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Formulation And Evaluation Of Anti-Ulcer Floating Tablet Using Swellable Polymers

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Abstract

Present study involves the formulation and evaluation of floating tablets Ranitidine hydrochloride by direct compression method by using HPMC K4M, HPMC K100M as a synthetic polymers and Gellan Gum (low acyl) as a natural polymer with addition of sodium bicarbonate and citric acid as effervescent agent. The physicochemical compatibility of the drug and the polymers was studied by infrared spectroscopy and differential scanning calorimetry. The results suggested that drug and the polymers were physicochemically compatible with each other. The effect of synthetic and natural polymers on the drug release and floating properties of tablet were investigated. Formulation was optimized on the basis of pre compression and post compression parameters, floating lag time, total floating time and *in vitro* drug release study was carried out. The floating lag time, dissolution studies indicated that formulation F11 with drug: polymer ratio 5:4 exhibited sustained release of drug and followed Korsemeyer Peppas kinetics. Natural polymer (Gellan Gum) showed better results for sustained drug release properties than synthetic polymer. The floating lag time was found to be increase significantly with increase in concentration of polymer and drug release was found to decrease with increase concentration of polymers.

Keywords: Floating drug delivery, Natural polymers, Synthetic polymers, Ranitidine Hydrochloride.

Introduction

Oral route is the most common and convenient route used for the administration of drug. The dosage form given through the oral route is more flexible to design as compared to other routes of administration [1]. Gastro retentive drug delivery system is the system in which the gastric residence time is prolonged thereby targeting the site specific drug release in the upper gastrointestinal tract for local as well as systemic effects [2, 3]. This dosage form remains in gastric region for longer period of time. The delivery of drugs by oral route is the most preferred route for drug delivery as it has various advantages such as ease of administration, patient compliance, low cost therapy and flexibility in formulation [4]. In spite of these advantages, this system has limited success in case of drugs with a poor absorption window throughout the gastrointestinal tract (GIT). Modifying the GI transit time is most challenging in the development of oral controlled drug delivery system. This is because gastric emptying is dependent on the dosage form and fasted state of the stomach. Normal GRT (Gastric residence time) ranges in between 5 min – 2 hours [5]. In the fasted state the activity is governed by MMC (Migrating Myoelectric Complex). This MMC is also termed as interdigestive myoelectric cycle and hence the transit of dosage forms [6]. Ranitidine hydrochloride (Ranitidine HCl) is a histamine H_2-receptor antagonist. It is widely prescribed in active duodenal ulcers, gastric ulcers, Zollinger-Ellison syndrome, gastro esophageal reflux disease, and erosive esophagitis. A conventional dose of Ranitidine HCl (150 mg) can inhibit gastric acid secretion up to five hours, but not up to long time. While 300 mg dose of Ranitidine HCl leads to plasma fluctuations; thus a sustained release dosage form of Ranitidine hydrochloride is most efficient. Ranitidine HCl has short biological half-life (~2.5 – 3 hours) also favors development of a sustained release formulation.

Ranitidine HCl is BCS class III drug [7, 9] and it absorbed only in the proximal part of the small intestine and has about 50% absolute bioavailability. Moreover, poor bioavailability of ranitidine from the colon is due to colonic metabolism of Ranitidine [8]. The gastro retentive drug delivery systems can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability.

The main objective of this study was to formulate and evaluate floating effervescent tablet of Ranitidine HCl. The tablets were formulated by using synthetic polymer, Hydroxylpropylmethyl cellulose (HPMC) K4M and HPMC K100 M and natural polymer Gellan Gum (low acyl).

Materials And Methods

Materials

Ranitidine HCl was obtained as a gift sample from Markson Pharma, Goa. HPMC K4M and HPMC K100M were purchased from Rajesh Chemicals, Mumbai. Gellan Gum (Low Acyl) was received as a gift sample from CP Kelco, Mumbai. All other excipients used were of an analytical grade.

Methods

Preparation and evaluation of Dry Mixture

The floating tablets of Ranitidine HCl were prepared by direct compression method by using uniform blend of powder mixture. For this purpose, all the ingredients were weighed accurately. Then all the ingredients (except magnesium stearate and talc) were mixed properly and the passed through sieve no 80. Then all the ingredients were blended uniformly and finally magnesium stearate and talc were added to the mixture as post lubricant and mixed uniformly.

The prepared dry mixture was evaluated for micromeritic properties including bulk density, tapped density and compressibility index parameters.

Preparation of Ranitidine Hydrochloride Floating Tablets

Table 1: Composition of floating tablet formulation of Ranitidine HCl.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Ranitidine HCL	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150
HPMC K4M	50	100	150	-	-	-	50	100	50	-	-	-	100	100	100
HPMC K100M	-	-	-	50	100	150	50	50	100	100	100	100	-	-	-
Gellan Gum	-	-	-	-	-	-	-	-	-	10	20	30	10	20	30
Sodium bicarbonate	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50
Citric acid	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
PVP	-	-	-	-	-	-	-	-	-	10	10	10	10	10	10
Lactose	125	75	25	125	75	25	75	25	25	55	45	35	55	45	35
Magnesium Stearate	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Talc	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10

Floating tablets of Ranitidine HCl producing effervescence were prepared by direct compression method, using varying concentrations of different grades of polymers (HPMC K4 M and HPMC K100M and Gellan Gum) with sodium bicarbonate and citric acid. All the ingredients were weighed accurately and passed through sieve no 80. Then, (except Magnesium stearate and talc) all other ingredients were blended uniformly using glass mortar and pestle. After sufficient mixing of drug as well as other components, Talc and magnesium stearate were added, as post lubricant. The total weights of the tablets were kept constant for all formulations around 400 mg. Tablets were prepared by using a single punch tabletting machine (Hilab Chemicals, Mumbai, India) with 13 mm punches. The different batches of formulation were prepared as shown in table 1.

Characterization of Ranitidine HCl and polymers

FTIR analysis

Infrared spectrum of Ranitidine HCl was determined on Fourier Transform Infrared spectrophotometer using KBr dispersion method. The base line correction was done using dried potassium bromide. Then the spectrum of dried mixture of drug and potassium bromide was run [10]. Infrared absorption spectrum of Ranitidine HCl, Polymers and physical mixture of Ranitidine HCl and Polymers was carried out to determine chemical interaction between drug and polymer.

Differential scanning calorimetry

Differential scanning calorimetry (DSC) studies were carried out using Mettle-Toledo DSC 821 instrument. Indium and zinc standards were used to calibrate the DSC temperature and enthalpy scale. The powdered samples (5 mg) are hermetically sealed in aluminum crucibles and heated at a constant rate of 10 C/min over a temperature range of 25–250 C. Inert atmosphere was maintained by purging nitrogen gas at flow rate of 30 mL/min. results were obtained in triplicates for each sample.

Evaluation of Tablet Formulation.

Hardness and Friability

The hardness of the tablet was determined by using Pfizer hardness tester [11]. The friability of tablets was determined using Roche Friabilator. Twenty previously weighed tablets were rotated at 25 rpm for four minutes. The tablets were dedusted and re-weighed to calculate the percentage of friability. [11, 12].

Thickness

The thickness in millimeters (mm) was measured individually for 10 pre weighed tablets by using Vernier Callipers. The average

thickness and standard deviation were reported. The results were as shown in table 4.

Weight variation

Twenty tablets were selected randomly from each batch and average weighed individually. The weight of individual tablet compared with the average weight.

Drug Content Estimation

Ten tablets were randomly sampled from each formulation batch, finely powdered and individually estimated for the drug content after suitable dilution, using UV-VIS spectrophotometer (UV-1600, Shimadzu) at 314 nm [13].

In vitro buoyancy studies

The *in vitro* buoyancy was determined by floating lag time and total floating time. The study was performed in 100 ml beaker containing simulated gastric fluid, pH 1.2 as per USP. The time taken by the tablet to rise to the surface and float was taken as floating lag time[FLT] and the duration for which the dosage form constantly remained on the surface of medium was determined as the total floating time [TFT] [14,15].

Determination of Swelling Index

The swelling index of the tablet was determined in 0.1N HCl (pH 1.2) at room temperature. The swollen weight of the tablet was determined at predefined time intervals. The swelling index was expressed in percentage and is calculated by using following formula [16]. The swelling index is shown in figure 3.

$$SI = \frac{W_1 - W_0}{W_0} \times 100$$

Where,

W_1: weight of tablet at time t

W_0: Initial weight of tablet

In vitro drug release studies

The release rate from Ranitidine HCl floating tablets was determined using United States Pharmacopeia (USP) dissolution testing apparatus II (paddle method) under sink conditions. The dissolution medium used was 900 ml of 0.1N HCl solution pH (1.2) at 37± 0.5ºC. The stirring speed was 50 rpm. 5 ml of sample was withdrawn for every one hour for each formulation. The sample were diluted suitably and filtered. The required dilutions were made and the solution was analyzed for the drug content by using UV spectrophotometer (Shimadzu UV -1600) at λ max 314 nm. From the above readings the percentage drug release was calculated and this was plotted against function of time to study the pattern of drug release [13].

Stability studies

Stability studies were carried out for optimized formulation (F11) according to the International Conference on Harmonization (ICH) guidelines. The samples were stored in closed HDPE bottles along with 1 g desiccant at temperature 40±2ºC and 75±5 % Relative Humidity for 3 months. Samples were withdrawn after 1, 2, and 3 months of intervals and were evaluated for drug content, floating lag time and in vitro percentage drug release [17].

Results And Discussion

FTIR analysis

FTIR study of the drug (Ranitidine HCl), Polymers (HPMC K4M, Gallen gum and HPMC K100M) and physical mixture of drug and Polymer were characterized by FTIR spectra, using KBR pellets. It was found that the spectra and value of sample Ranitidine HCl and polymers were match with official standards. No change occurred in peak pattern of FTIR spectra of pure drug, pure excipients in physical mixture of drug and polymers shown in figure 1. Hence drug and polymers were found to be compatible with each other.

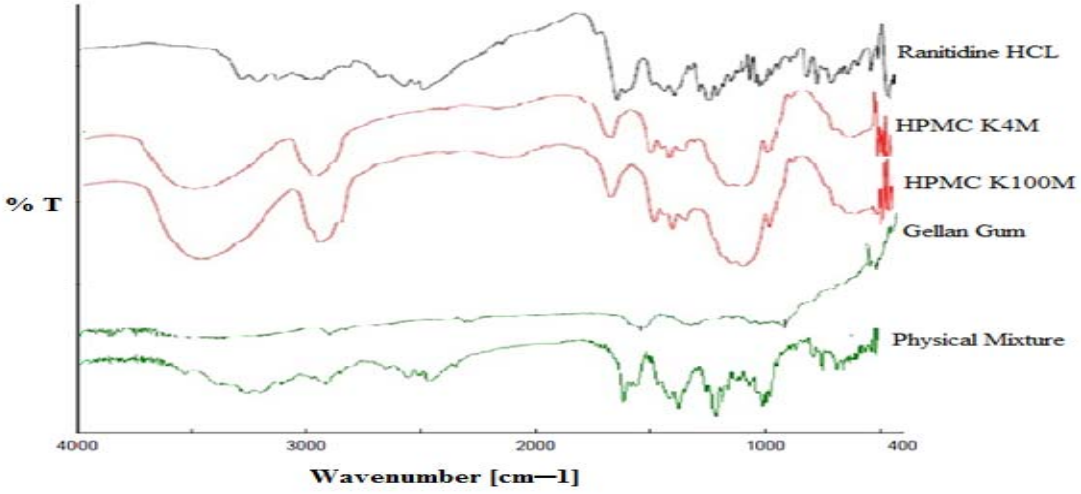


Figure 1: FTIR Compatibility study of drug and excipients.

Table 3: Interpretation of FT-IR Spectrum of drug and polymer combination.

Sr. No	IR Spectrum	Observed IR Peaks (cm^{-1})	Functional groups	Stretching/deformation
1	Ranitidine HCL	3190.46 3106.04		O-H stretching O-H stretching
		2973.62 2948.49		C-H stretching C-H stretching
		1620.17, 1589.72	Furan Nitrogen	N-H bending N-H bending
		1473.27 1418.46		C-H bending C-H bending
		698.74		C-CL
2	Combination of Polymer and Ranitidine HCL	3451.64		O-H stretching
		2923.97		C-H stretching
		1620.09		N-H bending
		1457.17 1379.67		C-H bending C-H bending

Differential Scanning Calorimetry

The DSC thermogram of pure Ranitidine HCl has shown a sharp endotherm at 148.32 C corresponding to its melting point. This sharp endothermic peak signifies crystalline nature of pure Ranitidine HCl. While optimized batch (F11) showed the endothermic peak at139.39 C with the loss of its sharp appearance and other peak of an excipients shown in figure 2. The broadening and shifting of peak towards the left side shows the entrapment of drug into formulation.

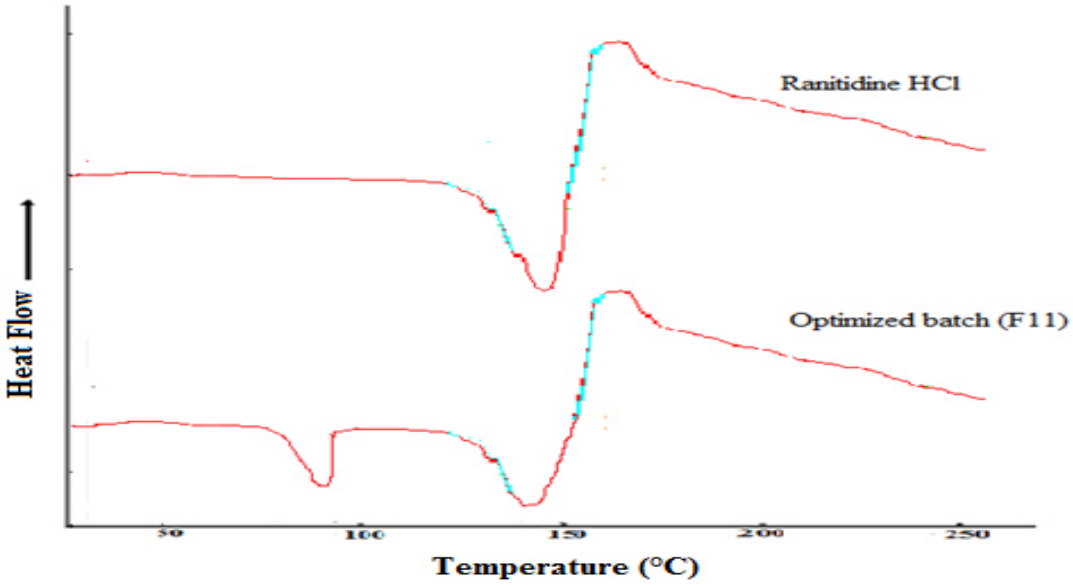


Figure 2: DSC thermogram of Ranitidine HCl and optimized formulation (F11).

Evaluation of physical properties of pre-compressed granules

The physical properties like Compressibility index (CI), Angle of repose and Hausners ratio were calculated and tabulated in table 2. The results of the physical properties of many of the blends were in the limits and comply with the standards.

Table 2: Evaluation of Dry Mixture.

Batch Code	Angle of repose (□)	Bulk density (gm/cm3)	Tapped density (gm/cm3)	Hausners ratio (HR)	Carr index (CI)
F1	27.74±0.21	0.370±0.02	0.465±0.038	1.22±0.14	18.50±0.48
F2	22.87±0.56	0.344±0.05	0.408±0.018	1.18±0.30	15.68±0.12
F3	24.74±0.0.51	0.322±0.08	0.400±0.023	1.24±0.36	19.50±0.18
F4	25.40±0.12	0.363±0.05	0.444±0.023	1.22±0.12	18.24±0.39
F5	21.99±0.54	0.333±0.06	0.400±0.019	1.20±0.13	16.75±0.51
F6	23.02±0.21	0.317±0.09	0.400±0.046	1.26±0.006	20.75±0.14
F7	23.26±0.66	0.384±0.02	0.454±0.041	1.18±0.11	15.41±0.16
F8	25.68±0.43	0.363±0.06	0.434±0.029	1.19±0.24	14.58±0.27
F9	24.65±0.20	0.357±0.08	0.434±0.052	1.21±0.30	17.74±0.34
F10	25.26±0.42	0.408±0.04	0.487±0.043	1.19±0.10	16.22±0.23
F11	24.93±0.33	0.400±0.02	0.487±0.024	1.21±0.31	17.86±0.34
F12	22.39±0.61	0.392±0.05	0.500±0.015	1.27±0.27	21.06±0.12
F13	24.18±0.30	0.392±0.02	0.465±0.035	1.18±0.12	15.69±0.37
F14	25.96±0.22	0.384±0.02	0.465±0.046	1.21±0.16	17.41±0.21
F15	26.24±0.57	0.377±0.06	0.476±0.010	1.26±0.25	20.79±0.24

(Mean ± S.D., n = 3).

Evaluation of physicochemical properties of tablets

The physical characteristics of tablets such as tablet hardness, friability, weight variation and drug content for all the formulations were determined. The hardness of the tablets of all formulations passed the test as per the acceptance criteria. The friability and weight variation was found to be within the limits specified in pharmacopoeia. The percentage drug content of all the formulations complies with official specifications. The values are given in table 4.

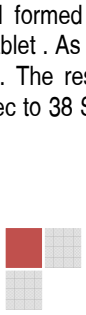
Table 4: Evaluation of Ranitidine Hydrochloride Floating Tablets.

Batch Code	Hardness (kg/cm^2)	Thickness (mm)	Diameter (mm)	Friability (%)	Drug Content Uniformity (%)	Weight Variation Average weight in (mg)	Floating Lag Time (Sec)	Total floating Time(Hours)
F1	4.8±0.23	4.0±0.03	13±0.02	0.58±0.02	98.35±0.12	0.400±0.80	28	4
F2	5.2±0.05	4.1±0.01	13±0.01	0.75±0.03	98.18±0.58	0.400±1.25	24	8
F3	5.4±0.32	4.2±0.05	13±0.04	0.90±0.07	97.65±0.72	0.400±1.20	35	12
F4	4.9±0.16	4.0±0.04	13±0.02	0.54±0.05	97.35±0.18	0.400±0.90	32	4
F5	5.1±0.20	4.1±0.02	13±0.01	0.45±0.02	98.64±0.96	0.400±1.26	24	10
F6	5.5±0.32	4.2±0.08	13±0.05	0.64±0.10	98.77±0.78	0.400±1.22	42	12
F7	5.1±0.34	4.0±0.01	13±0.02	0.58±0.10	97.84±0.32	0.400±1.48	34	8
F8	5.5±0.12	4.2±0.04	13±0.05	0.64±0.04	98.36±0.98	0.400±1.30	30	10
F9	5.5±0.25	4.2±0.05	13±0.04	0.68±0.06	98.72±0.14	0.400±1.32	30	10
F10	5.2±0.24	4.0±0.01	13±0.02	0.50±0.02	98.10±0.78	0.400±1.20	28	□12
F11	5.2±0.15	4.0±0.02	13±0.02	0.54±0.04	98.27±0.14	0.400±1.05	30	□12
F12	5.5±0.10	4.1±0.02	13±0.02	0.48±0.04	98.69±0.34	0.400±1.10	38	□12
F13	5.0±0.26	4.0±0.02	13±0.02	0.48±0.06	98.98±0.74	0.400±1.32	30	10
F14	5.2±0.18	4.0±0.02	13±0.02	0.52±0.04	98.34±0.88	0.400±1.44	33	10
F15	5.6±0.04	4.0±0.04	13±0.01	0.46±0.08	97.48±0.32	0.400±1.06	37	10

(Mean ± S.D., n = 3).

In vitro buoyancy studies

All the formulations were prepared by effervescent approach .*In vitro* Buoyancy and Total floating time were determined by using 100 ml beaker containing 0.1N HCl as shown in figure 3, the gas generated is trapped and protected within the gel formed by hydration of polymers thus decreasing density of the tablet . As the density of tablet falls <1, the tablet become buoyant. The result showed that the floating lag time was in range of 24 sec to 38 Sec



and total floating time in range of 4 hours to 12 hours. (Table 4) Both floating lag time and total floating time increases with increase in concentration of polymers[18].Total floating time for the formulations containing HPMC K100M with Gallen gum were maintained their matrix integrity for more than 12 hours shown in table 4.

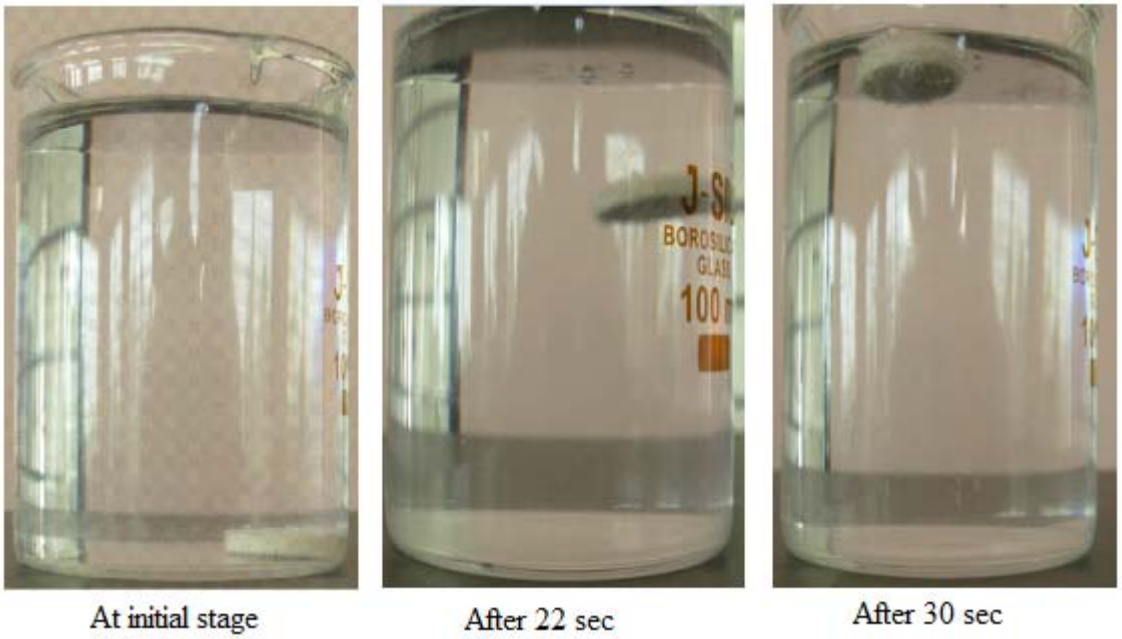


Figure 3: In-Vitro Buoyancy Studies of Ranitidine HCl Floating Tablet (F11).

Swelling index

The swelling index was calculated with respect to time. As time increase, the swelling index was increased, because weight gain by tablet was increased proportionally with rate of hydration. Later on, it decreased gradually due to dissolution of outermost gelled layer of tablet into dissolution medium. The direct relationship was observed between swelling index and HPMC concentration and as HPMC concentration increase, swelling index was increased. Results are shown in figure 4 and figure 5.

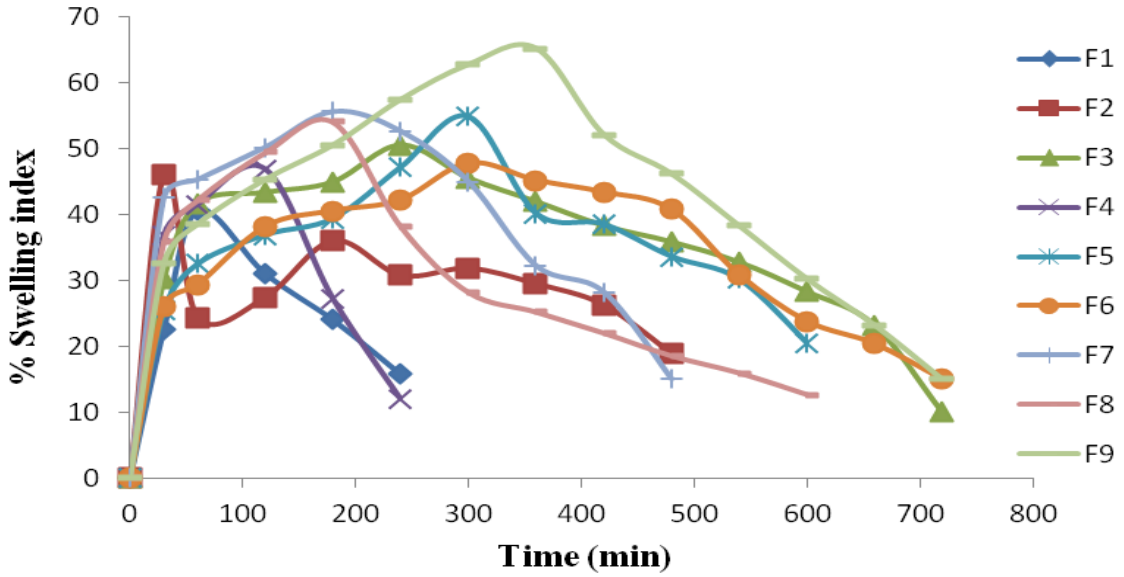


Figure 4: Swelling index of F1-F9 Formulations.

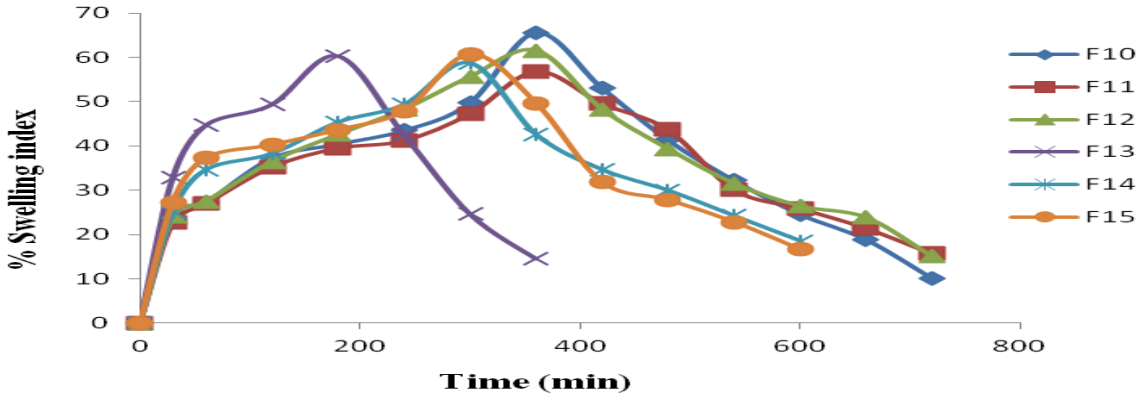


Figure 5: Swelling index of F10-F15 Formulations.

In vitro dissolution studies

All the formulations were subjected to *in vitro* dissolution studies using USP dissolution testing apparatus II (paddle method) in 900 ml of 0.1N HCl for 12h. The formulations F1,F2,F3, containing different concentration of HPMC K4M shows that the drug release vary from 85.84±2.12% - 97.36±1.73% while formulation F4, F5, F6, containing different concentration of HPMC K100 M shows that the drug release vary from 82.52±1.27% - 95.71±1.12% within 12h. The formulation F7, F8, F9 containing the combination of polymers HPMC K4M and HPMC K100M the proportion of polymers are taken in ratio 1:1, 2:1 and 1:2 respectively, shows that the drug release vary from 92.48±1.32% - 95.22±1.85% while formulation F10, F11, F12 containing combination of polymers Gellan Gum and HPMC K100M shows that the drug release vary from 89.21±2.12% - 92.65±1.73% within 12h. The formulation F13, F14, F15 containing combination of polymers Gellan Gum and HPMC K4M shows that the drug release vary 88.87±2.12% - 94.29±1.73%. There is increase in floating lag time as the concentration of Gellan gum is increased. Faster drug release from batch containing HPMC K4M was probably due to faster diffusion of soluble drug out of the matrix. Water soluble polymer forms pores for entry of solvent molecules [19, 20]. At higher polymer loading, the viscosity of the gel matrix is increased which results in a decrease in the effective diffusion coefficient of the drug and hence decreased drug release into the dissolution medium so decrease in drug release rate [21]. The results from in-vitro buoyancy studies, in-vitro drug release were found that the optimized formulation F11 showed slow and sustained release of ranitidine hydrochloride over a period of 12 hours over other batches. Drug release kinetics study shows, the best fitting model for optimized batch is Korsemeyer Peppas Model and the r^2 value is 0.9897 shown in table 5.

From the *in vitro* dissolution study it was concluded that release from the tablet matrix is largely dependent on the polymer swelling, drug diffusion and matrix erosion. Large concentration of high viscosity polymer induces the formation of strong viscous gel layer that slowed down the rate of water diffusion into the tablet matrix, which may result in the retardation or decreases the drug release. Dissolution profiles for all batches were shown in figure 6 and figure 7.

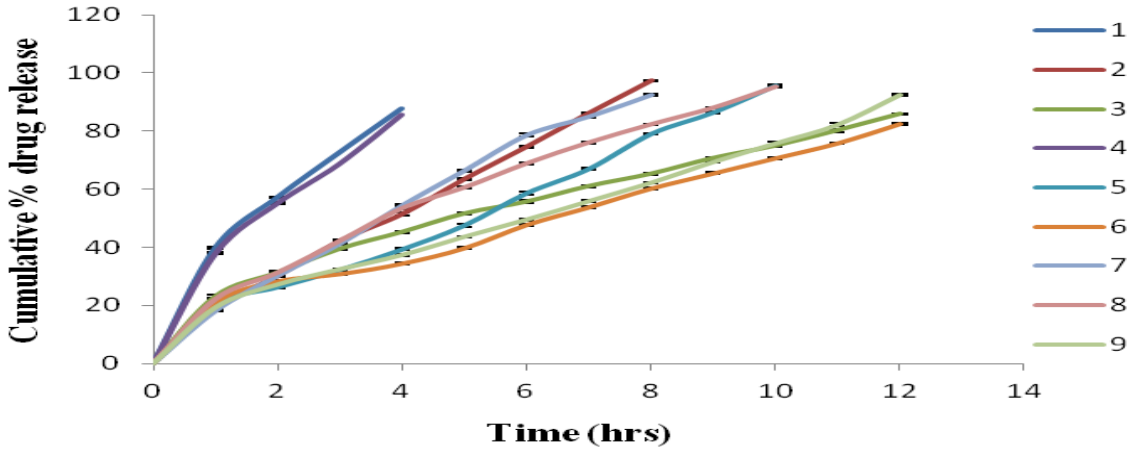


Figure 6: Comparison of in vitro dissolution profile of F1-F9.

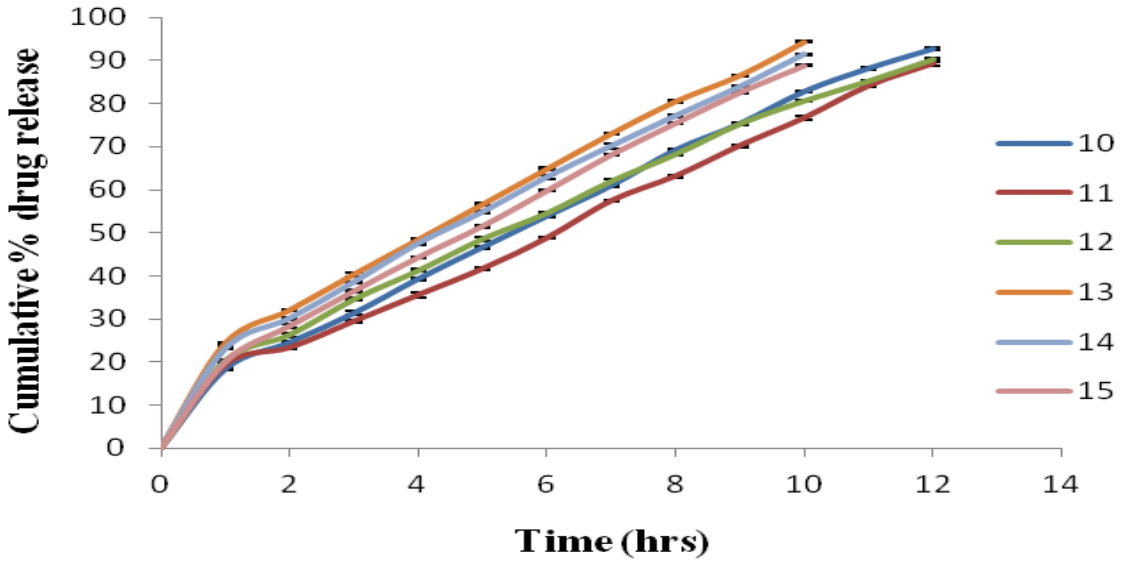


Figure 7: Comparison of in vitro dissolution profile of F10-F15.

Table 5: Drug Release Kinetics of Ranitidine HCl Floating tablets.

Batch Code	Zero order	First order	Higuchi	Hixson- crowel	Korsemeyer Peppas	Best Fitting Model
F1	0.9744	0.9965	0.9996	0.9996	0.9999	Peppas
F2	0.9935	0.8762	0.9598	0.9554	0.9975	Peppas
F3	0.9068	0.9861	0.9971	0.9839	0.9982	Peppas
F4	0.9763	0.9973	0.9993	0.9995	0.9997	Peppas
F5	0.9901	0.8947	0.9498	0.9570	0.9783	Zero order
F6	0.9581	0.9784	0.9769	0.9876	0.9770	Hixson crowel
F7	0.9885	0.9609	0.9655	0.9902	0.9986	Peppas
F8	0.9581	0.9544	0.9873	0.9912	0.9981	Peppas
F9	0.9742	0.9263	0.9695	0.9707	0.9882	Peppas
F10	0.9820	0.9549	0.9693	0.9873	0.9928	Peppas
F11	0.9854	0.9550	0.9576	0.9812	0.9897	Peppas
F12	0.9244	0.9956	0.9925	0.9927	0.9950	First order
F13	0.9622	0.9479	0.9843	0.9857	0.9930	Peppas
F14	0.9643	0.9638	0.9837	0.9898	0.9934	Peppas
F15	0.9756	0.9703	0.9773	0.9918	0.9957	Peppas

Stability studies

Stability studies were carried out as per ICH guidelines and results were represented in Table 6. Drug content and drug release revels that after 3 months of stability studies there was no significant difference in Drug content, floating lag time and drug release (figure 8).

Table 6: Evaluation of optimized formulation (F11) after stability period.

Parameters	Period			
	Before	After 30 days	After 60 days	After 90 days
Floating lag time (s)	30	30	30	31
Drug content	98.27±0.14	98.13±0.17	98.02±0.57	97.95±0.89
Drug release after 12 h	89.212	89.532	89.745	90.071

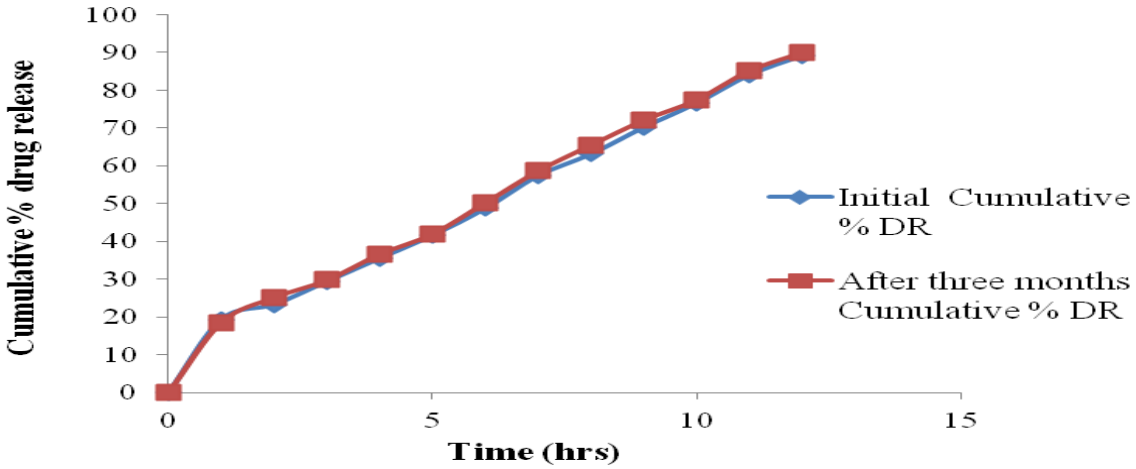


Figure 8: % Drug Release study after Stability Study of optimized formulation (F11).

Conclusion

From the above study it was concluded that, HPMC K4M, HPMC K100M and Gellan Gum are compatible with Ranitidine hydrochloride based on the results obtained from compatibility studies and hence they are suitable for floating tablets of Ranitidine hydrochloride. From the *in-vitro* buoyancy studies it was concluded that, Gellan gum shows somewhat more floating lag time than HPMC K4M and HPMC K100M respectively. The floating lag time was found to be significantly increased with increase in concentration of polymer. The formulation containing HPMC K4M shows greater percentage of drug release as compared to other polymers containing formulations. Natural polymer (Gellan gum) showed slow and sustained release of ranitidine hydrochloride over the synthetic polymers. As the concentration of polymer increases the percentage drug release decreases. Finally, it was concluded that natural polymer (Gellan Gum) can be successfully used for the sustained release of ranitidine hydrochloride through floating drug delivery.

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