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Formulation and Evaluation of Floating Microspheres of Rabeprazole Sodium

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ABSTRACT

The aim of current research was to prepare and evaluate the floating microspheres of Rabeprazole sodium to prolonging its gastric retention time. Rabeprazole sodium is a proton pump inhibitor which acts by suppressing gastric H^+, K^+ ATpase at the secretory surface of the gastric parietal cells. It has poor oral bioavailability (52%) and short half life (1-2h) owing to its poor absorption in the lower git tract. The floating microspheres of Rabeprazole sodium were prepared by emulsion solvent diffusion method using Eudragit RS 100 and HPMC K4M as polymers and using dichloromethane and ethanol as a solvent system. The prepared microspheres were evaluated for micromeretic properties, percentage yield, particle size, percentage yield, entrapment efficiency, *in-vitro* floating efficiency and *in-vitro* drug release studies. The prepared microsphere were found to be spherical and free flowing and remain buoyant for more than 8 h and percentage yield was found to be in the range 86.95% to 66.03%. The drug entrapment efficiency was found to be 90.12% to 59.87%, particle size in the range of 208µm to 550µm. *In-vitro* release studies showed that drug is released from the formulation over period of 12h in a sustained manner and the release mechanism followed a fickian type.

KEYWORDS: Microspheres, Rabeprazole sodium, emulsion Solvent diffusion method, Eudragit RS 100, HPMC K4M.

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INTROUCTION:

Oral drug delivery has been known for decades as the most widely utilized route for administering drugs among all the routes that have been employed for the systemic delivery of drugs *via* various pharmaceutical products of different dosage forms. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration without any expertise assistance, patient compliance, flexibility in formulation.[1] Gastroretentive drug delivery system (GRDDS) is one of the novel approach in this area. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the GIT and maintain an effective drug concentration in the systemic circulation for a long time. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the GIT.[2]

The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, floatation, sedimentation, expansion modified shape systems, or by the simultaneous administration of pharmacological agent**.**[3] Floating systems was firstly developed by Davis in 1968. Floating drug delivery system is an effective technology to prolong the gastric residence time in order to improve the bioavailability of the drug. Floating drug delivery systems have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time.[4]

Microspheres can be defined as solid, approximately spherical particles ranging in size from 1 to 1000 micrometer. The Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, which are biodegradable in nature. Solid biodegradable microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drugs.[5] Gastro-retentive floating microspheres are low-density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. As the system floats over gastric contents, the drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration.[6]

The objective of current study was to formulate and evaluate of floating microspheres of rabeprazole sodium. Rabeprazole sodium was chosen as a drug candidate for floating microspheres

formulation owing to its poor oral bioavailability (52%) and short half life (1-2h) because it is poorly absorbed in lower Git tracts. Rabeprazole sodium is a benzimidazole derivative and potent anti-ulcer agent.[7,8] Moreover, rabeprazole sodium belongs to BCS class III and hence possesses high aqueous solubility and low permeability. To improve the oral bioavailabilty and half life of drug floating microspheres were prepared using rate controlling polymer Eudragit RS 100 and hydrophilic polymer HPMC K4M by emulsion solvent diffusion techniques.

EXPERIMENTAL

Materials

Pure Rabeprazole sodium was obtained from Alkem laboratory Ltd. Mumbai exgratis, The other chemicals were obtained from authenticated manufacturers i.e Eudragit RS 100 (Leo chem. Bangalore, Karnataka), Hydroxy methyl cellulose (Leo Chem. Mumbai), Ethanol (Nice Chemicals Pvt. Ltd, Cochin, Kerala), Dichloromethane (Ranbaxy fine chemical. Ltd, New Delhi, India), Polyvinylalcohol (Ranbaxy fine chemical. Ltd, New Delhi). All other reagents used were of analytical grade.

Method of Preparation of Floating Microspheres

Floating microspheres having rabeprazole sodium (60 mg) were prepared using emulsion solvent diffusion technique. Nine different formulations (F1 to F9) were prepared using a polymer mixture of Eudragit RS100, Hydroxypropylmethylcellulose (HPMC K4M). After number of initial trials Eudragit RS100 concentration was fixed to 400 mg in each formulation where as concentration of HPMC K4M was varied from 0-80 mg as show in table 1. In each formulation the drug polymer mixture was dissolved in a blend of ethanol (8mL) and dichloromethane (8mL). The resultant mixture was dropped into 0.75% polyvinyl alcohol solution (200mL). The solution was stirred with a propeller type agitator at 40^0C temperature for 1h at 300 rpm. The formed floating microspheres were passed through Sieve no-12, washed with water and dried at room temperature using desiccators

Evaluation of Floating Microspheres

The prepared floating microspheres of rabeprazole sodium were evaluated for their quality control tests like micromeretics studies, percentage yield, drug entrapment efficiency, particle size and shape analysis, FTIR studies, scaning electron microscopy, *In-vitro* buoyancy, *In-vitro* drug release studies etc.

Table No. 1: Composition of various formulations of floating microspheres containing Rabeprazole sodium

Formulation code	Drug (mg)	Polymer ratio (mg)		Organic solvent ratio (1:1mL)	
		Eudragit RS 100	HPMC K4M	Ethanol	Dichloromethane
F1	60	400	-	8	8
F2	60	400	10	8	8
F3	60	400	20	8	8
F4	60	400	30	8	8
F5	60	400	40	8	8
F6	60	400	50	8	8
F7	60	400	60	8	8
F8	60	400	70	8	8
F9	60	400	80	8	8

MICROMERETICS STUDIES[9]

The following micromeretic properties were studied for the developed floating microspheres of rabeprazole sodium.

Bulk Density/ Tapped Density

Both bulk density (BD) and tapped density (TD) were determined. A suitable amount of microspheres from each formulation, was introduced into a 100 mL measuring cylinder. After observing its initial volume, the cylinder in the density tapper instrument and density is measured according to USP method II (up to1250 taps). The tapping was continued until no further change in volume was noted. Volume of packing after tapping was noted. BD and TD were calculated using eqn. 1 and 2 respectively.

BD = weight of the powder / volume of the packing **…(1)**

TD = weight of the powder / tapped volume of packing **…(2)**

Compressibility Index

Compressibility index of the microspheres was determined by Carr's compressibility index as given by eqn. 3 and inference was drawn on the basis of values of % compressibility shown in table 15.[10,11]

Carr's index (%) = [(TD – BD) x 100] / TD **...(3)**

Angle of Repose

Static angle of repose was measured according to the fixed funnel and free standing core method of Banker and Anderson. Microspheres were carefully poured through the funnel until the apex of the conical pile so formed just reached the tip of the funnel. Height of instrument was fixed to 4 cm. Thus, with r being the radius of the base of the microspheres conical pile and the angle of repose (θ) was calculated by using the eqn. 4.[10,11]

$\tan \theta = h/r$ **…(4)**

Hausner's Ratio

It is the ratio of tapped to bulk density and was calculated by using the eqn. 6.[12]

Hausner's ratio = TD/BD **…(5)**

Percentage Yield

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. The percentage yield of floating microspheres was calculated using eqn.6[13]

% Yield = (Actual weight of product / Total Weight of excipient and drug) × 100 **...(6)**

Drug Entrapment Efficiency

To determine the incorporation efficiency, microspheres were taken, thoroughly triturated and suspended in a minimal amount of alcohol. The suspension was suitably diluted with water and filtered to separate shell fragments. Drug content was analyzed spectrophotometrically at 260.5 nm. The drug entrapment efficiency of floating microspheres was calculated using eqn. 7[13]

Drug entrapment efficiency (%)= Actual drug content X 100/Theoretical drug content **…(7)**

Particle Size and Shape

The particle size of the microspheres was measured using an optical microscopic method and the mean particle size was calculated by measuring 25 particles with the help of a calibrated ocular micrometer with stage micrometer.[9]

Fourier Transform Infrared Spectroscopy Studies

The drug - polymer interaction and also degredation of drug while processing for microspheres was determined by Fourier Transform Infra-Red (FTIR) spectroscopy studies. The FT-IR spectra of the samples were recorded in the KBr disk using IR Spectrophotometer.

Scaning Electron Microscopy Studies

The external and internal morphology of the microspheres were studied using Scanning Electron Microscopy (SEM). The samples for SEM were prepared by lightly sprinkling on a double adhesive tape stuck to an aluminum stub. The stubs were then coated with platinum to a thickness of about 10 Å under an argon atmosphere using a gold sputter module in a high vacuum evaporator. The stub containing the coated samples was placed in the scanning electron microscope (JSM- 6360A; JEOL, Tokyo, Japan) chamber. The samples were then randomly scanned, and photomicrographs were taken at the acceleration voltage of 20 kV.[14]

In-Vitro Floating Efficiency

Fifty milligrams of the floating multiparticulates were placed in 100 mL of the simulated gastric fluid (SGF, pH 2.0) containing 0.02% w/v Tween 20. The mixture was stirred at 100 rpm with a magnetic stirrer. After 8 hours, the layer of buoyant multiparticulate was pipetted 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 was achieved. Both the fractions of microspheres were weighed and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles.The floating efficiency of floating microsphere can be calculated by eqn. 8

$$\text{Buoyancy (\%)} = (Wf / Wf + Ws)x100 \quad \textbf{...(8)}$$

Where, Wf and Ws are the weights of the floating and settled microparticles.[9]

In-Vitro Drug Release Studies

Release rate of drug from hollow floating microspheres was determined using USP dissolution apparatus type II at 37 ± 0.5^0C. The dissolution test was carried out using 900 mL of 0.1 N HCl dissolution medium at 100 rpm for the required period of time. At an appropriate interval, specific volume of aliquots were withdrawn and replaced with an equivalent volume of fresh dissolution medium to maintain the constant volume of dissolution medium. The sample solutions were filtered through Whatman filter paper and solutions were analysed using UV spectrophotometer.

Kinetic Analysis of Dissolution Data

The dissolution data of floating microspheres of rabeprazole sodium of optimized formulation F6 was fitted to zero order, first order, Higuchi's and Korsmeyer-Peppas model to ascertain the kinetic modeling of drug release.

RESULTS AND DISSCUSION

All the nine floating microspheres formulations of rabeprazole sodium were evaluated in terms of floating parameters.

Micromeretics Studies

Micromeritic properties of the prepared microspheres of various formulations F1 to F9 were evaluated for bulk density, tapped density, Carr's index, angle of repose and hausner's ratio. BD and TD for all the formulations were found in the range between 0.375 to 0.750 and 0.432 to 0.750 respectively. Compressibility index of the microspheres of various formulations was found in the range of 6.28% to 13.19%. These values indicate the excellent flow properties. Because in the range of 5-15% carr's index shows excellent flow respectively. The angle of repose of the floating microspheres of various formulations was in the range 22.98^0 to 27.35^0, indicating that the studied floating microspheres have good to excellent flow properties, because θ should be 25^0-30^0 and $<25^0$ shows good flow properties respectively. The hausner's ratio of the floating microspheres of various formulations was in the range 1.06 to 1.15 indicating that the studied floating microspheres have good flow rate. Because the range of hausner's ratio less than 1.25 shows good flow. The results suggest that all the values are within the range, which indicates good flow properties the values were given in table 2.

Table-2 Micromeretics studies of floating microspheres of rabeprazole sodium

Formulation code	Bulk density (gm/cm)	Tapped density (gm/cm)	Carr's index (%)	Angle of repose	Hauner's ratio
F1	0.462	0.493	6.28	27.35	1.06
F2	0.461	0.500	7.80	25.70	1.08
F3	0.666	0.750	11.20	26.56	1.12
F4	0.385	0.421	8.50	25.76	1.09
F5	0.625	0.689	9.28	24.31	1.102
F6	0.461	0.530	13.01	24.91	1.14
F7	0.500	0.542	7.74	22.98	1.08
F8	0.468	0.500	6.40	25.82	1.06
F9	0.375	0.432	13.19	25.11	1.15

Percentage Yield

The percentage yield of produced floating microspheres of rabeprazole sodium of various formulations F1 to F9 was found to be in the range of 86.95% to 66.03% as shown in table 3.

Table-3: Evaluation parameters of floating microspheres of rabeprazole Na of various formulations F1 to F9.

Formulation code	Percentage yield	Drug entrapment efficiency	Particle size (µ m)	Shape of microspheres	Percent buoyancy after 8h
F1	86.95±0.85	90.12±0.53	550±1.15	Spherical	90±0.06
F2	82.97±0.15	84.6±3.02	450±0.09	Spherical	87±0.12
F3	78.53±0.14	81.63±2.02	420±0.55	Spherical	89±0.16
F4	76.47±0.96	78.73±2.00	384±0.63	Spherical	82±1.09
F5	70.63±2.81	76.48±2.14	337±2.23	Spherical	77±0.03
F6	68.56±1.23	73.01±2.81	312±2.56	Spherical	75±0.20
F7	67.31±3.81	68.46±1.07	280±1.08	Spherical	73±1.32
F8	66.03±1.53	63.29±0.98	246±3.21	Spherical	69±0.56
F9	64.79±2.38	59.87±1.58	208±1.78	Spherical	64±2.45

It has been observed that percentage yield decrease F2 to F9. However, low percentage yield in some formulation may be because of microspheres lost during successive decantation during washing process. Parallel trend was observed in case of floating microspheres of metformin HCL.[15]

Drug Entrapment Efficiency

The formulation containing drug : HPMC K4M : Eudragit RS 100 ratio, The drug entrapment efficacies of different formulations were in the range of 90.12% to 59.87
is shown in table 3. It indicating that the drug entrapment efficiency slightly decrease with increase in the concentration of HPMC K4M.

Particle Size and Shape

The particle size and shape of the microspheres was measured using optical microscope. The particle size of the floating microspheres of rabeprazole sodium of various formulations was found to be in the range of 208µm to 550µm and spherical it is shown in table 3. It was observed that the mean particle size of the floating microspheres was significantly decreased with increased in the concentration of HPMC K4M and with the concentration of Eudragit RS 100 the paricle size increased.

Fourier- Transform Infrared Spectroscopy Studies

The rabeprazole sodium along with the physical mixture of Eudragit RS 100 and HPMC K4M was kept at different environment condition to observe the physical compatibility of the drug with excepient. A comparision of the initial sample, control sample and the samples kept at different environmental condition for physical changes was visually done periodically at different times. No physical changes were observed with respect to colour, odour, lump formation etc. The result obtained from Physical compatibility studies were confirmed by FT-IR studies (Fig. 1, 2). Compares FT-IR spectra of pure drug and its mixture with Eudragit RS 100 and HPMC K4M

On comparing the above two spectra it is evident that all the peaks of rabeprazole sodium were present in the sample (Drug + Excipient) kept under compatility studies. Therefore, it can be concluded that there was no physical and chemical changes occured indicating that excipients are sssscompatible with the drug.

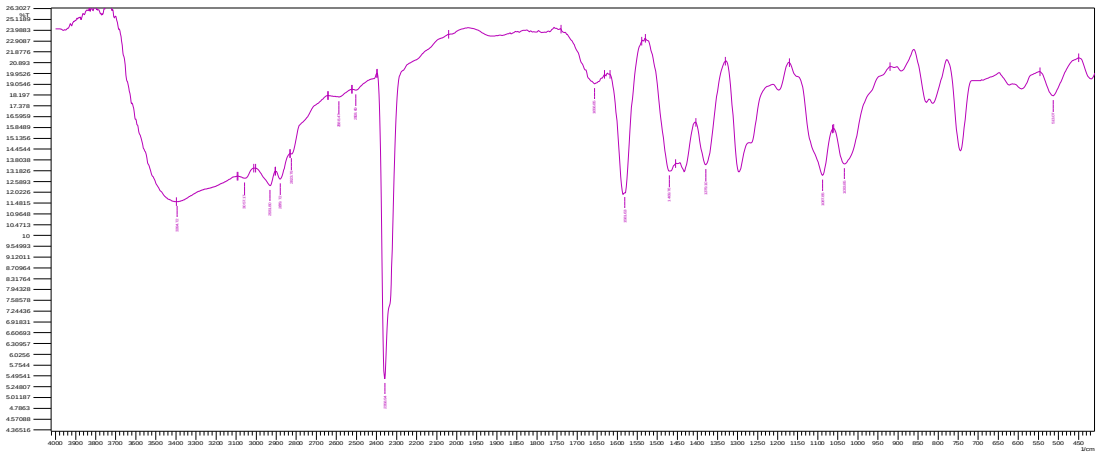

Fig.1: FT-IR spectra of pure drug

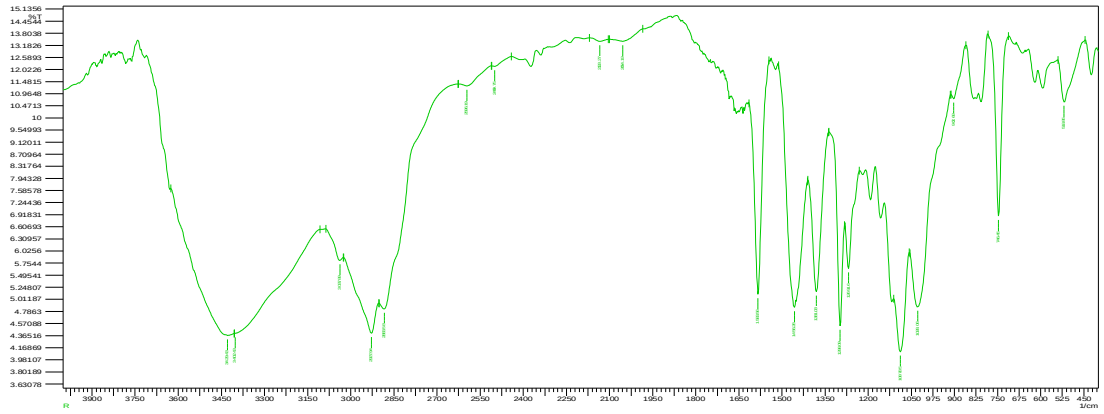

Fig.2: FT-IR spectra of Drug + excipients

SCANING ELECTRON MICROSCOPY

Morphology of floating microspheres of F6 formulation was examined by scaning electron microscope. The view of the microspheres showed hollow structure with a smooth surface morphology (fig. 3). It is also evident from fig 3 that the outer shell of microspheres is porous. The porous shell was obtained may be due to evaporation of solvent entrapped within the shell of microsphere.

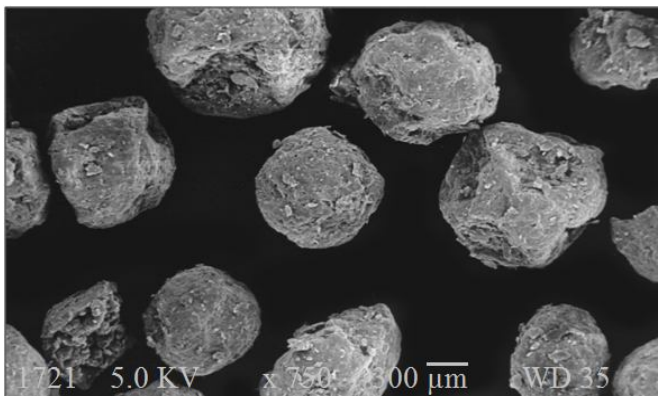

Fig.3: SEM of floating microspheres of Rabeprazole sodium

IN-VITRO FLOATING EFFICIENY

The in-vitro floating efficiency of floating microspheres of rabeprazole sodium of various formulations is shown in table 3. When the floating microspheres of rabeprazole sodioum are dispersed in simulated gastric fluid without enzymes, owing to high water solubility, Eudragit RS 100 goes into solution forming pores on microspheres due to matrix erosion. This phenomenon leads the microspheres to float. From the results of floating efficiency we can conclude that floating microspheres prepared using Eudragit RS 100 and HPMC K4M showed good floating properties. However, as the ratio of HPMC K4M increased the floating behavior get reduced. This may be attributed to increased weight of microspheres. Parallel results were obtained with sitagliptin phosphate and metformin HCL.[15,16]

IN-VITRO RELEASE STUDIES

The *in-vitro* release studies were conducted to investigate the effect of polymer Eudragit RS 100 and HPMC K4M on the release rate of floating microsphere of rabeprazole sodium. The release of drug from a floating microspheres occur through diffusion mechanism due to drug polymer affinity that control the release of drug from the formulation. The *in-vitro* release of drug of different formulation are depicted in table 3 and graphically in fig.4. Maximum drug release rate (92.85%) was observed with formulation F6 having 50mg of HPMC K4M. It is evident from table 26 that as the concentration of HPMC K4M increase beyond 50mg, drug release rate decreases. This may be attributed to the increases in thickness of the outer surface of microspheres with increasing concentration of polymer HPMC K4M.

Table-3: In-vitro Drug release of floating microspheres of rabeprazole sodium of various formulations F1 to F4

Time in hours	Cumulative percentage drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.08	7.981	8.306	5.296	11.065	13.843	13.130	8.991	16.89	11.670
0.16	11.065	12.067	17.428	17.229	26.586	20.165	13.130	23.5	16.342
0.33	17.358	17.358	23.492	23.471	35.520	29.212	25.262	32.441	26.521
0.50	21.306	23.047	28.342	26.471	44.383	38.188	31.820	38.167	31.880
0.75	25.488	28.471	34.776	32.874	58.879	44.102	42.701	44.563	37.621
1	31.647	33.532	40.679	40.174	65.954	50.853	53.489	50.038	44.335
2	36.524	42.855	46.402	44.516	71.183	59.400	60.744	56.829	51.428
3	39.406	53.093	52.933	55.879	77.401	66.835	69.315	62.674	56.599
4	43.855	60.087	61.610	63.784	81.272	78.249	73.198	66.930	61.418
6	49.093	65.784	65.685	70.749	86.746	83.904	77.058	74.791	68.644
8	58.530	70.749	69.984	77.361	89.006	89.282	80.927	77.823	72.826
12	67.397	75.361	77.385	85.803	90.321	92.853	87.474	83.761	80.567

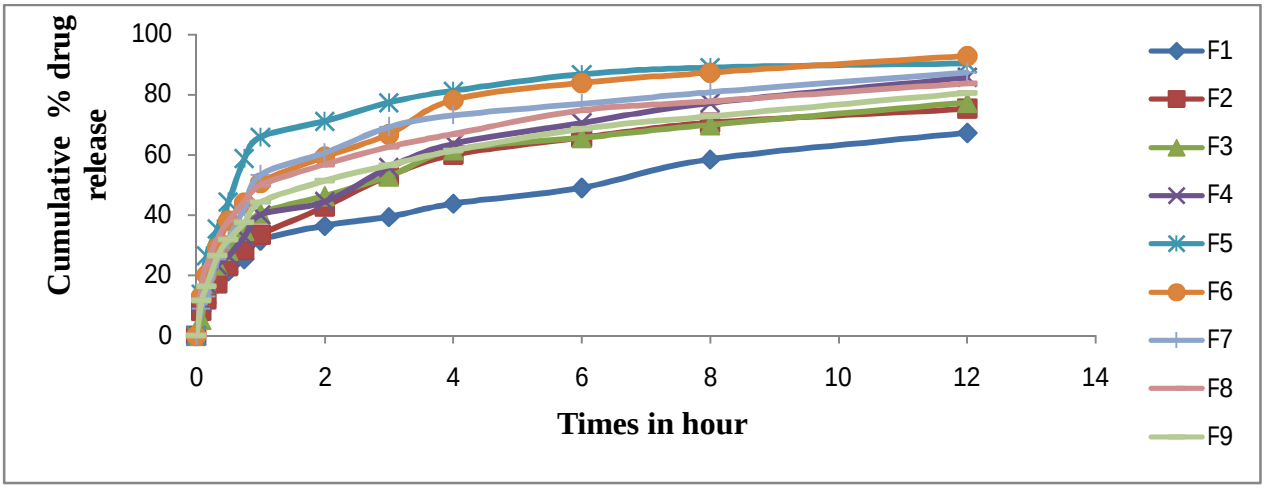

Fig.4: Plot between cumulative % drug release vs time of F1 to F9 formulation

Kinetic Analysis

The release kinetics was found out by using zero order, first order, Higuchi, Peppas model. The results were shown in table 4. On the basis kinetic analysis it can be conclude d that the drug release from the studied formulation followed Korsemeyer-peppas model as it has highest value of r^2. . From the

table it has been observed that the regression value (n-value) of the formulation was 0.380 suggesting that the drug was released by fickian diffusion mechanism.

Table-4: Parameters obtained from kinetic analysis of F6

Zero order	**Slope (K)**	7.096
	Intercept	30.83
	R^2	0.735
First order	**Slope (K/2.303)**	0.039
	K	0.092
	Intercept	1.830
	R^2	0.950
Higuchi model	**Slope (K)**	27.29
	Intercept	14.15
	R^2	0.920
Koresmeyer peppas Model	**Slope (n)**	0.380
	Intercept (log k)	0.212
	K	1.633
	R^2	0.961

CONCLUSION

In this investigation, Rabeprazole sodium floating microspheres with Eudragit RS 100 polymers were successfully prepared by the emulsion solvent diffusion method. Different percentage yield, paricle size, percentage entrapment efficiency, and *in-vitro* floating efficiency were obtaining by varying the concentration of HPMC K4M in different formulations. *In-vitro* release studies showed that the drug is released from the formulation over period of 12h in a sustained manner & the release mechanism followed a fickian type. The release amount of Rabeprazole sodium from floating microspheres suggested that Rabeprazole sodium floating microspheres have potential to retain in stomach for sufficient long period and prolonging its duration of action of and biovailability. In future *in-vivo* studies should be conducted so that such type of formulation of Rabeprazole sodium could find place in pharma market.

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