutically effective range required for treatment, only when taken several times a day. This outcome in noteworthy variance in drug levels. Recently, several technical advancements have prompted the advancement of several novel drug delivery systems (NDDS) that could transform the method of medication and give several therapeutic benefits. The significant goals of these new drug delivery systems are: First, it would be a single dose, which discharges the active ingredient over an increased period of time. Second, it should deliver the active entity directly to the site of action, in this way, limiting or eliminating side effects. To defeat the restrictions of traditional drug delivery systems, floating drug delivery systems have been created. Drugs that have a tight retention time in the gastrointestinal tract (GIT) will have low absorption. For these drugs, gastroretentive drug delivery systems provide the supremacy in extending the duration of the gastric emptying time. Floating microspheres are gastro-retentive drug delivery systems dependent on the non-effervescent approach. Empty microspheres are in a strict sense, spherical empty particles without the core. These microspheres are distinctively free-flowing powders comprising of proteins or synthetic polymers, ideally having a size range of fewer than 200 micrometers. Gastroretentive floating microspheres are low-density systems that have adequate buoyancy to float over gastric content and endure buoyant for a prolonged period of time. The drug is released slowly at the ideal rate bringing about increased gastric retention with decreased variances in plasma drug concentration. Floating microspheres to enhance patient compliance by diminishing dosing frequency, the greater therapeutic effect of short half-life drugs can be attain [1].

The present study includes the formulation and in-vitro evaluation of floating microspheres of Ranitidine Hcl under the gastro retentive drug delivery system for enhancing bioavailability by extending gastric retention time. In the present work, Ranitidine Hcl was picked as the drug to be assimilated into the individual polymer like HPMC K15 M and EC. Ranitidine HCl is a drug recommended to treat disorders brought about by excess stomach acid. Ranitidine HCl is a histamine 2 blockers similar to Rantac 150, Zinetac 150 and Aceloc. H_2 blockers are a class of drugs that obstruct the activity of histamine at the histamine H_2 receptors of the parietal cells in the stomach. This lower the production of stomach acid .H_2 antagonists can be utilized in the treatment of dyspepsia, peptic ulcers, and gastroesophageal reflux disease. It is inadequately absorbed from the lower GIT and has a short elimination half-life (2 h). The Ranitidine Hcl has an oral bioavailability of approximately 52% 8. Ranitidine HCl is less receptive to the impact of genetic polymorphisms for CYP2C19, bringing about a minor impact on its pharmacokinetics and pharmacodynamics [2, 3, 4, 5].

Materials and Methods

Ranitidine Hcl has obtained from Aurobindo lab Hyderabad. India as a gift sample, HPMC K15 was provided by Shreeji chemicals, Mumbai. Ethylcellulose was purchased from Rolex chemicals, Mumbai. Ethanol was obtained from S D fine chemical Ltd, Chennai, Span 80, dichloromethane also obtained from S D fine chemical Ltd, Chennai. Each and every ingredient was of analytical grade.

Selection of vehicle

The solubility of Ranitidine Hcl was checked in different solvents like water and methanol, ethanol, chloroform and ethyl acetate, ether and n-hexane. Studies revealed that was Ranitidine Hcl was found to be very soluble in water and methanol, freely dissolvable in ethanol, chloroform, and ethyl affirmed by analyzing the sample by quantitative determination by UV spectroscopy. Wavelength scan was done from 400-200 nm and maximum absorbance was found at 313nm [6].

Drug polymer interaction (FTIR) study

FTIR spectroscopy was performed on Fourier transformed infrared spectrophotometer (IR-Affinity-1, Shimadzu, Japan). The pellets of drug and potassium bromide were formulated by compacting the powders at 20 psi for 10 min on KBr-press and the spectra were checked in the wavenumber range of 4000-600 cm-1. FTIR study was carried on Ranitidine Hcl, a physical mixture of Ranitidine Hcl and polymers.

Preparation of Ranitidine Hcl floating microspheres

Method used**:** Emulsification – solvent evaporation method Floating microspheres were developed by a single emulsion solvent evaporation method. Accurately weighed drug and individual polymer like Ethylcellulose and HPMC K15 were dissolved in dichloromethane and ethanol (1:1) to form a homogenous polymer solution. This mixture is mixed in 100 ml light liquid paraffin containing 0.01% span 80 keep up at 30-40C at a subsequent time it stirred at ranging agitation speed for 30 min to enable the volatile liquid to vaporize. The floating microspheres formed were filtered, washed several times with petroleum ether and dried properly in a vacuum. The microspheres were then kept in a desiccator above fused calcium chloride [7, 8, 9].

Formulation Design

Formulation design for Ranitidine HCL floating microspheres using different ratios of drug and polymers (1, 2 & 3 HPMC K15M & 4, 5 & 6 ethylcellulose). Shown in table 1

Table 1: 1, 2 & 3 HPMC K15M & 4, 5 & 6 ethylcellulose

S. No	Batch code	Drug: Polymer	Organic solvent system
1	F1	1:1	Dichloromethane: Ethanol
2	F2	1:2	Dichloromethane: Ethanol
3	F3	1:3	Dichloromethane: Ethanol
4	F4	1:1	Dichloromethane: Ethanol
5	F5	1:2	Dichloromethane: Ethanol
6	F6	1:3	Dichloromethane: Ethanol

Evaluation of Ranitidine HCL Floating Microspheres

Drug polymer interaction (FTIR) study

FTIR spectroscopy was carried out on Fourier transformed infrared spectrophotometer (IR-Affinity-1, Shimadzu, Japan). The spectra were studied in the wavenumber range of 4000-600 cm-1. FTIR study was carried on Ranitidine Hcl loaded floating microspheres.

Micromeritic properties

Angle of repose

The angle of repose of different formulations was measured according to fixed funnel standing method (n = 3) θ = tan-1h / r where θ is the angle of repose, r is the radius, and h is the height

Scanning electron microscopy (S.E.M)

To determine the texture, particle size distribution, surface topography, and to examine the morphology of the sectioned or fractured surface S.E.M has been utilized. SEM is the most frequently used method to distinguish drug delivery systems and ease of operation. SEM studies were carried out by using a JEOL JSM T- 330A scanning microscope (Japan). Dry Ranitidine Hcl floating microspheres were placed on an electron microscope brass stub and coated within an ion sputter. The random scanning of the stub is used for talking the image of Ranitidine Hcl floating microspheres

Particle size analysis

Determination of average particle size of Ranitidine Hcl floating microspheres was carried out by optical microscopy in which stage micrometer was retained. A small quantity of Ranitidine Hcl floating microspheres was laid out on a clean glass slide and an average size of 300 Ranitidine Hcl floating microspheres was determined in each batch[10,11].

Percentage yield

The percentage yield of prepared Ranitidine Hcl floating microspheres was determined by using the formula.

$$\text{Percentage Yield} = \frac{\text{Practical Yield}}{\text{Theoretical Yield}} \text{X } 100$$

Buoyancy percentage

50 milligrams of the floating microspheres were put in 0.1M

HCL, 100 ml containing 0.02 w/v%span 80 in a 250ml beaker. The mixture was agitated at 100 rpm in a magnetic stirrer. Pipette out the layer of buoyant microsphere and segregated by filtration process after 12 hrs. From the sinking particulate layer, the Particles were confined by the filtration process and then Particles of both types were dried in a desiccator until we will observe a constant weight.

$$\text{Buoyancy (\%)} = \frac{\text{Wf}}{\text{Wf} + \text{Ws}} \text{ X } 100$$

Where, Wf and Ws are the weights of the floating and settled microspheres, respectively.

Determination of percentage drug entrapment (PDE) [12, 13, 14]

The effectiveness of drug entrapment for every batch was determined in terms of % drug entrapment as per the following formula.

$$\text{PDE} = \frac{\text{Practical Drug Loading}}{\text{Theoretical Drug Loading}} \text{ X } 100$$

Preparation of standard calibration curve of Ranitidine Hcl in 0.1M HCL Scanning of Ranitidine Hcl by UV-spectrophotometer in 0.1M HCL

I Stock: Accurately weighed 100 mg of Ranitidine Hcl, put into a 100 ml volumetric flask then dissolved in 0.1M HCL and make up the volume with 0.1M HCL.

II Stock: Pipette out 1ml of stock solution-I into a 10 ml volumetric flask and make up the volume with 0.1M HCL.

Procedure for calibration of Ranitidine HCL in 0.1M HCL at λmax 313 nm

From the Ranitidine Hcl standard stock solution (1000µg/ml), a 1ml solution was diluted to 10 ml using 0.1M HCL solution to get concentrations of 100 µg/ml. from this solution, aliquots of, 0.5 ml, 1.0 ml, 1.5 ml, 2.0 ml, 2.5 ml, 3.0 ml from standard drug solution were diluted to 10 ml with 0.1M. The absorbance of these solutions was estimated at 313 nm 0.1M HCL as a blank.

Theoretical drug content

Theoretical drug content was determined by calculation assuming that the entire Ranitidine Hcl present in the polymer solution used gets entrapped in Ranitidine Hcl floating microspheres, and no loss take place at any stage of preparation of Ranitidine Hcl floating microspheres Where, Wf and Ws are the weights of the floating and settled microspheres, respectively.

Practical drug content

Procedure: Practical drug content was analyzed by using the following procedure, weighed the amount of Ranitidine Hcl floating microspheres equivalent to 8 mg of Ranitidine Hcl floating microspheres were dissolved in 100 ml of 0.1 M HCL. This solution was kept overnight for the complete dissolution of the Ranitidine Hcl floating microsphere in 0.1M HCL. This solution was filtered and further diluted to make a concentration of 10 µg/ml solution. The absorbance of the solutions was estimated at 275.43nm using a double beam UV-Visible spectrophotometer against 0.1M HCL solution as blank and calculated for the % of the drug present in the sample.

***In vitro* dissolution studies Calibration curve of Ranitidine 0.1M HCL**

The procedure for the calibration of Ranitidine Hcl is the same as mentioned underdetermination of percentage drug entrapment.

Procedure for In vitro dissolution study

The release rate of Ranitidine Hcl floating microspheres was determined by employing the USP XXIII apparatus by rotating the basket method. The dissolution test was performed using 900 ml 0.1M HCL, in 37 ± 0.5℃ at 50 rpm. Ranitidine HCl floating microspheres equivalent to 20 mg were put in a basket to keep away from the floating of microspheres. A test (5 ml) of the solution was withdrawn from the dissolution apparatus hourly for 12 hrs, and the samples were replaced with a fresh disintegration medium. The samples were passed through what man channel paper and the absorbance of these solutions was measured at 313 nm. Dissolution profiles of the formulations were analyzed by plotting drug release versus time plot. Data obtained was also subjected to kinetic treatment to understand the release mechanism.

Kinetics of drug release

To analyze the drug release kinetics and mechanism, the cumulative release data were fitted to models representing zero-order (Q v/s t), first-order [Log(Q0-Q) v/s t], Higuchi's square root of time (Q v/s t1/2) and Korsmeyer Peppas double log plot (log Q v/s log t) respectively, where (Q0-Q) is the cumulative % of drug remaining after time t. and Q is the cumulative % of drug released at time t

In short, the results obtained from *in vitro* release studies were plotted in four kinetics models of the data treatment as follows.

1. Cumulative % of drug release Vs. Time (zero-order rate kinetic
2. Log cumulative % of drug retained Vs. Time (first-order rate kinetics)
3. Cumulative % of drug release vs. √T (Higuchi's classical diffusion equation)
4. Log of cumulative % drug release Vs. log Time (Peppas exponential equation)

Differential Scanning Calorimetry (DSC)

The physical state of the drug in the Ranitidine Hcl floating microspheres was analyzed by DSC. The thermograms of Ranidine Hcl, Ranitidine Hcl floating microspheres with different polymers were obtained at a scanning rate of 10℃/min conducted over a temperature range of 25–350ºC, respectively.

XRay power Diffractometry (XRD) study 18

X-ray diffractometry of the RanitidineHcl and RanitidineHcl microspheres was performed by a diffractometer using a model (Joel JDX-8030, Japan) equipped with a graphite crystal monochromator (Cu-Kα) radiations to observe the physical state of Ranitidine Hcl in the microspheres

Results and Discussion

Drug polymer interaction (FTIR) study

From the spectra of RanitidineHcl, physical mixture of Ranitidine Hcl and individual polymer, Ranitidine Hcl loaded microspheres it was observed that all characteristic peaks of

Ranitidine Hcl were present in the combination spectrum, thus indicating compatibility of the Ranitidine Hcl and polymer FTIR Spectra shown in Figure 1 to 5.

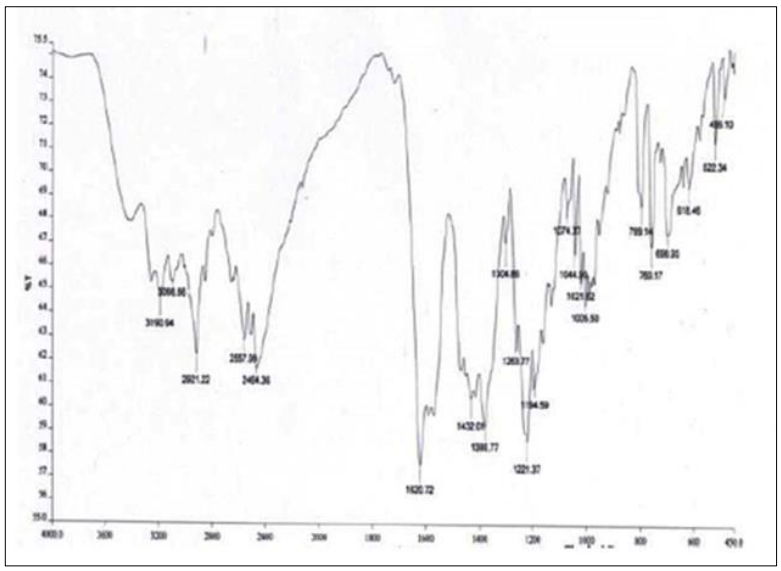

Fig 1: FTIR spectra of the physical mixture of Ranitidine HCl

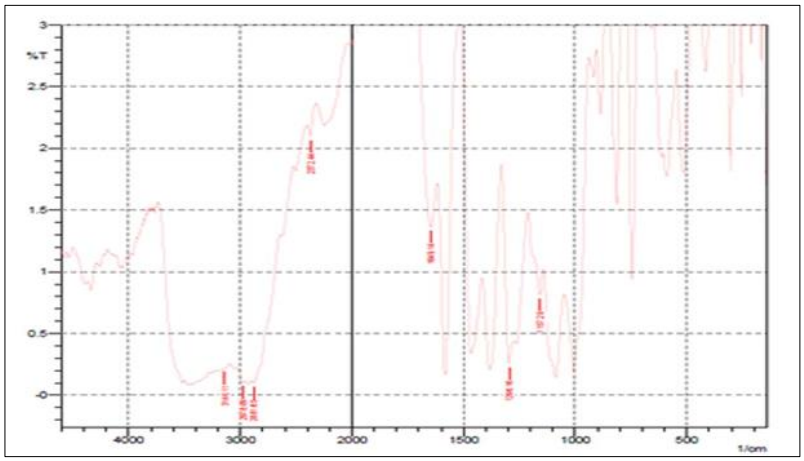

Fig 2: FTIR spectra of the physical mixture of Ranitidine Hcl and HPMC K15 M

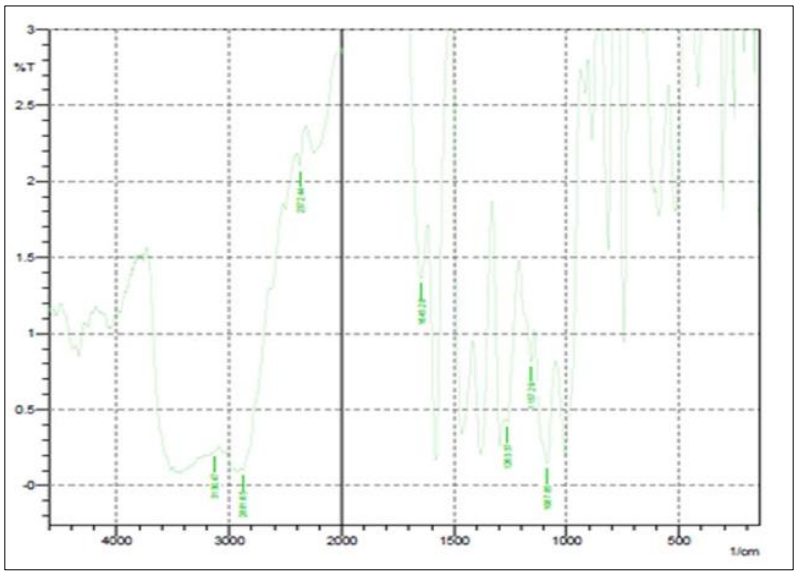

Fig 3: FTIR spectra of the physical mixture of Ranitidine Hcl and ethyl cellulose

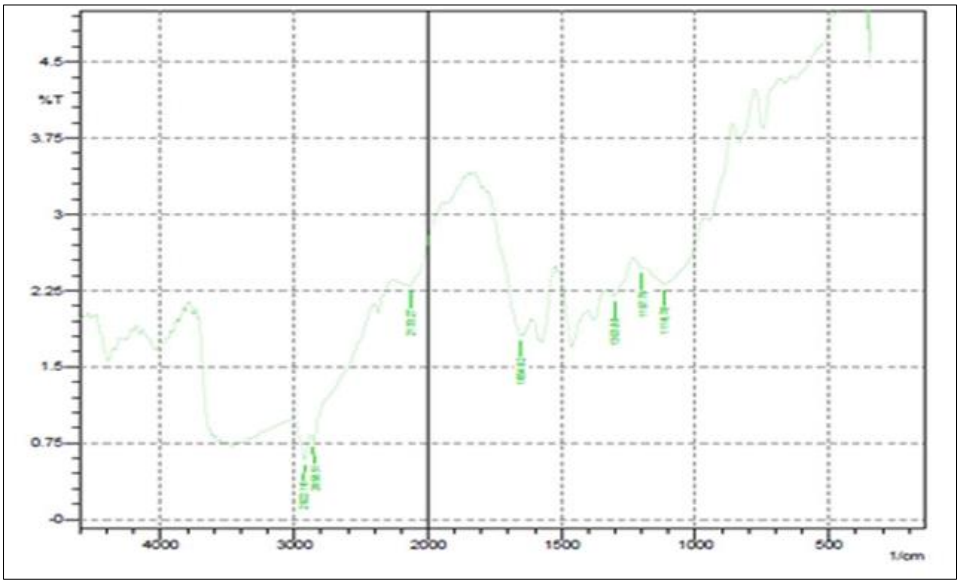

Fig 4: FTIR Spectra of Formulation of drug with HPMC K15 M

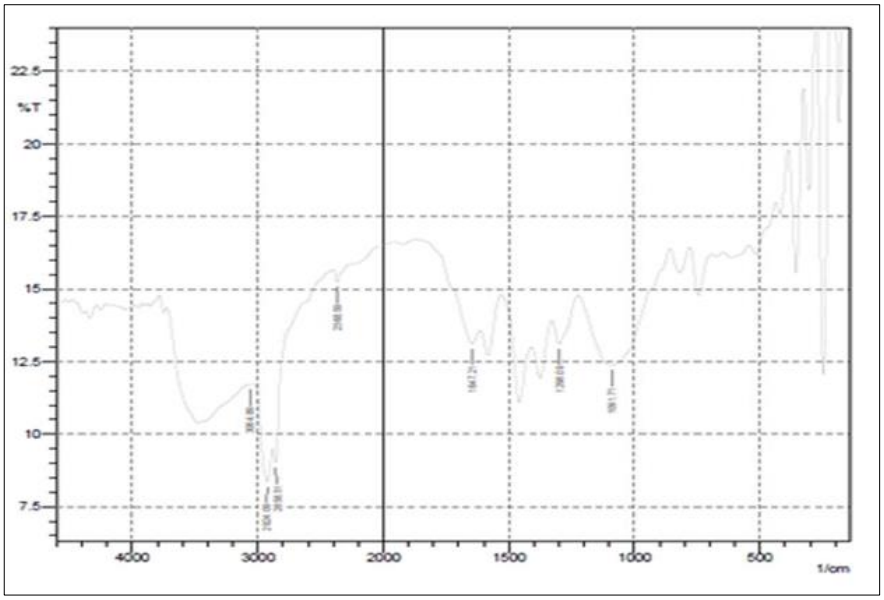

Fig 5: FTIR spectra of formulation of drug with ethyl cellulose

Angle of repose

The formulations with HPMC K15 M and EC show angle of repose value in the range of 20^0.16' to 28^0.22' given in table 2 i.e., less than 30, which shows good flow properties of the formed microparticles.

Table 2: The range of 20^0.16' to 28^0.22'

S.NO	Pure drug	F1	F2	F3	F4	F5	F6
Angle of repose	32º.38´	24º.41´	22º.25´	20º.16´	28º.22´	26º.44´	23º.12´

Surface morphology of ranitidine HCl microspheres

The surface morphology of the Ranitidine Hcl floating microspheres was studied by SEM. SEM photographs of the various formulations were shown in Figure 6. Surface smoothness of the Ranitidine Hcl floating microspheres was increased by increasing the polymer conc., which was confirmed by SEM. At lower polymer conc. (1:1) the rough and wrinkled surface of Ranitidine Hcl floating microspheres was obtained. Fig6 and at higher polymer concentration (1:3) the Ranitidine Hcl Microspheres with HPMC K15M contain smooth surface and smaller in size compare to the microspheres with ethyl cellulose

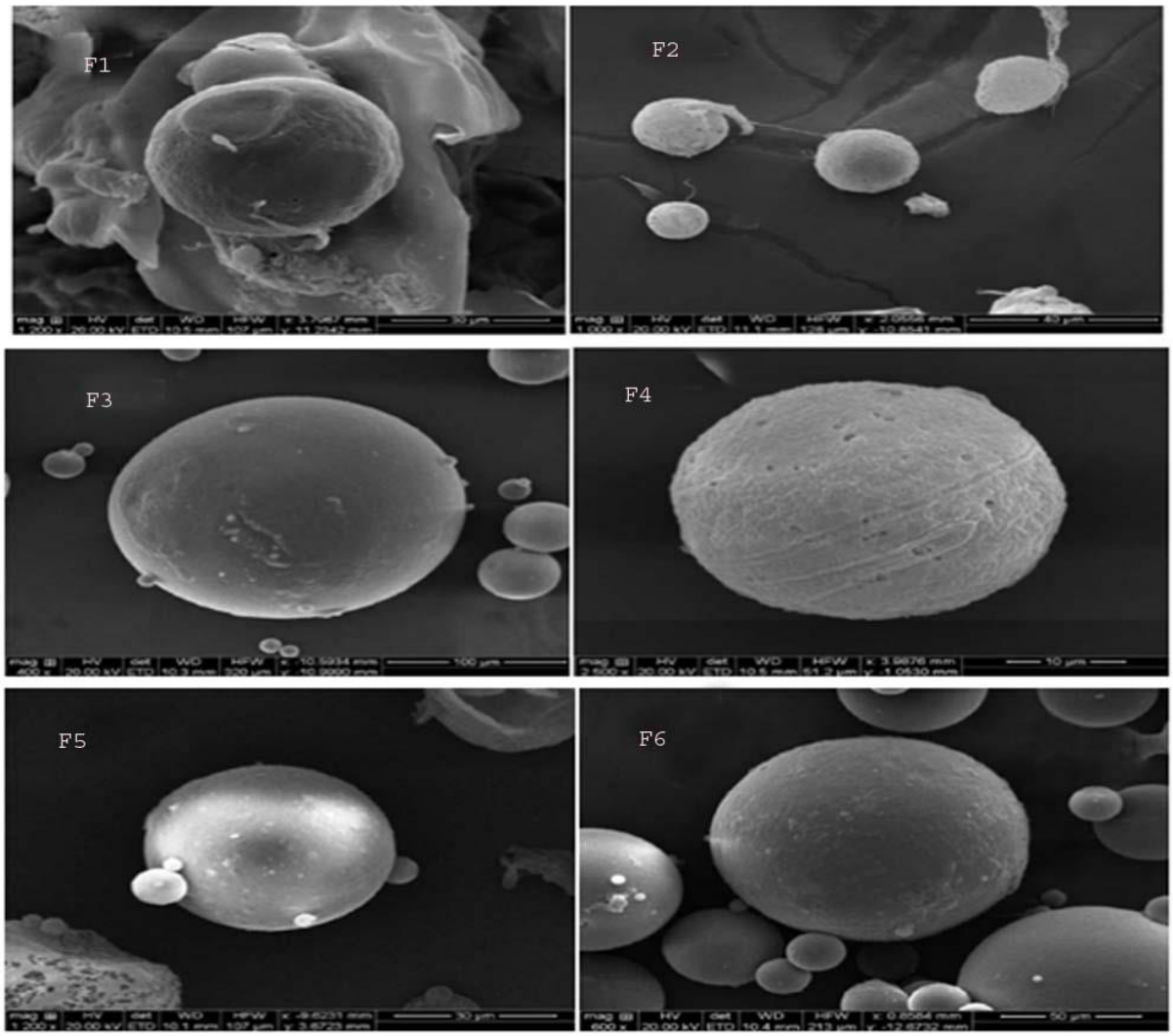

Fig. 6: SEM photographs of Ranitidine HCL floating microspheres

Ranitidine HCL F1, F2, F3, F4, F5 and F6 refers to Ranitidine HCL floating microspheres prepared by using HPMC K15 M and EC with drug: polymer ratio 1:1, 1:2, 1:3, 1:4, 1:5 and 1:6.(HPMC K 15M 1,2,3 & ethyl cellulose 4,5,6)

Determination of Average particle size

As the Ranitidine HCL to polymer ratio was increased, the mean particle size of Ranitidine HCL floating microspheres was also increased in Table 3. The significant increase maybe because of the increase in the viscosity of the droplets (may be due to the increase in the concentration of polymer solution). Ranitidine HCl floating microspheres with HPMC K15M having a size range less when compared to that of ethylcellulose which was shown in table 3.

Table 3: Average diameter of ranitidine HCL floating microspheres

S.no	Formulation	Average particle size
1	F1	74.33
2	F2	75.42
3	F3	77.53
4	F4	87.27
5	F5	91.84
6	F6	94.58

Buoyancy percentage

The microspheres floated for prolonged time over the surface of the dissolution medium without any apparent gelation. As the polymer concentration increases the buoyancy time increases. The results obtained are given in table 4.

Table 4: Buyounancy % of Ranitidine Hcl floating microspheres

S.no	Formulation	%Buoyancy
1	F1	78.40±1.02
2	F2	83.45±1.8
3	F3	91.15±1.01
4	F4	67.30±1.01
5	F5	74.32±1.69
6	F6	79.30±1.60

Percentage of drug entrapment efficiency

Entrapment efficiency increases with an increase in polymer concentration. From the results, it can be inferred that there is a proper distribution of Ranitidine HCL in the microspheres and the deviation is within the acceptable limits. A maximum of 88.60% drug entrapment efficiency was obtained in the Ranitidine HCL floating microspheres which were prepared by using HPMC K15 M. A maximum of 82.22% drug entrapment efficiency was obtained in the Ranitidine HCL floating microspheres which were prepared by using Ethylcellulose. It was further observed that the drug entrapment was proportional to the Ranitidine HCL: polymer ratio and size of the Ranitidine Hcl floating microspheres. By increasing the polymer concentration, the encapsulation efficiency was increased. The results are shown in Table 5.

Table 5: Drug entrapment efficiency of Ranitidine HCL floating microspheres

Formulation Code	Percentage yield	Drug content (%)	Entrapment Efficiency (%)
F1	84.02	17.65	69.80±1.10
F2	88.67	14.95	77.88±0.98
F3	92.88	12.57	88.60±1.12
F4	69.00	31.29	52.74±1.02
F5	76.01	28.96	65.12±1.11
F6	81.33	24.44	82.22±2.25

In-vitro dissolution studies

The *in vitro* performance of Ranitidine HCL floating microspheres showed prolonged and controlled release of Ranitidine HCl. The results of the *in vitro* dissolution studies show a controlled and predictable manner as the polymer concentration increases the drug release from the floating microsphere decreases. The formulations with HPMC K15M i.e.F1 95.25% to F3 78.35% are shown in Table 6 and Figure 7. The formulations with Ethylcellulose i.e.F4 86.48% to F6 64.35% are shown in Table 7 and Figure 8.

Table 6: *In vitro* release data of Ranitidine HCL floating microspheres with HPMC K15M

S.no	Time	% cum. drug release F1±SD	%cum. drug release F2±SD	%cum. drug release F3±SD
1	0	0	0	0
2	1	17.38±0.32	13.47±0.10	12.35±0.13
3	2	25.47±0.22	17.52±0.16	18.37±0.20
4	3	32.49±0.12	28.31±0.11	24.31±0.10
5	4	39.43±0.16	32.36±0.29	30.31±0.04
6	5	46.55±0.13	41.81±0.23	36.34±0.26
7	6	55.32±0.16	51.27±0.24	42.33±0.41
8	7	64.92±0.33	56.68±0.22	48.37±0.16
9	8	76.13±0.26	70.1±0.12	54.36±0.07
10	9	87.77±0.14	75.62±0.21	60.37±0.16
11	10	92.26±0.24	83.74±0.27	66.39±0.16
12	11	93.07±0.42	85.95±0.18	72.39±0.36
13	12	95.25±0.37	88.98±0.26	78.35±0.43

Table 7: In vitro release data of Ranitidine HCL floating microspheres with Ethyl Cellulose

S.no	Time	%cum drug release F4	%cum drug release F5	%cum drug release F6
1	0	0	0	0
2	1	21.44±0.60	10.52±0.64	7.64±0.50
3	2	28.60±0.49	15.63±0.57	13.38±0.54
4	3	33.50±0.69	21.50±0.60	17.78±0.60
5	4	38.69±0.68	27.37±0.62	23.57±0.68
6	5	45.60±0.67	32.56±0.59	28.45±0.60
7	6	53.68±0.60	38.40±0.56	34.01±0.58
8	7	60.46±0.67	43.68±0.60	38.65±0.60
9	8	67.54±0.58	49.43±0.56	44.44±0.69
10	9	75.63±0.68	54.62±0.64	49.52±0.73
11	10	80.43±0.56	60.49±0.52	54.54±0.66
12	11	84.45±0.59	66.33±0.60	59.56±0.56
13	12	86.48±0.53	71.55±0.56	64.35±0.66

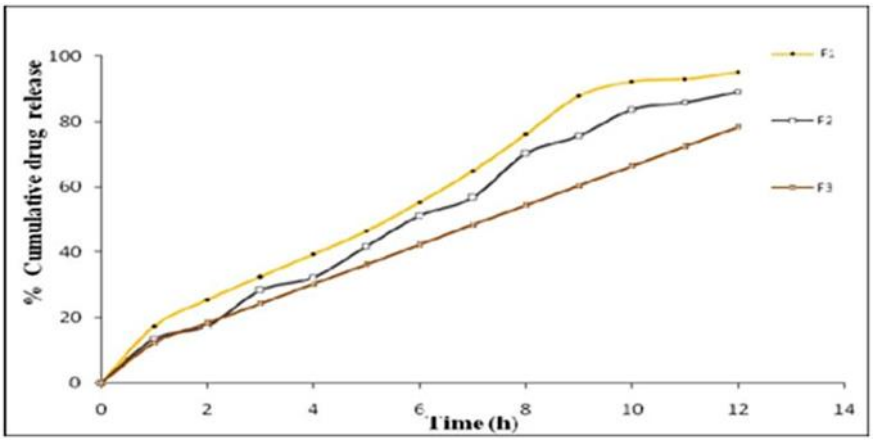

Fig 7: Comparative *in vitro* release profile of Ranitidine HCL floating microspheres with HPMC K 15 M

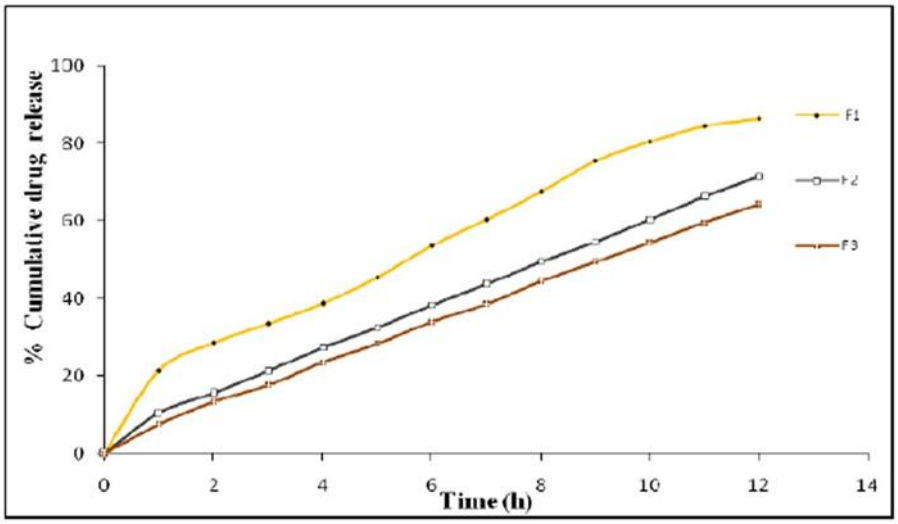

Fig 8: Comparative *in vitro* release profile of Ranitidine HCL floating microspheres with Ethyl Cellulose

Kinetics of drug release

The slopes and the regression coefficient of determinations (r2) were listed in Table 8. The coefficient of determination indicated that the release data were best fitted with zero-order kinetics. Higuchi equation explains the diffusion-controlled release mechanism. The diffusion exponent 'n' values of the Korsmeyer-Peppas model were found to be in the range of 0.5 to 1 for the RPS floating microspheres prepared with HPMC K15 M and EC indicating Non-Fickian of the drug through RPS floating microspheres.

Table 8: Pharmacokinetic release of Ranitidine Hcl floating microspheres with HPMC K15M and EC

Formulation	Zero order	First order	Higuchi matrix	Peppas plot r^2 value n value	
F1	0.9795	0.9244	0.9473	0.9821	0.7420
F2	0.9884	0.9532	0.9376	0.9819	0.8361
F3	0.9959	0.9671	0.9764	0.9928	0.7628
F4	0.9747	0.9704	0.9721	0.9751	0.6046
F5	0.9971	0.9773	0.9454	0.9936	0.7942
F6	0.9988	0.9854	0.9378	0.9979	0.8682

DSC Thermograms

To confirm the physical state of Ranitidine Hcl in the microspheres, DSC of the RPS, RPS loaded floating microspheres with individual polymers were carried out and shown in Fig 9 to 11. The DSC trace of Ranitidine Hcl showed a sharp endothermic peak at 141.89 ℃, it is a melting point. RPS floating microspheres with HPMC K15M and EC showed the same thermal behavior 147.18 ℃ and 147.32 ℃ respectively indicating that there was no interaction between the RPS and the polymer in the solid-state. The melting point range of Ranitidine Hcl is between 40-142 ℃, thus indicating there is no change of Ranitidine Hcl in a pure state. The absence of an endothermic peak of the RanitidineHcl at 141 ℃ in the DSC of the Ranitidine Hcl floating microspheres suggests that the Ranitidine Hcl existed in an amorphous or disordered crystalline phase as a molecular dispersion in a polymeric matrix.

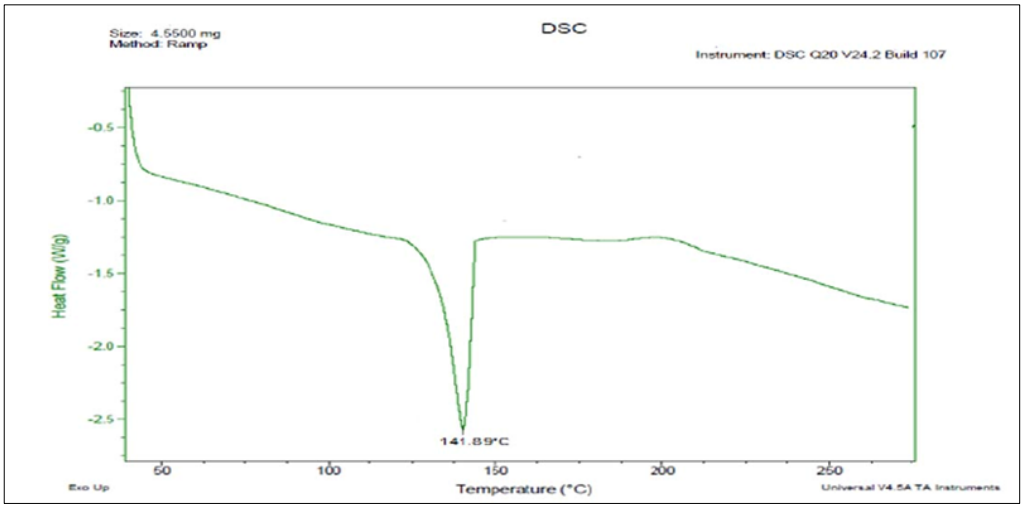

Fig 9: DSC of pure drug Ranitidine HCl

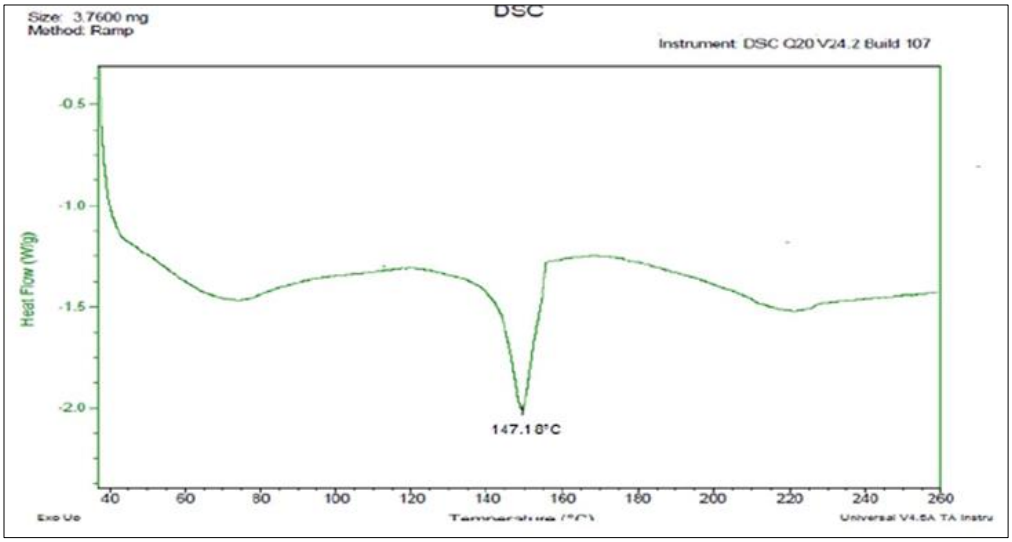

Fig 10: DSC of formulation with HPMC K15 M

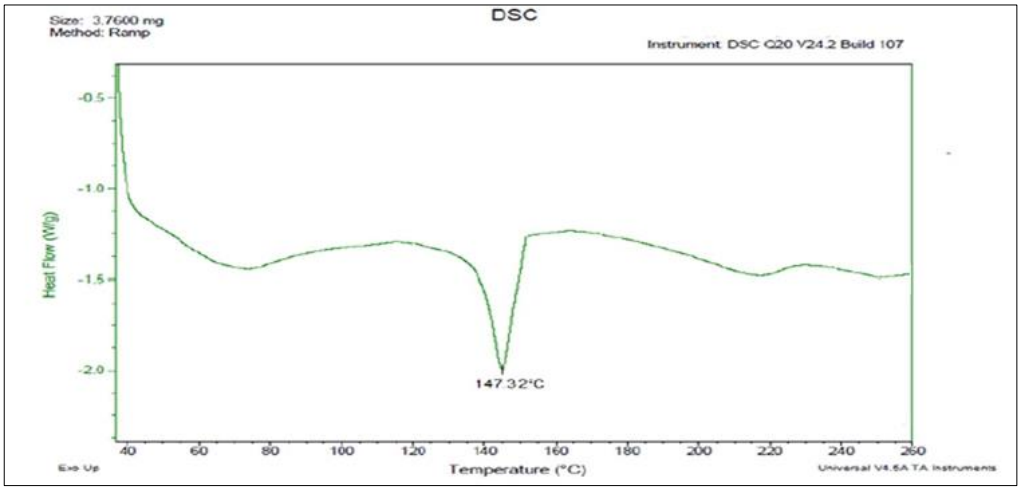

Fig 11: DSC of formulation with Ethylcellulose

X-Ray Diffraction Thermograms

To confirm the physical state of the Ranitidine HCL in the microspheres, powder X-ray diffraction studies of the Ranitidine HCL, Ranitidine HCl microspheres with individual polymers were carried out. X-ray diffractograms were shown in Figure 12 to 14 and showed that the Ranitidine Hcl is still present in its lattice structure where it is completely amorphous inside the RPS microspheres. This may be due to the conditions used to prepare the Ranitidine HCl microspheres lead to cause complete drug amorphization.

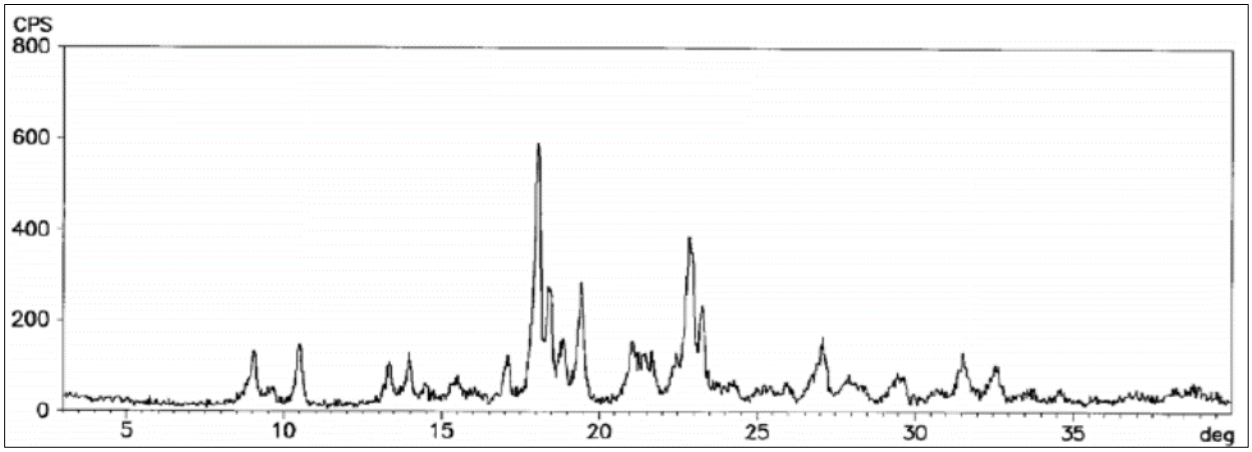

Fig 12: XRD thermogram of Ranitidine HCl

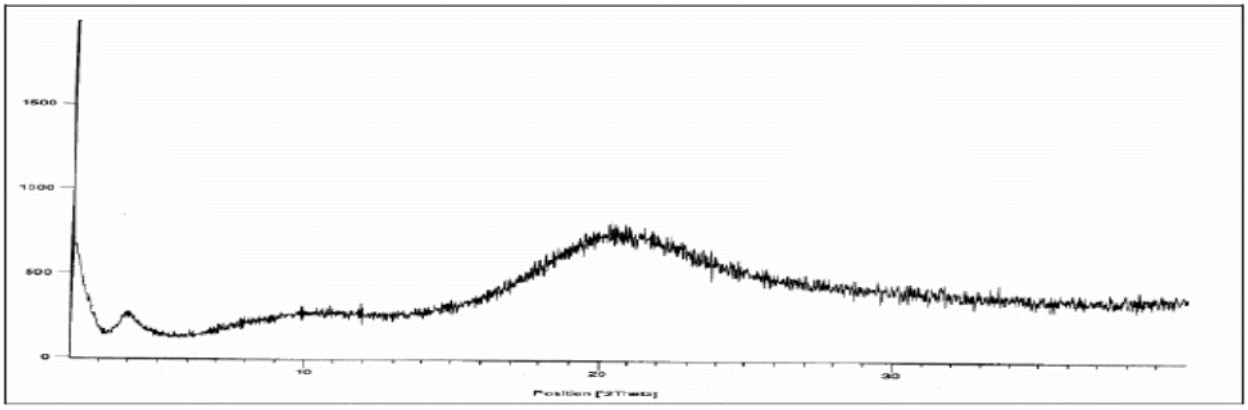

Fig 13: XRD thermogram of Ranitidine Hcl formulation with HPMC K15 M

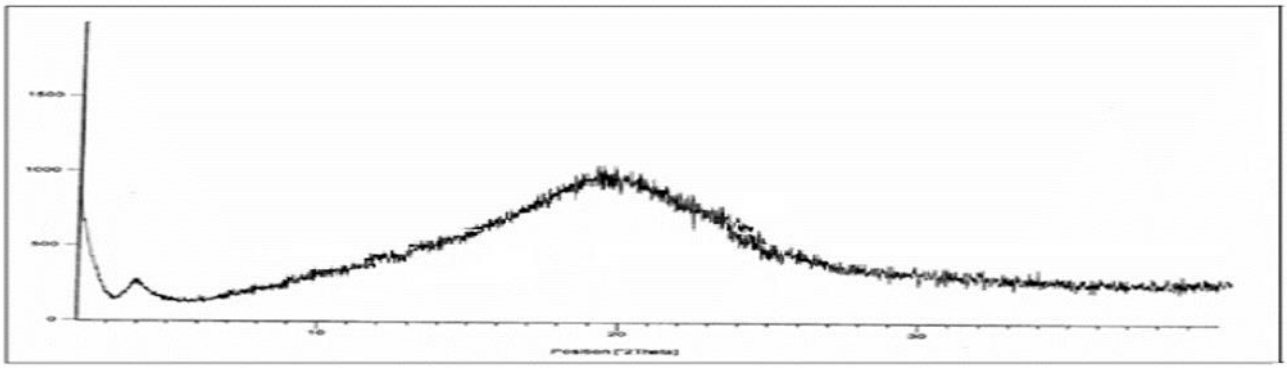

Fig 13: XRD of formulation of Ranitidine HCL with EC

Conclusion

The concept of formulating floating microspheres containing Ranitidine HCL offers a suitable, practical approach to achieve a prolonged therapeutic effect by continuously releasing the medication over an extended period of time. Floating microspheres of Ranitidine HCL were prepared successfully by emulsion solvent evaporation method using the different concentrations of individual polymers like HPMC K15 M, and EC utilizing prolonging its gastric retention thus improving the oral bioavailability of the drug. It would be faster and more economical to alter beneficially the properties of the existing drugs than developing new drug entities hence this formulation will be boon to novel drug dosage forms.

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Conflict of interest

The authors declare that they have no conflict of interest. The article does not contain any studies with animals or human participants performed by any of the authors.

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