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FORMULATION AND CHARACTERIZATION OF STOMACH TARGETED MUCOADHESIVE TABLETS OF RANITIDINE HYDROCHLORIDE

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ABSTRACT

Ranitidine is a non-imidazole blocker of those histamine receptors that mediate gastric secretion (H2 receptors). It is used to treat gastrointestinal ulcers. The aim of the present work is to prolong the drug retention time of ranitidine hydrochloride by formulating the stomach targeted mucoadhesive tablets using various bioadhesive polymers. The tablets were formulated by direct compression technique using excipients like Sodiumcarboxymethylcellulose, carbopol934P and HydroxypropylmethylcelluloseK4M, PEG6000, magnesium stearate, talc and lactose. The compressed tablets were characterized for pre compression parameters such as angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio and also post compression parameters like weight variation, drug content, thickness, hardness, swelling index, wash out time, mucoadhesive strength and in vitro drug release. All Formulated tablets showed satisfactory results for pre-compression and post-compression parameters. Among all formulations, F3 with combination of carbopol934P and sodium carboxymethyl cellulose showed greater *in vitro* drug release of 96.84 after 24 hrs, better mucoadhesive strength and good swelling. Hence formulation F3 was optimized and the stability studies were carried out according to ICH guideline which showed that the formulation F3 was stable after storage at 40±2°C and 75%±5% RH for three months.

KEYWORDS: **Ranitidine hydrochloride, mucoadhesive drug delivery system, Sodiumcarboxymethylcellulose, Carbopol 934P, Hydroxypropylmethylcellulose, bioadhesive polymers**

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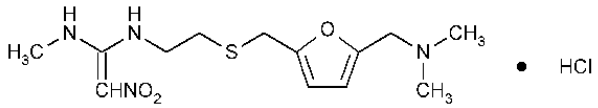
INTRODUCTION

The aim of mucoadhesive drug delivery system is to release the drug to the site and maintain the drug concentration[1]. Mucoadhesion can be defined as capacity of materials adherences to the biological tissue for comprehensive period of time. Mucoadhesion concept was introduced in the drug delivery system in early of 1980s. Because of its various advantages mucoadhesive drug delivery system has got very important role in novel drug delivery systems[2]. Mucoadhesive dosage forms were developed to prolog the residence time at the site of application releasing the drug at controlled rate for significant therapeutic action[3]. It keeps the delivery system adhering to the mucus membrane[4]. Mucoadhesive drug deliveries bypass the first-pass hepatic metabolism. The mucoadhesive drug delivery system may include buccal delivery system, Sublingual delivery system, virginal delivery system, rectal delicacy system, Nasal delivery system Ocular delivery system, Gastro intestinal delivery system [1,2,3,4]. The rate of mucus turnover can be affected by the presence of a mucoadhesive device and the nature of the surface presented to the mucoadhesive formulation can vary significantly depending on the body site and the presence of local or systemic disease. Ranitidine an H2-receptor antagonist, often shortened to H2 antagonist, used to block the action of histamine on parietal cells in the stomach, decreasing acid production by these cells. These drugs are used in the treatment of dyspepsia. They suppress the normal secretion of acid by parietal cells and the meal-stimulated secretion of acid. They accomplish this by two mechanisms: histamine released by ECL cells in the stomach is blocked from binding on parietal cell H2 receptors which stimulate acid secretion, and other substances that promote acid secretion (such as gastrin and acetylcholine) have a reduced effect on parietal cells when the H2 receptors are blocked. The principal route of excretion is the urine. Figure 1shows the chemical structure of ranitidine hydrochloride.

Figure 1
Chemical structure of ranidine hydrochloride



MATERIALS AND METHODS

MATERIAL

Ranitidine hydrochloride was obtained as a gift sample from Orchev Pharma Pvt. Ltd, Gujarat. Carbopol 934P, HPMC K4M were obtained from Hniosome Healthcare Pvt. Ltd., Punjab. Sodium CMC, PEG 6000, Magnesium state and Talc were procured from SD Fine Chemicals, Mumbai and Lactose DC was received from Cipla India Pvt. Ltd., Goa (India).

METHOD:

Formulation of mucoadhesive tablets of ranitidine hydrochloride

Mucoadhesive tablets of ranitidine hydrochloride were prepared by direct compression technique using different concentration of various polymers like Carbopol 934, HPMC K4M, PEG 6000 based on the need of method. Table 1 shows the different formulations of the tablets. All the excipients were powdered and passed through mess-60 sieve. Ranitidine and mucoadhesive polymers were mixed by blending uniformly in glass mortar and pestle for a suitable time period. Then lactose DC, PFG6000 and magnesium stearate were added and blending was continued further for 2-3 minutes, then tablets were compressed with 9 mm punch. The weight of the tablets was kept constant. Each tablet contains 50mg of ranitidine hydrochloride and tablet has an approximate weight of 200mg. Pre compression parameters such as Angle of Repose (θ) was evaluated for all the formulated formulation were evaluated and it varies from 27.23 to 32.08. Bulk Density exhibited from 0.356 to 0.385 (gm/cm^3) for all the formulations. Tapped Density varies from 0.503 to 0.568 (gm/cm^3). Carr's Index shown from 16.15 to 19.15(%) and Hausner's Ratio was evaluated for all the preparations and it was found to be 1.17 to 1.31 (Hg). All the pre-compression parameters evaluated for all the formulations (F1-F6) were summarized in the Table 2.

Table 1
Formulations of ranitidine hydrochloride mucoadhesive tablets (F1-F6)

S. No.	Ingredients	F1	F2	F3	F4	F5	F6
1	Ranitidine Hydrochloride	50	50	50	50	50	50
2	Carbopol 934P	50	75	100	-	-	-
3	HPMC K4M	-	-	-	50	75	100
4	Sodium Carboxy Methyl Cellulose	10	10	10	10	10	10
5	PEG 6000	10	10	10	10	10	10
6	Magnesium Stearate	2.5	2.5	2.5	2.5	2.5	2.5
7	Talc	1	1	1	1	1	1
8	Lactose DC	76.5	51.5	26.5	76.5	51.5	26.5

Table 2
Pre-compression Parameters For all the formulations (F1-F6)

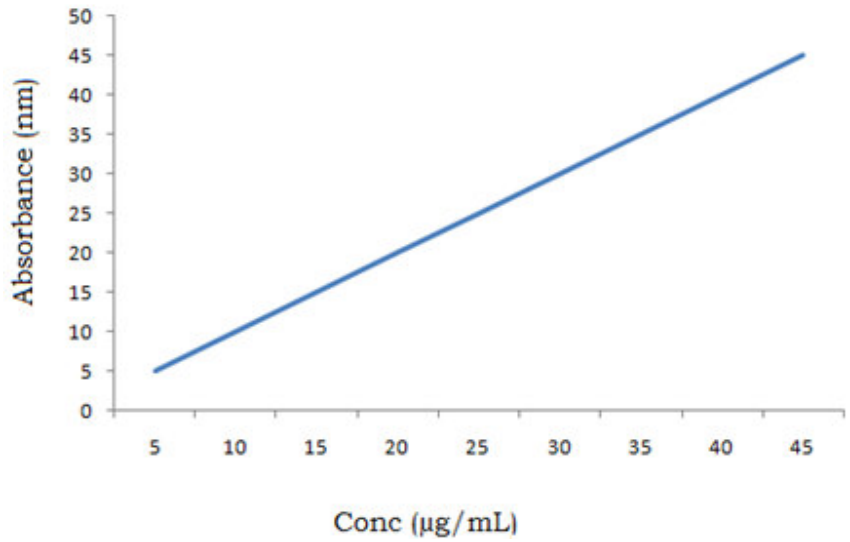
Sl. No.	Formulation Code	Angle of Repose (Θ)	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Carr's Index (%)	Hausner's Ratio (Hg)
1	F1	27.23	0.385	0.568	16.15	1.17
2	F2	29.15	0.384	0.503	18.24	1.24
3	F3	31.06	0.366	0.515	19.15	1.31
4	F4	29.12	0.356	0.509	17.14	1.21
5	F5	30.24	0.365	0.521	17.96	1.28
6	F6	32.08	0.383	0.532	18.31	1.29

Evaluation of tablets
The following tests were carried out on compressed tablets.

Physical appearance
Physical appearance includes tablets size, shape color, odor, taste, surface texture, physical flows and consistency.

Drug content
Five tablets were powered in mortar. The equivalent quantity of powdered tablets was weighted and extracted with 0.1N Hcl and filtered. Then suitably diluted and analysed by UV spectroscopy. A linear calibration curve was constructed with Beer's range of 5 to 50 µg/ml. Ranitidine hydrochloride exhibits maximum absorbance at 326 nm (λmax). Figure 2 shows the calibration curve range for ranitidine hydrochloride.

Figure 2
Calibration curve for ranitidine hydrochloride



Correlation coefficient: 0.9991
Slope: 0.9168
Intercept: 0.008416

Hardness
Hardness was measured by monsanto hardness tester. The hardness was measured for all the formulations and the tablets shows hardness from 6.1 to 6.5 (Kg/cm^2). The hardness of the formulated tablets was summarized in the table 4. This shows that there is no significant deviation in all the prepared formulations. All the formulated tablets shown good hardness indicates that all the tablets possessed good mechanical strength.

Thickness
Thickness of the tablet was measured using mitutoyo digital vernier caliper. The thickness of the tablets varies from 3.02±0.01 to 3.21±0.03 mm. The thickness of all the formulated tablets were tabulated in table 4 and no significant deviation was observed in all the formulations.

Weight variation test
Twenty tablets were taken randomly from each batch and weighted individually. The average weight and standard deviation of twenty tablets was calculated. The weight variation of the tablets from different batches varies from 201±0.01 to 204±0.03 (mg). The batch passes the test for weight variation test if not more than two of the individual tablet weight deviates from the average weight by more than the percentage shown in Table 3 and none deviate by more than twice the percentage shown.[12] Table 4 shows the weight variation of different formulated formulations.

Table 3
% Deviation for weight variation

Average weight of tablets	Percentage deviation
130 or less	10
130-324	7.5
More than 324	5

Friability

Friability was evaluated using Roche friabilator; twenty tablets were weighed initially and were rotated at 25 rpm for 4 mins in Roche friabilator. After rotation tablets were taken and made them dust free and weighed again. The following formula was used to calculate percentage friability.[13]

$\%F = [1-(W_0/W)] \times 100$
Where,
%F= Percentage Friability
W_0= Initial weight of the tablets
W= Weight of the tablets after rotation

Friability test was carried out for all the formulations and it shows from 0.71 to 0.82 % and friability evaluated for all the formulation was summarized in the table 4.

Table 4
Post-compression Parameters For all the formulations (F1-F6)

Sl. No.	Formulation Code	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Weight Variation (mg)	Drug Content Uniformity (%)
1	F1	3.19±0.02	6.1	0.71	201±0.01	98.37
2	F2	3.21±0.03	6.4	0.78	202±0.03	98.89
3	F3	3.15±0.01	6.5	0.81	202±0.02	99.36
4	F4	3.02±0.01	6.2	0.72	204±0.03	98.31
5	F5	3.04±0.01	6.4	0.76	202±0.02	98.94
6	F6	3.05±0.03	6.4	0.82	201±0.03	99.24

mm: milli meter ,
Kg/cm^2: Kilogram per centimeter square mg: milli gram

Mucoadhesive strength test

A modified physical balance was used to evaluate the mucoadhesive strength of the tablet[5]. In this balance right pan was replaced with glass slide and right pan weight made equal with left pan by additional weight. A teflon block was kept with buffer 0.1N Hcl pH 1.2 in a beaker which was kept below side of the balance. A model membrane i.e. rat stomach mucosa was used and 0.1 N Hcl of pH 1.2 was used a moistening fluid. Rat stomach mucosa was tied with teflon block with thread and buffer volume was maintained up to surface of the mucous in the beaker the formulated tablet was attached to the glass slide of the balance and then made the contact between mucosa and tablet. A load of 0-01gm was kept on glass slide for some constant time (preload time) to form adhesion bond between mucosa and tablet. The preload time was kept constant for all the formulations. The preload was removed and water drops of 100 drops per minute were added to the bottle which was kept on left pan of the balance. Water drops was added until the mucoahesive tablet was detached from the mucosa and the stopped. Then the water weighed in grams. Force of adhesion was evaluated by using the following the formula.

$$\text{Force of adhesion (N)} = \frac{\text{Mucoadhesive strength}}{1000} \times 9.81$$

Wash off test

Mucoadhesive properties of formulated tablets were evaluated by wash off method. In this method pieces of mucosa were mounted on to the glass slide were connected with suitable support. Two tablets were attached on to the arm of a USP tablet disintegrating test machine was given a slow regular up and down movement in the Phosphate buffer pH 7.4 at 37°C. Time taken to detach both the tables was considered[6, 7].

Swelling index[8]

There is increase in weight and volume because of
absorption of liquid by the tablet excipients. This is may be due to capillary spaces saturation with in particles or macromolecule hydration. Through pores liquid enters the particles and bind to large molecules, breaking the hydrogen

bond and resulting in the swelling of particles. Swelling can be evaluated in terms of % weight gain by the tablet. Tablet was weighed and placed in a beaker filled with a buffer solution. At each interval of time the tablet was removed and weighed. This procedure was followed up to 12 hours.

$$\text{Swelling Index \%} = \frac{(Wt - Wo)}{Wo} \times 100$$

Where, Wt = Weight of the tablet at the time t
Wo = Weight of the tablet before placing in the beaker.
***In vitro* dissolution studies**

Dissolution of the tablets was evaluated using USP XXIII dissolution type II apparatus using paddle. The tablet was fixed to peddle by hydration mechanism. The dissolution vessel was filled with 900mL of buffer (0.1N Hcl) of pH 1.2 and temperature was maintained at 37 ± 0.5°C. Peddle speed was maintained at 100 rpm. 1mL of sample was taken out at predetermined intervals of time upto 12 hours and the same volume of fresh buffer was replaced to maintain vessel condition. The withdrawn samples were diluted to 10mL with 0.1N Hcl, filtred and analyzed on UV spectrophotometer at 294 nm using 0.1N Hcl as a blank. Percentage cumulative drug release was calculated.

Accelerated stability studies
The stability studies were done in compliance with ICH guidelines. The Thermo lab TH 90S stability chamber was used to evaluate the stability studies. The temperature and relative humidity selected was 40 ±2°C and 75±5% for a period of three months. Table 5 summarizes the stability parameters of formulation F3.

Table 5
Stability Parameters for Optimized Formulation F3

Sl. No.	Parameter	Data after three months
1	Hardness	6.6
2	Bioadhesive Strength	19.89
3	Swelling Index	186
4	Surface pH	7.2
5	*Invitro* Dissolution	96.89

RESULTS AND DISCUSSION

Mucoadhesive strength
The mucoadhesive strength was evaluated for all the formulations. (Fig.3) Modified balance method was used to evaluate the mucoadhesive force (Fig.4). Constant time of 15 minutes constant time was maintained during evaluation. Polymer viscosity and concentration plays an important role in mucoadhesion. By evaluation of the mucoadhesive strength of all the formulations was concluded by increasing the concentration of Carbopol 934P, mucoadhesive strength can be increased. High molecular weight and high viscosity polymers will have higher adhesive strength.[10] Mucoadhesive strength was evaluated for all the formulations and exhibits from 19.15 to 19.88 (gm). Compared to all the formulation F3 shown greater mucoadhesive strength of 19.88 gm.

Figure 3
Mucoadhesive strength of all the formulations (F1-F6)

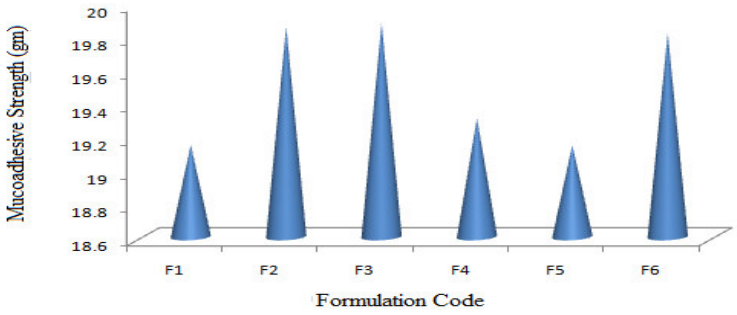
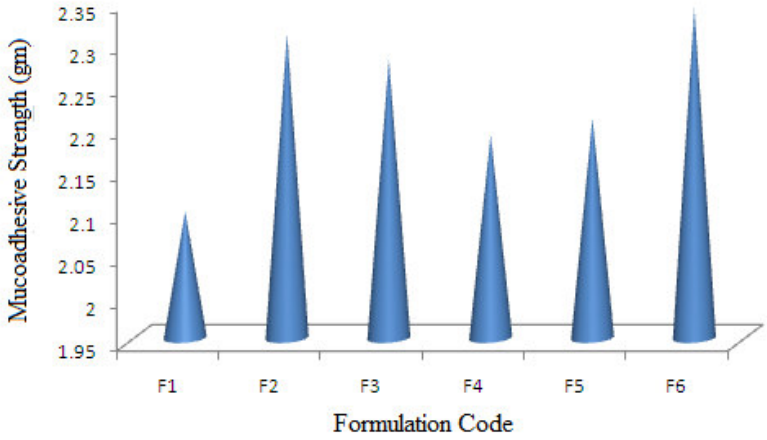


Figure 4
Adhesion force of all the formulations (F1-F6)



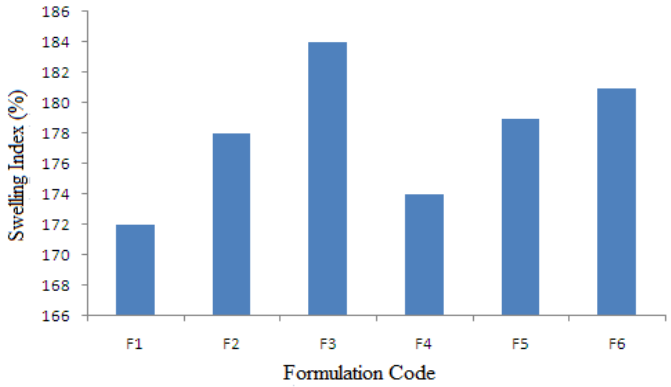
Swelling Index

Tablet of F3 formulation show high swelling index which contains Carbopol 934P with SCMC. Matrix integrity, viscosity and adhesion capacity of polymer plays a major role in swelling process. Decrease in percentage of polymer carbopol 934P showed the decrease in swilling value of the formulations[11]. Figure 5 shows that polymer with higher concentration and viscosity had a lower swelling value because this restricts the movement of polymers. Formulation F1 shown less % swelling index of 172 whereas F3 shown good %swelling index of 184 compared to all the formulation after 12 hours.The results were tabulated in the table6.

Table 6
Special parameters *for all the formulations (F1-F6)*

Sl. No.	Formulation Code	Mucoadhesive Strength (gm)	Mucoadhesion Force (N)	Swelling Index (%) after 12 hours
1	F1	19.15±0.03	2.10±0.08	172±0.02
2	F2	19.86±0.01	2.31±0.05	178±0.03
3	F3	19.88±0.05	2.28±0.03	184±0.01
4	F4	19.31±0.03	2.19±0.06	174±0.03
5	F5	19.15±0.02	2.21±0.01	179±0.02
6	F6	19.82±0.06	2.34±0.05	181±0.01

Figure 5
% swelling index of all the formulations



In vitro dissolution studies

From dissolution study was conducted for all the formulations F1-F6 and it was found that the increased viscosity and quantity of carbopol 934 P and HPMC K4M shows the decrease in rate of drug release. A higher viscosity particle swells more slowly and produces a smaller volume of swollen particles. At higher polymer level formation of a tightly swollen gel layer results in decreased mobility of insoluble drug particles in swollen matrices which causes decreased dissolution rate. Table 7 shows the drug release profile for all the formulations. From In vitro dissolution study it was found that the formulation F1 shown % drug release of 92.21 and F3 shown 96.84% of drug release after 24 hours compared to all the formulations.

Table 7
In vitro dissolution profile for all the formulations (F1-F6)

Sl. No.	Formulation Code	Cumulative % drug release after 24 hours
1	F1	92.21
2	F2	92.86
3	F3	96.84
4	F4	93.14
5	F5	93.46
6	F6	94.98

peppas is found to be 0.615 indicates F3 followed the fickian release. The formulations were fitted to zero order, first order, Higuchi's model and korsmeyer purpose model and from the respective values of slope, intercept and r^2 value was calculated. These values are shown in table 8. The model that best fits the drug release data was evaluated by the correlation coefficient (r). The n-value of korsmeyer.

Table 8
Kinetic data of all the formulations (F1-F6)

Sl. No.	Formulation Code	Zero Order	First Order	Higuchi's	Krosmeyer Peppas	
		Correlation Coefficient 'r'	Correlation Coefficient 'r'	Correlation Coefficient 'r'	Correlation Coefficient 'r'	Slope 'n'
1	F1	0.987	0.797	0.993	0.981	0.516
2	F2	0.989	0.799	0.993	0.983	0.524
3	F3	0.991	0.882	0.995	0.986	0.529
4	F4	0.984	0.789	0.992	0.982	0.543
5	F5	0.988	0.798	0.993	0.981	0.549
6	F6	0.989	0.881	0.996	0.982	0.549

CONCLUSION

Stomach targeted mucoadhesive tablets of ranitidine hydrochloride, which were prepared by direct compression method using carbopol 934P, HPMC K4M, SCMC and PEG6000 shown good mucoadhesive strength. Kinetic study shows that the drug was released by fickian diffusion. The F3 formulation shown good short term stable. Long term stability studies and in vitro studies in human subjects need to be carried out to market the formulations.

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