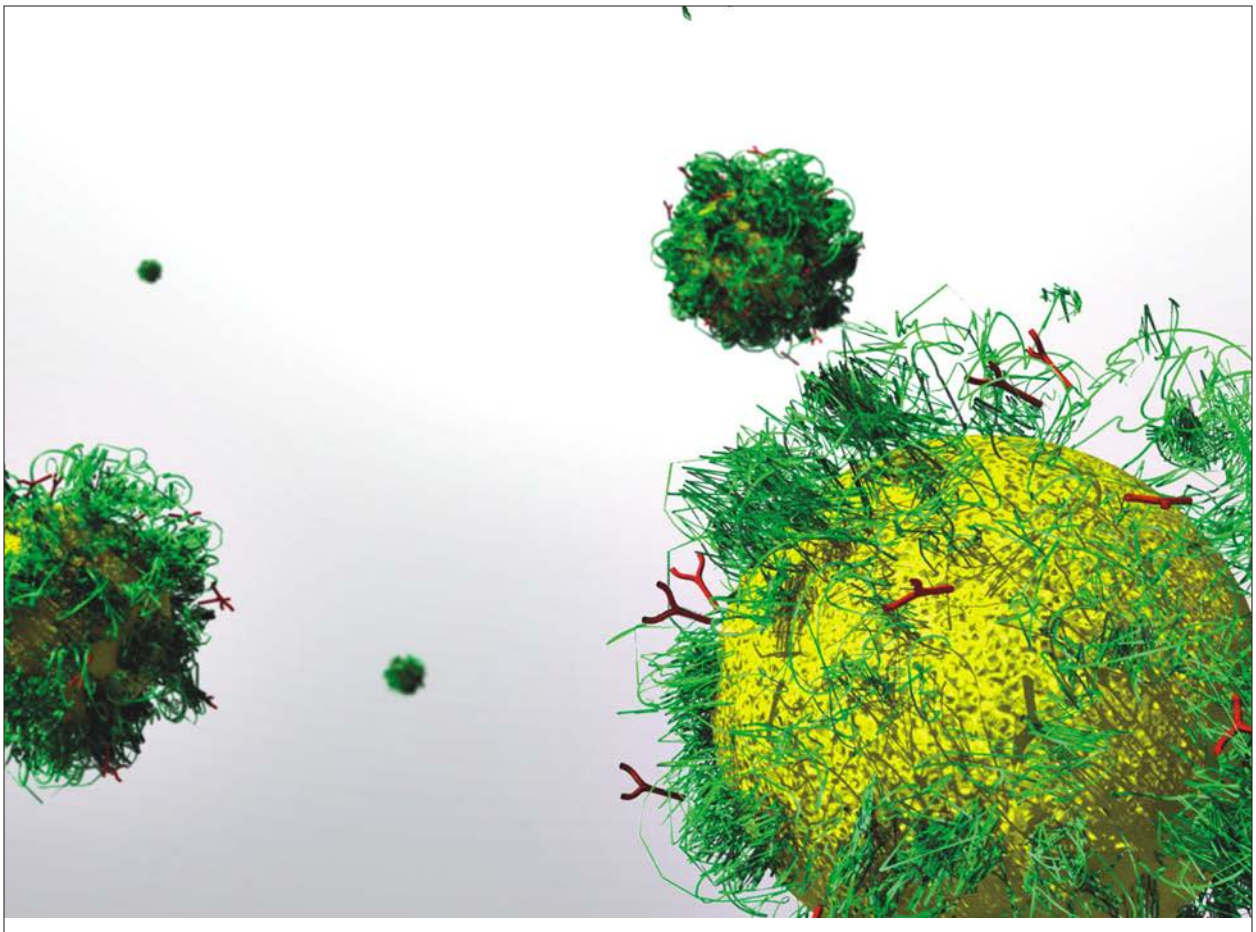

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Preparation and Evaluation of Floating Matrix Tablet of Ranitidine

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ABSTRACT

Ranitidine hydrochloride has a short biological half-life (2.1±0.2 h) and 50% absolute bioavailability. Development of sustained release formulation of ranitidine hydrochloride can be advantageous, that can provide prolong gastric retention and increase efficacy of the dosage form. Calculate theoretical release profile from floating matrix tablets of ranitidine and perform the drug excipient interaction study. *In vitro* dissolution studies, dissolution profiles, drug: polymer ratio, effect of low density copolymer PSDVB on the release profile of chitosan-carbopol 940 floating matrix tablets, geometry on release, effect of diluents were performed. Select the best batch and swelling index, kinetic modeling of drug release, accelerated stability and *in vivo* study were carried out. No chemical interaction between ranitidine hydrochloride and the polymers used. Result shows loss of integrity with the increase in concentration of carbopol 940. Significant changes in the floating lag time of the formulation with increased amount of co-polymer. With increasing initial tablet radius, the volume of the system and, thus, the amount of drug available for diffusion increases, resulting in increased absolute amounts of drug released. In contrast, the relative surface area of the device decreases and the amount of drug released in%/ time unit decreased. The x-ray and swelling index shows significant result in batch A12. The present investigation shows that the chitosan-carbopol 940 mixed matrices can be used to modify release rates in hydrophilic matrix tablets prepared by direct compression.

Key words: Co-polymer, carbopol, chitosan, sustain release

INTRODUCTION

Ranitidine hydrochloride is a histamine H2-receptor antagonist. It is widely prescribed in active duodenal ulcers, gastric ulcers, Zollinger-Ellison syndrome, gastroesophageal reflux disease and erosive esophagitis. The recommended adult oral dosage of ranitidine is 150 mg twice daily or 300 mg once daily. The effective treatment of erosive esophagitis requires administration of 150 mg of ranitidine 4 times a day. A conventional dose of 150 mg can inhibit gastric acid secretion up to 5 h but not up to 10 h. An alternative dose of 300 mg leads to plasma fluctuations; thus a sustained release dosage form of ranitidine hydrochloride is desirable (Somade and Singh, 2002). The short biological half-life of drug (~2.5-3 h) also favors development of a sustained release formulation.

A traditional oral sustained release formulation releases most of the drug at the colon, thus the drug should have absorption window either in the colon or throughout the gastrointestinal tract. Ranitidine is absorbed only in the initial part of the small intestine and has 50% absolute bioavailability (Lauritsen *et al.*, 1990; Grant *et al.*, 1989). Moreover, colonic metabolism of ranitidine is partly responsible for the poor bioavailability of ranitidine from the colon (Basit and Lacey, 2001). These properties of ranitidine hydrochloride do not favor the traditional approach to sustained release delivery. Hence, clinically acceptable sustained release dosage forms of ranitidine hydrochloride prepared with conventional technology may not be successful.

The gastroretentive 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.

It is also reported that oral treatment of gastric disorders with an H_2-receptor antagonist like ranitidine or famotidine used in combination with antacids promotes local delivery of these drugs to the receptor of the parietal cell wall. Local delivery also increases the stomach wall receptor site bioavailability and increases the efficacy of drugs to reduce acid secretion (Coffin and Parr, 1995). This principle may be applied for improving systemic as well as local delivery of ranitidine hydrochloride, which would efficiently reduce gastric acid secretion.

Several approaches are currently used to prolong gastric retention time. These include floating drug delivery systems, also known as hydrodynamically balanced systems, swelling and expanding systems, polymeric bioadhesive systems, modified-shape systems, high-density systems and other delayed gastric emptying devices (Singh and Kim, 2000; Chawla and Bansal, 2003). The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release.

In context of the above principles, a strong need was recognized for the development of a dosage form to deliver ranitidine hydrochloride in the stomach and to increase the efficiency of the drug, providing sustained action. The present investigation applied a systematic approach to the development of gastroretentive ranitidine hydrochloride dosage forms.

MATERIALS AND METHODS

Ranitidine hydrochlorides (Mann Pharmaceuticals Pvt. Ltd., Mehsana, India), Low Density Powder-Poly (Styrene Divinyl Benzene) Copolymer, Chitosan (Central Institute of Fisheries Technology, Cochin.), Carbopol 940 (S. D. Fine Chemicals Ltd., Mumbai, India.), Lactose, Talc, Magnesium stearate were used.

Methodology

Estimation of ranitidine hydrochloride: A solution of ranitidine hydrochloride was prepared in 0.1 N HCl and UV spectrum was taken using Shimadzu UV-1601 UV/V is double beam spectrophotometer. The UV maxima of ranitidine hydrochloride was found to be 315 nm in 0.1 N HCl

Preparation of standard calibration curve of ranitidine hydrochloride: Ranitidine Hydrochloride (10 mg) was dissolved in 0.1 N HCl and volume was made up to 100 mL in 100 mL volumetric flask. This solution (100 mcg mL^{-1}) was further diluted with 0.1 N HCl to obtain solution of 10 to 100 mcg mL^{-1}. Absorbance of each solution was measured at 315 nm using Shimadzu

UV-1601 UV/V is double beam spectrophotometer and 0.1 N HCl as reference standard. The standard curve was generated for the entire range from 10 to 100 mcg mL^{-1}.

Calculation of theoretical release profile of ranitidine hydrochloride from floating matrix tablets

Calculation of the immediate release dose:

$$IR = \frac{Css \times V_d}{F} = \frac{36 \times 1.4}{50} = 100.8 \text{ mg}$$

Calculation of maintenance dose (MD):

$$MD = IR\ [(1 + 0.693t)/t_{1/2}] = 100.8\ (1 + 0.693*8)/\ 2 = 279.41 \cong 300 \text{ mg}$$

Where:

IR = Immediate release

C_{SS} = Concentration at steady state

V_d = Volume of distribution

F = Fraction bioavailable

MD = Maintenance dose

t = Time upto which sustain release is required and $t_{1/2}$ = half life

According to the theoretical profile the drug release in 1st h should be 100.8 mg (33.60%). In the remaining 7 h the drug release should be (300-100.8 =) 199.2 mg. So, after 1 h 28.46 mg (9.48%) drug should be release at every hour shown in Table 1.

Drug excipient interaction study: The pure drug, ranitidine hydrochloride and a mixture of it with the polymer chitosan-carbopol 940 and PSDVB copolymer powder was mixed separately with IR grade KBr and corresponding pellets were prepared by applying 10 tons of pressure in the hydraulic press. The pellets were scanned over a wave number range of 400 to 4000 cm^{-1} in FTIR 8400S model instrument.

Preparation of floating matrix tablets: Different tablets formulations were prepared by direct compression technique. All the powders were passed though 80 mesh sieve. Required quantity of drug, matrix polymer and low-density copolymer were mixed thoroughly. Talc and magnesium

Table 1: Theoretical release profile of ranitidine hydrochloride

Time (h)	Theoretical drug release (%)
1	33.60
2	43.08
3	52.56
4	62.04
5	71.52
6	81.00
7	90.48
8	99.96

stearate were finally added as glident and lubricant, respectively. The blend was compressed (12 mm diameter, flat punches) using multipunch tablet compression machine (Cadmach, Ahmedabad, India). Each tablet contained 336 mg of ranitidine hydrochloride (336 mg equivalent to 300 mg of ranitidine) and other pharmaceutical ingredients as listed in table in each section.

***In vitro* dissolution studies:** The release rate ranitidine from floating tablets (n = 3) was determined using The United States Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 mL of 0.1 N HCl, at 37±0.5°C and 75 rpm. A sample (10 mL) of the solution was withdrawn from the dissolution apparatus hourly for 8 h and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45 μ membrane filter and diluted to a suitable concentration with 0.1 N HCl. Absorbance of these solutions was measured at 315 nm using a Shimadzu UV-1601 UV/Vis double beam spectrophotometer. Cumulative percentage of drug release was calculated using the equation obtained from a standard curve.

Comparison of dissolution profiles: The similarity factor (f_2) given by SUPAC guidelines for modified release dosage form was used as a basis to compare dissolution profile. The dissolution profiles are considered to be similar when f_2 is between 50 and 100 (Dettmar *et al*., 1999). The dissolution profiles of products were compared using f_2. This similarity factor is calculated by following formula (Costa and Lobo, 2001):

$$f_2 = 50 \times \log \{[1+(1/n)\sum_{j=1}^{n} |R_j - T_j|]^{-0.5} \times 100$$

where, n is the number of dissolution time and R_j and T_j are the reference and test dissolution values at time t.

Determination of drug: polymer ratio (chitosan concentration) using USP apparatus II: In an attempt to determine drug: polymer ratio formulation batch A1 was prepared. Dissolution of the tablets (n = 3) was carried out using 0.1 N HCl at 37±0.5°C (900 mL using USP apparatus II at 75 rpm). The drug release was measured. The formulated batch was evaluated for the *in vitro* buoyancy test shown in Table 2.

Effect of drug: polymer ratio (carbopol 940 concentration) on release profile using USP apparatus II: Formulation batch A2 was prepared to determine drug: polymer ratio using carbopol 940 as the matrix forming agent. Dissolution of the tablets (n = 3) was carried out using 0.1 N HCl

Table 2: Determination of polymer (chitosan) concentration

Ingredients	A1
Ranitidine hydrochloride	336
Chitosan	150
Magnesium stearate	5
Talc	10

*All the quantities are in mg

Table 3: Determination of polymer (carbopol 940) concentration

Ingredients	A2
Ranitidine hydrochloride	336
Carbopol 940	200
Magnesium stearate	5
Talc	10

*All the quantities are in mg

Table 4: Determination of polymer (chitosan-carbopol 940) concentration

Ingredients	A3	A4	A5	A6	A7	A8
Ranitidine hydrochloride	336	336	336	336	336	336
Chitosan	100	100	100	100	25	50
Carbopol 940	25	50	75	100	100	100
Magnesium stearate	5	5	5	5	5	5
Talc	10	10	10	10	10	10

*All the quantities are in mg

Table 5: Determination of PSDVB copolymer concentration on drug release profile

Ingredients	A9	A10	A11	A12
Ranitidine hydrochloride	336	336	336	336
Chitosan	50	50	50	50
Carbopol 940	100	100	100	100
Poly (Styrene-divinylbenzene)	30	50	70	100
Magnesium stearate	5	5	5	5
Talc	10	10	10	10

*All the quantities are in mg

at 37±0.5°C (900 mL using USP apparatus II at 75 rpm). The drug release was measured. The formulated batch was evaluated for the *in vitro* buoyancy test shown in Table 3.

Effect of drug: polymer ratio (chitosan-carbopol 940 concentration) on release profile using USP apparatus II: To determine drug: polymer ratio formulation batch A3 was prepared with a blend of chitosan and carbopol 940 in different ratios. Dissolution of the tablets (n = 3) was carried out using 0.1 N HCl at 37±0.5°C (900 mL using USP apparatus II at 75 rpm). The drug release was measured. The formulated batch was evaluated for the *in vitro* buoyancy test shown in Table 4.

Effect of low density copolymer PSDVB on the release profile of chitosan-carbopol 940 floating matrix tablets: To study the effect of buoyancy by low density copolymer, i.e., PSDVB on *in vitro* buoyancy and drug dissolution profile different formulation batches containing 30, 50, 70 and 100 mg PSDVB copolymer, i.e., approximately 5, 10, 12 and 17% were formulated shown in Table 5.

Effect of tablet geometry on release profile of chitosan-carbopol 940 floating matrix tablets: To study the effect of tablet geometry on the release profile of matrices, the two different batches having different radius and constant thickness were prepared keeping ratio of ingredients same. Among them one batch having 3.8 mm radius, 5.2 mm thickness (7.6 mm round punch) and the other having 6.0 mm radius, 5.2 mm thickness (12 mm punch) were compressed.

Table 6: Determination of effect of diluents on drug release

Ingredients	A14	A15	A16	A17
Ranitidine hydrochloride	336.0	336	336.0	336
Chitosan	37.5	25	37.5	25
Carbopol 940	75.0	50	75.0	50
PSDVB	100.0	100	100.0	100
Lactose	37.5	75	-	-
DCP	-	-	37.5	75
Magnesium stearate	5.0	5	5.0	5
Talc	10.0	10	10.0	10

*All the quantities are in mg

Effect of diluents on release profile of chitosan-carbopol 940 floating matrix tablets: To see the effect of diluents on the release rate of chitosan-carbopol 940 floating matrix tablet different formulation batches containing lactose and dicalcium phosphate (DCP) were formulated. The release profile obtained after 8 h has been shown Table 6.

Selection of the best batch: The comparative results of different formulation batches were compared with theoretical dissolution profile by similarity factor f_2 test and the floating lag time of each batch.

***In vitro* buoyancy studies of batch a12:** The *in vitro* buoyancy was determined by floating lag time method described by Rosa *et al*. (1994).

The tablets were placed in 100 mL beaker containing 0.1 N HCl. The time required for the tablets to rise to the surface and float was determined as floating lag time.

Swelling index: The swelling index of tablets was determined n 0.1 N HCl (pH 1.2) at room temperature. The swollen weight of the tablets was determined at predefined time intervals. The swelling index was calculated by the following equation:

$$\text{Swelling index} = \frac{W_t - W_0}{W_0}$$

where, W_0 is the initial weight of tablet and W_t is the weight of the tablet at time t.

Kinetic modeling of drug release: The dissolution profile of the best batch was fitted to zero-order, first-order, Higuchi and Hixon-Crowell models to ascertain the kinetic modeling of drug release. The method of Bamba and Puisieusx (1979) was adopted for deciding the most appropriate model. To analyze the mechanism of drug release from the matrix tablets, the release data were fitted to the following equations:

Zero-order equation:

$$m = k_0 t$$

where, m is the % drug unreleased at time t and k_0 is the release rate.

First-order equation:

$$m = e^{a} \times e^{-bt}$$

where, a is the intercept and b is the slope

Higuchi's equation:

$$m = 100\text{-}q \times \text{sq root of time}$$

where, q is the Higuchi constant (% per sq root of time)

Hixon-Crowell equation:

$$m = ((100) \times (1/3)\text{-}k \times t)^{3}$$

where, k is Hixon Crowell constant $(mass/(time))^{1/3}$.

Accelerated stability study of the optimized batch: Gastro retentive tablets of ranitidine hydrochloride formulated in the present study were subjected to accelerated stability studies in aluminum/aluminum pouch pack as aluminum strip is considered the best protecting packaging material but in the present study simulation was made using aluminum foil pouch. As the dosage form is formulated for site specific drug delivery to stomach, no change should occur in its floating lag time and drug dissolution profile. Dose dumping and failure of buoyancy are probable effects anticipated during the stability study of such dosage forms. The tablets of optimized batch were packed in aluminum pouch and charged for accelerated stability studies at 40°C and 75% RH for 3 months in a humidity jar. Floating lag time and drug dissolution profile of exposed sample was carried out.

***In vivo* study:** The study was carried out by administering the gastroretentive tablets to human volunteer. The tablet was administered in the fasting state. The X-Ray opaque formulation was administered along with 250 mL of water. The subjects were allowed to remain in sitting or up right position. A light meal was given to volunteer 2 h after administration of the tablet to evaluate effect of food of gastroretentive property. The position of tablet was monitored by X-Ray screening technique X-Ray photographs were taken after 3 and 7 h to monitor tablet position in human gastrointestinal tract.

RESULT AND DISCUSSION

Estimation of ranitidine hydrochloride: Table 7 shows standard calibration curve of ranitidine hydrochloride in 0.1 n HCl.

Calculation of theoretical release profile of ranitidine hydrochloride from floating matrix tablets.

Drug excipient interaction study: In the present study, Fig. 1-5 show that there is no chemical interaction between ranitidine hydrochloride and the polymers used. Drug has given peaks due to furan ring, secondary diamine, alkene and two peaks due to nitro functional groups. Form the figure it was observed that there were no changes in these main peaks in IR spectra of mixture of drug and polymers, which show there were no physical interactions because of some bond formation between drug and polymers.

Table 7: Standard calibration curve of ranitidine hydrochloride in 0.1 N HCl

	Absorbance				
Concentration (µg mL^{-1})	1	2	3	Average absorbance	Calculated absorbance
0	0.000	0.000	0.000	0.000	0.003
10	0.041	0.041	0.041	0.041	0.039
20	0.079	0.080	0.077	0.078	0.075
40	0.151	0.150	0.151	0.151	0.147
60	0.215	0.213	0.212	0.213	0.219
80	0.275	0.278	0.277	0.277	0.291
100	0.372	0.375	0.378	0.375	0.363
Correlation Co-efficient : 0.9962					
Absorbance = 0.0036x conc. + 0.0025					

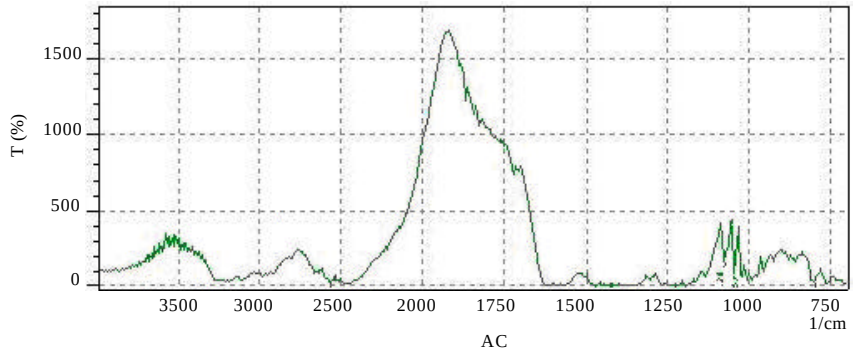

Fig. 1: Infrared spectra of ranitidine hydrochloride

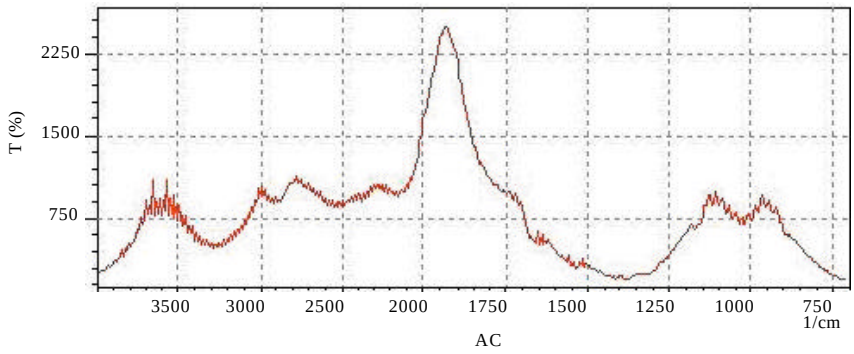

Fig. 2: Infrared spectra of chitosan

Determination of drug: polymer ratio (chitosan concentration) using usp apparatus II: Chitosan is a natural polysaccharide polymer (Sabinus *et al.*, 2000). Chitosan was taken as matrixing polymer in the concentration of 30% w/w. The tablets did not float all the time but there was gradual absorption of medium (0.1 N HCl) into the tablets. After complete swelling of the polymer; gradual erosion of the tablet started by dispersion to completely erode the tablets within 1 h and twenty five minutes. The dissolution in the 1st h was 94.56%. It was thus concluded that

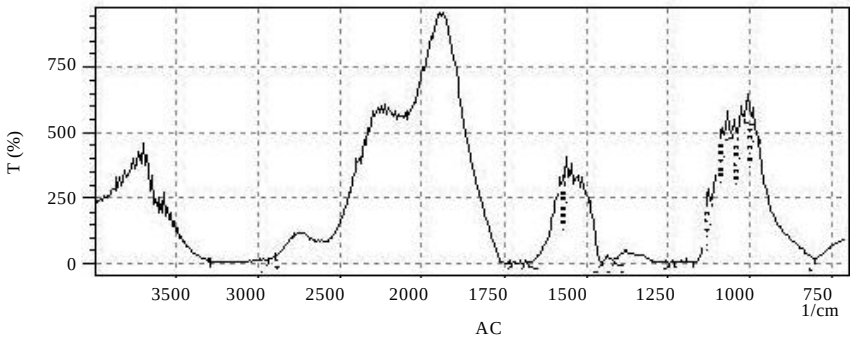

Fig. 3: Infrared spectra of carbopol 940

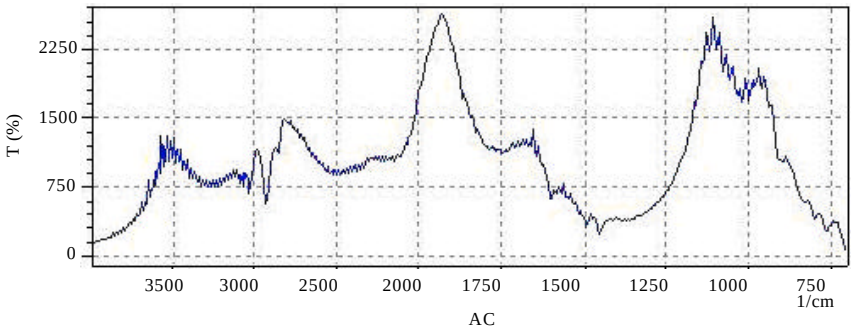

Fig. 4: Infrared spectra of poly (Styrene-divinylbenzene)

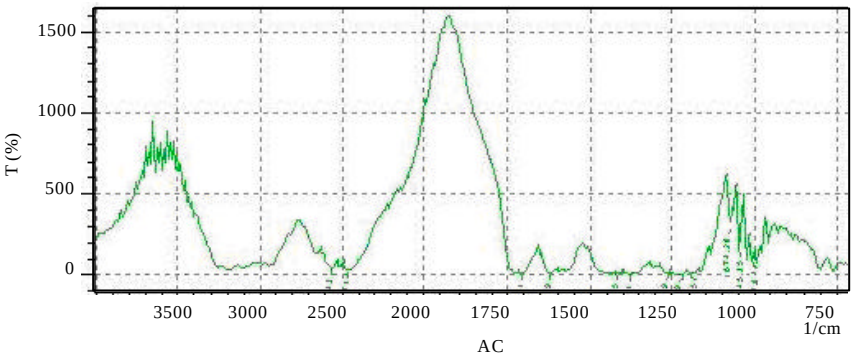

Fig. 5: Infrared spectra of best batch (A12)

chitosan alone was not a proper choice to produce required integrity of the tablet and prolonged drug release. Further it was decided to select carbopol 940 as the matrix forming polymer (Siepmann *et al.*, 2002) shown in Table 8.

Effect of drug: polymer ratio (carbopol 940 concentration) on release profile using USP apparatus II: Carbopol 940 is a synthetic polymer. It is a polymer of acrylic acid and forms hydrogel in water or alkaline solution due to hydration of the carboxyl groups in its structure. For

Table 8: Effect of polymer concentration on drug dissolution profile

Time (h)	A1	Theoretical profile
0	0	0.00
1	94.56	33.60
2	-	43.08
3	-	52.56
4	-	62.04
5	-	71.52
6	-	81.00
7	-	90.48
8	-	99.96
FLT (sec)	No	
Similarity factor (f_2)	6.984	

Table 9: Effect of polymer concentration on drug dissolution profile

Time (h)	A2	Theoretical profile
0	0.00	0.00
1	23.26	33.60
2	30.38	43.08
3	42.14	52.56
4	51.81	62.04
5	57.01	71.52
6	61.03	81.00
7	69.75	90.48
8	73.56	99.96
9	80.79	
10	85.34	
11	89.77	
12	94.27	
FLT (sec)	No	
Similarity factor (f_2)	38.89 (at 8 h)	

drugs that are primarily released in the acidic region of the gastrointestinal tract (GIT), carbopol 940 seemed to be most suitable polymer (Siepmann *et al.*, 2002). Carbopol 940 in the concentration of approximately 36% in the formulated tablets led to gradual swelling of the tablet. The drug release was in a controlled manner for a period of >12 h. The dissolution profile obtained in the 1st h was very less which was 23.26%. The reading obtained at 8 h was 73.56% which was much below our requirement. But at the same time the problem of erosion and loss of integrity was over come with the use of carbopol 940. Looking to the results obtained from chitosan (Table 8) and carbopol 940 (Table 9, 10) as matrix forming agents, a blend combination of chitosan and carbopol 940 was decided to be prepared.

Effect of drug: polymer ratio (chitosan-carbopol 940 concentration) on release profile using USP apparatus II: Various ratios of chitosan and carbopol 940 (4:1, 2:1, 4:3, 1:1 resp.) were taken and the dissolution profiles were obtained. Batch A3 dispersed completely in 5 h while batches A4 and A5 dispersed completely in 6 h. At the same time batch A6 dispersed completely in 7½ h. In the batches containing more concentration of chitosan (100 mg) compared to carbopol 940 (25, 50, 75 and 100 mg) there was erosion of the tablets because of the chitosan. Then a reverse

Table 10: Effect of polymer concentration on drug dissolution profile

Time (h)	A3	A4	A5	A6	A7	A8	Theoretical profile
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	46.09	31.21	28.32	30.38	36.58	23.35	33.60
2	55.94	53.12	53.48	47.62	51.95	39.71	43.08
3	70.94	66.79	68.85	57.39	62.56	52.96	52.56
4	89.15	77.77	72.70	77.64	70.67	60.31	62.04
5	98.84	89.35	81.65	86.52	76.66	75.38	71.52
6	-	95.86	91.82	94.46	89.36	83.97	81.00
7	-	-	-	98.93	95.39	89.66	90.48
8	-	-	-	-	102.23	95.66	99.96
FLT (sec)	No	No	No	No	No	No	
Similarity factor (f_2)	11.838	15.449	15.653	21.767	57.646	66.787	

order was followed i.e., with more concentration of carbopol 940 (100 mg) as compared to chitosan (25 and 50 mg) as batches A7 and A8. There was no loss of integrity of the tablets in this case. Thus, it became clear that there was decrease in loss of integrity with the increase in concentration of carbopol 940. This was directly proportional to the drug release from the hydrophilic matrices. The drug release after the 1st h, from the formulation batches A7 and A8 was 36.58 and 23.35%, respectively. The *in vitro* drug release after 8 h, from the formulation batches A7 and A8 was 102.23 and 95.66%, respectively. Though the drug release from the batch A7 was 36.58% after 1st h, it was not considered optimized drug: polymer ratio for further studies of different formulations and processing variables since its similarity factor (57.646) was less than that of batch A8 (663.787). To determine effect of low density copolymer PSDVB on the drug release rate of chitosan-carbopol 940 floating matrix tablets formulation batches having 336 mg of ranitidine hydrochloride, 50 mg of chitosan and 100 mg of carbopol 940 was appropriate because the tablets also maintained its integrity for more than 24 h shown in 10.

Effect of low density copolymer PSDVB on the release profile of chitosan-carbopol 940 floating matrix tablets: The effect of PSDVB copolymer on drug release profile was checked out on formulations containing approximately 5, 10, 12 and 17% of the copolymer. The results obtained from *in vitro* dissolution study revealed that there is no significant change in drug dissolution profile with increase or decrease in PSDVB low density copolymer concentration. The drug release in the 1st h for all the four batches A9 to A12 was approximately near to 33% and that after 8 h was near to 97% (>90%). The similarity factor for batches A9 to A12 in ascending order of batch numbers was 69.489, 68.576, 63.239 and 57.334, respectively. During the *in vitro* buoyancy test, a significant change was observed in the floating lag time of the formulation with increased amount of PSDVB. No floating of the tablets was achieved in lower concentrations of PSDVB copolymer, i.e., upto 12%. Evaluating all the parameters batch A12 was selected as the optimized batch since it had the minimum concentration of low density copolymer required to float the tablets (FLT: approximately 10 sec) and similarity factor between 50 and 100 shown in Table 11.

Effect of tablet geometry on drug release profile: A simple, but very effective tool for modifying the release kinetics from matrix tablets is to vary their geometry. Varying the initial radius of cylindrical tablets strongly affects the resulting drug release rate, which can be predicted theoretically (Vargas and Ghaly, 1999). The release rate of ranitidine HCl from chitosan-carbopol

Table 11: Effect of PSDVB copolymer on drug release profile

Time (h)	A9	A10	A11	A12	Theoretical profile
0	0.000	0.000	0.000	0.000	0.00
1	32.860	34.920	34.100	30.380	33.60
2	40.250	42.560	46.890	48.460	43.08
3	50.620	49.810	55.280	64.570	52.56
4	65.510	65.820	66.890	70.870	62.04
5	71.820	73.970	78.710	78.530	71.52
6	86.660	89.750	91.150	88.840	81.00
7	90.180	94.790	94.980	95.110	90.48
8	96.710	96.560	97.190	97.680	99.96
FLT (sec)	No	No	No	10.000	
Similarity factor (f_2)	69.489	68.576	63.239	57.344	

Table 12: Effect of tablet geometry on drug release profile

Time (h)	A12 (6.0 mm)	A13 (3.8 mm)	Theoretical profile
0	0.000	0.000	0.00
1	30.380	26.350	33.60
2	48.460	32.210	43.08
3	64.570	39.560	52.56
4	70.870	43.620	62.04
5	78.530	49.950	71.52
6	88.840	55.940	81.00
7	95.110	63.850	90.48
8	97.680	71.640	99.96
FLT (sec)	10.000	6.000	
Similarity factor (f_2)	57.334	34.643	

940 based devices with 17% w/w low density copolymer and 67.2% w/w drug loading as a function of initial tablet radius (3.8-6.0 mm at a constant tablet height of 5.2 mm) had a very pronounced effect on the absolute drug release rate. With increasing initial tablet radius, the volume of the system and, thus, the amount of drug available for diffusion increases, resulting in increased absolute amounts of drug released. In contrast, the relative surface area of the device decreases and the amount of drug released in%/ time unit decreased shown in Table 12.

Effect of diluents on release profile of chitosan-carbopol 940 floating matrix tablets: The effect of adding water-soluble (lactose) and water-insoluble (DCP) fillers to low density matrix tablets containing ranitidine hydrochloride, PSDVB copolymer and chitosan-carbopol 940 blend on the resulting drug release kinetics. Clearly, the release increased when adding the fillers, however no differences were seen between the two different fillers at the investigated filler percent of 25% and 50% each. The slight increase in drug release can probably be explained by the less tight hydrogel structures upon swelling. Vargas and Ghaly (1999) and Rosa *et al.* (1994) did also not observe any significant difference between lactose, MCC and DCP when used as filler in theophylline containing HPMC K4M-based matrix tablets with respect to the resulting drug release kinetics (containing up to 59% w/w filler). Thus, chitosan-carbopol 940 is clearly the dominating compound controlling the release rate of the drug in the investigated low density matrix tablets shown in Table 13.

Table 13: Effect of diluents on drug release

Time (h)	A14	A15	A16	A17	Theoretical profile
0	0.000	0.000	0.000	0.000	0.00
1	38.320	38.560	39.410	41.540	33.60
2	50.620	52.350	56.590	58.380	43.08
3	65.940	68.940	69.560	71.550	52.56
4	72.140	76.140	77.340	79.310	62.04
5	81.570	89.570	84.110	89.950	71.52
6	89.970	92.970	92.020	94.650	81.00
7	95.670	97.670	98.840	98.140	90.48
8	99.100	99.930	99.520	101.200	99.96
FLT (sec)	72.000	90.000	80.000	88.000	
Similarity factor (f_2)	53.542	46.479	46.568	42.817	

Table 14: Comparisons of check points between batch A12 and theoretical dissolution profile

Check points	A12	Theoretical dissolution profile
t_{50}	3.779	4.156
t_{90}	7.311	7.763

Table 15: Results of model fitting of batch A12

Intercept slope R^2 F-value			
Zero-order plot	First-order plot	Higuchi plot	Hixon crowell
+18.518	+0.188	0.9115	106.72
+4.843	+0.756	0.5297	141.17
-1.511	+4.655	0.9944	6.81
+5.571	+0.384	0.9584	10.06

Selection of the best batch: Further to evaluate complete similarity three check points (t_{50} and t_{90}) were considered in the dissolution profiles of A12 and theoretical profiles. The results in Table 14 also indicated similarity between A12 and theoretical dissolution profile shown in Table 14.

DISCUSSION

The pictorial results of *in vitro* buoyancy study of the best batch is shown in table 14, which clearly depicts the floating lag time, stable and persistent buoyancy and swelling characteristic of tablet.

Swelling index: Tablets composed of polymeric matrices build a gel layer around the tablet core when they come in contact with water this gel layer governs the drug release. Kinetics of swelling is important because the gel barrier is formed with water penetration. Swelling is also vital factor to ensure floating. To obtain floating, the balance between swelling and water acceptance must be restored (Baumgartner *et al*., 1998; Timmermans and Moes, 1990). The swelling index of the best batch after 8 h was 1.299 which may be because of high viscosity and high water retention property of carbopol 940 shown in Fig. 6a, b and Table 15.

The results of F-statistics were used for the selection of the most appropriate model. The goodness of fit test proposed by Bamba was used to determine the kinetics of drug dissolution

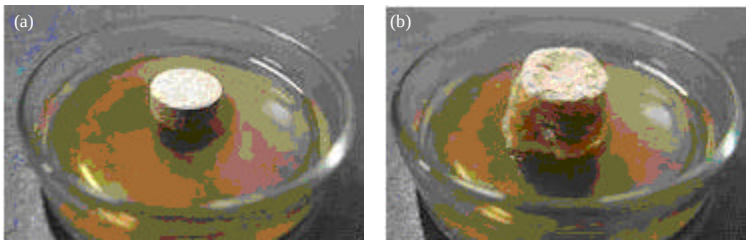

Fig. 6: Swelling index of batch A12. (a) at initial time (0.1 N HCl) and (b) after 8 h (0.1 N HCl)

Table 16: Results of accelerated stability studies

	Cumulative % drug release	
Time (h)	Initial	After three months
0	0.000	0.00
1	30.380	32.58
2	48.460	53.98
3	64.570	63.25
4	70.870	74.36
5	78.530	80.69
6	88.840	91.36
7	95.110	96.32
8	97.680	99.25
FLT (sec)	10.000	14.00
Similarity factor (f_2)	76.117	

profile. The release profile of the best batch, which showed highest similarity factor f2, was fitted to Higuchi model (F = 6.81). This superiority is however statistically insignificant with Hixon Crowell model (F = 10.06) while it significant with Zero order model (F = 106.72) as shown by the goodness of fit test (F-ratio test). But the priority should be given to the model with the least F-value. Thus, it may be concluded that the drug release from gastro retentive ranitidine hydrochloride tablet is best explained by Higuchi model. The values of slope and intercept for Higuchi model are 4.655 and-1.511, respectively.

The results of accelerated stability studies: The similarity factor was calculated for comparison of dissolution profile before and after stability studies. The f2 value was found more than 50 (~76.117) that indicate a good similarity between both the dissolution profiles. Similarly, no significant difference was observed in the floating lag time after stability studies. Hence, the results of stability studies reveal that the developed formulation has good stability shown in Table 16.

***In vivo* study:** The X-Ray photographs revealed that the tablet remained buoyant in stomach after 3 h, which indicated that there is no significant effect of food on floating property of tablet. This behavior may be attributed to bioadhesive and insolubility property of carbopol 940 in stomach fluid. An X-Ray photograph taken after 7 h confirm the presence of the tablet in the stomach shown in Fig. 7a and b.

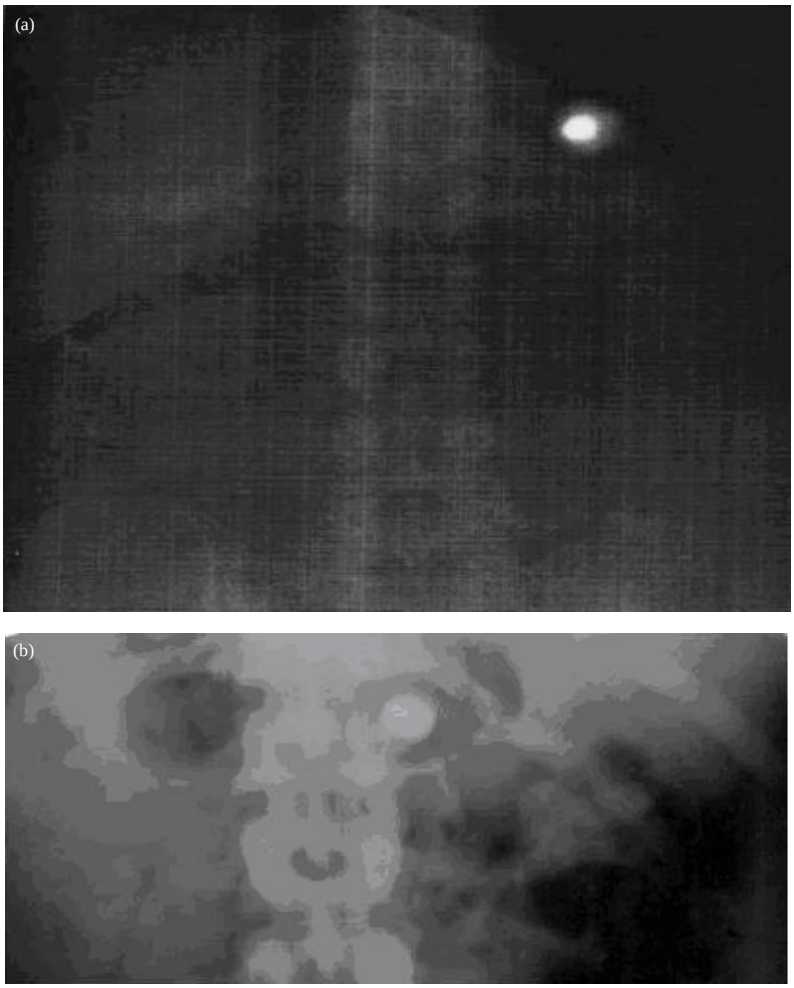

Fig. 7: X-Ray study of gastroretentive tablet (batch-A12). (a) after 3 h and (b) after 7 h

CONCLUSION

The present investigation shows that the chitosan-carbopol 940 mixed matrices can be used to modify release rates in hydrophilic matrix tablets prepared by direct compression. Incorporation of the highly porous low density copolymer in the matrix tablets provides densities that are lower than the density of the release medium. 17% w/w low density copolymer (based on the mass of the tablet) was sufficient to achieve proper *in vitro* floating behavior for at least 8 h. In contrast to most conventional floating systems (including gas-generating ones), these tablets floated almost immediately upon contact with the release medium, showing no lag times in floating behavior because low density is provided from the beginning (t = 10 sec). Extended floating times are achieved due to the air entrapped within the low density copolymer particles, which is only slowly removed from the system upon contact with the release medium. As expected, tablets without low density copolymer (e.g., consisting of 50 mg chitosan, 100 mg carbopol 940 and 336 mg ranitidine hydrochloride first sank before floating, showing no floating lag times. Adding only 17% w/w (based on the mass of the tablet) of the PSDVB copolymer reduced the lag times to 10 sec. The other most important thing that can be concluded from the study was that the formulation and process

variables play sole role in the release behavior of the matrices. Faster release of the drug from the hydrophihc matrix was probably due to faster dissolution of the highly water-soluble drug from the core and its diffusion out of the matrix forming the pores for entry of solvent molecules. So, we can obtain a formulation that has desired release profile by adjusting different parameters that ultimately effect release behavior of the matrices.

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