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Formulation and Evaluation of Mucoadhesive Gastroretentive Matrix Tablet of an Antiulcer Drug

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ABSTRACT

Ranitidine hydrochloride is a histamine H2-receptor antagonist that inhibits stomach acid production. It is absorbed in gastric pH and it is degraded into alkaline conditions. Therefore, an attempt was made to deliver the dosage form at the site of absorption by increasing the gastric retention time of the dosage form, thereby improving the bioavailability of the drug and to sustain the release of the drug. This is achieved by developing gastro retentive mucoadhesive drug delivery systems. Mucoadhesion keeps the delivery system adhering to the mucous membrane, hence significantly prolong the gastric retention time of the drugs. Prolonged gastric retention improves bioavailability, increases the duration of drug release, reduces drug waste, and improves the drug solubility that is less soluble in a high pH environment. Mucoadhesive tablets were prepared by direct compression method using various polymers such as HPMC K100M, Carbopol 934P, and Xanthan gum in different combinations and proportions. FT-IR studies shown there was no interaction between drug and polymers. Prepared tablets were subjected to various pre and post compression parameters such as bulk density, tapped density, Hausner ratio, Compressibility index, angle of repose, hardness, weight variation, % friability, thickness, drug content, swelling index, *In vitro* mucoadhesive strength, *In vitro* drug release profile, *In vitro* residence time and further subjected to stability studies . Results revealed that the tablet of all formulations has acceptable physicochemical parameters, which complied with Pharmacopoeial limits. The formulation F4 was optimized formulation based on its sufficient *in vitro* mucoadhesive strength, maximum *in vitro* residence time and better *in vitro* drug release profile up to 10 hrs. The combination of HPMC K100M and Xanthan gum in the ratio of 1:2 and 2:1 respectively were able to prolong the drug release for more than 10 hrs as compared to that of Xanthan gum alone. The values of Diffusional exponent suggest that the release of drug from the matrix was Non-fickian diffusion mechanism (diffusion followed by the erosion). The stability study during 3 months revealed that the optimized formulation remained stable at 40ºC and 75% relative humidity.

INTRODUCTION

The oral route is considered the safest and easiest route of drug administration. The reasons for selection of oral route include ease of administration, well known gastrointestinal physiology offering flexibility in dosage form design, requires least aseptic constraints and their easy manufacturing. Oral drug delivery systems are controlled release dosage forms and targeting dosage forms. Controlled release system provides the continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GIT. While in targeted preparations show their action in a specified area or tissue of the GIT (e.g.Colon, duodenum etc) despite its advantages there are so many disadvantages associated with controlled release system, which are as follows[1,2]:

- The Basic assumption is drug should absorb throughout the GI tract
- Limited gastric residence time
- Intersubject variability
- Drug should not be targeted to a specific region of GIT.

The above mention limitation of controlled release can be overcome by **'**Gastro retentive system**'.**

Gastro retentive dosage forms are one of the most widely known and accepted forms of oral controlled release drug delivery systems. The gastro-retentive system is an approach to prolong the gastric residence time, thereby targeting site-specific drug release in the upper GI tract for local or systemic effects[3]. Prolonged gastric retention improves bioavailability, increases the duration of drug release, reduces drug waste, and improves the drug solubility that is less soluble in a high pH environment. Also, prolonged gastric retention time (GRT) in the stomach could be advantageous for local action in the upper part of the small intestine e.g. treatment of peptic ulcer etc. The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of Mucoadhesion, flotation, sedimentation, expansion, modified shape systems, or by the simultaneous administration of pharmacological agents that delay gastric emptying[4].

Mucoadhesive drug delivery systems are used to enhance drug absorption in a site-specific manner. Mucoadhesion or bio adhesion can be defined as the state in which two materials, at least one of which is biological in nature, are held together for a prolonged time by means of

interfacial forces. For drug delivery purpose, the term "Bio adhesion" implies attachment of a drug carrier system to a specific biological location. The biological surface can be epithelial tissue or the mucous coat on the surface of a tissue. If the adhesive attachment is to a mucous coat, the phenomenon is referred to as "Mucoadhesion". Mucoadhesion is defined as the interaction between a mucin surface and a synthetic or natural polymer.

The matrix system is the most commonly used controlled release delivery system of rapidly released drugs. The drug is uniformly dissolved or dispersed in suitable polymeric materials. Most of these materials have either hydrophilic or hydrophobic properties, in which the retardant material and drug are homogeneously distributed or dissolved in the polymeric matrix. This is done either by wet granulation or by the direct compression technique. In the solid dosage form, where the drug is embedded in the matrix core of the retardant. Gradual dissolution of the matrix or gradual leaching of the drug from the retardant material[5,6] controls drug release.

Ranitidine is histamine H2-receptor antagonist blockers. They suppress the normal secretion of acid by parietal cells and the meal-stimulated secretion of acid. Used in the treatment of peptic ulcer disease (PUD), dyspepsia, stress ulcer prophylaxis, and gastroesophageal reflux disease (GERD), Zollinger Ellison syndrome, Erosive Esophagitis. It is absorbed in gastric pH and it is degraded into alkaline conditions. The biological half-life is 2-3 hrs and its bioavailability is only 50%[7].

The aim of proposed work was intended to formulate and evaluate mucoadhesive gastro retentive matrix tablet of Ranitidine HCl, with a view to prolonging the gastric retention time of the dosage form, thereby improving the bioavailability of the drug and to sustain the release of the drug.

The main objective of the present work was to prepare and evaluate mucoadhesive gastro retentive matrix tablet of Ranitidine HCl using various mucoadhesive polymers.

MATERIALS AND METHODS

MATERIALS

Ranitidine HCl was supplied from Yarrow Chem Products, Mumbai. HPMC K100M, Carbopol 934P was supplied from Yarrow Chem Products, Mumbai. Xanthan gum was

supplied from Balaji drugs. All other excipients and solvents used were of the analytical or pharmaceutical grade.

METHODS

➢ Preformulation studies[8]

❖ Determination of organoleptic properties

The physical appearance of the drug was observed and compared with the pharmacopoeial specifications.

❖ Determination of melting point

The melting point of Ranitidine HCl was determined by the open capillary method.

❖ Solubility

Small increments of Ranitidine HCl was added to 10 ml of solvent (distilled water, ethanol, and chloroform) in a 25 ml stoppered standard flask with vigorous shaking. Visually observed the solution, if the solution was clear and no undissolved particles were observed if it was insoluble, again another increment of particular solvent was added and the procedure was continued until undissolved Ranitidine HCl was found.

❖ Compatibility studies using FT-IR Spectroscopy[9]

FT-IR spectroscopy of pure drug (Ranitidine HCl) and physical mixture of drug and polymers was carried out to check the compatibility between the drug and polymers. The samples were prepared by mixing the drug alone and the drug with polymers in 1:1 ratio. The physical mixtures of (Ranitidine HCl) and polymers were scanned in the wavelength region between 400-4000 cm^{-1} and the spectrum were recorded. The compatibility between the drug and polymer were evaluated using FT-IR peak matching method.

➢ Preparation of Calibration Curve of Ranitidine HCl[10]

- **Preparation of simulated gastric fluid (0.1N HCl buffer p^H 1.2)**

2 gm NaCl and 7 ml HCl was added to 1000 ml standard volumetric flask and add sufficient distilled water to produce 1000 ml. The solution was checked for a pH of about 1.2.

- **Preparation of Calibration Curve of Ranitidine HCl in 0.1N HCl**

Accurately weighed 10 mg of pure drug (Ranitidine HCl) was transferred to 100 ml volumetric flask, dissolved in 0.1N HCl of pH 1.2 and made up to 100 ml with 0.1N HCl. From the above stock solution 0.5 ml, 1 ml, 1.5 ml, 2 ml, 2.5 ml was taken and further diluted to 10 ml with 0.1N HCl to obtain a concentration of 5, 10, 15, 20 and 25 µg/ml. The absorbance of each of these solutions was recorded at 315 nm in UV/ visible spectrophotometer against 0.1N HCl of pH 1.2 as blank. A graph of concentration vs absorbance was plotted.

➢ **Preparation of mucoadhesive gastro retentive matrix tablet of Ranitidine HCl by direct compression method[11].**

The formulations F1-F8 were prepared by direct compression method using varying percentages of HPMC K100M, Carbopol934P, and Xanthan gum. Microcrystalline cellulose was added as diluent. In this method, all the powders were passed through 80mesh sieve prior to mixing. The required quantity of the drug, various polymer mixtures and diluents were mixed. The blend was lubricated with magnesium stearate and talc and all the ingredients were again mixed. Then it was uniformly compressed into tablets using multistation tablet compression machine.

Table 1: Formulations of Ranitidine HCl mucoadhesive tablet

Ingredients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Ranitidine HCl	150	150	150	150	150	150	150	150
HPMC K100M	37.5	75	-	-	-	-	12.5	25
Carbopol934P	-	-	37.5	75	-	-	-	-
Xanthan gum	-	-	-	-	37.5	75	25	12.5
MCC	55	17.5	55	17.5	55	17.5	55	55
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	5	5	5	5	5	5	5	5
Total (mg)	250	250	250	250	250	250	250	250

➢ **Precompression parameters:**

❖ **Bulk density[12]:**

The bulk density of a powder is the ratio of the mass of the powder sample to its volume including the contribution of the interparticulate void volume. The bulk density is expressed in grams per milliliter (g/ml) or grams per cubic centimeter (g/cm^3). The bulk volume (V_b) and weight of the powder (M) were calculated using the formula.

$$\rho_b = M / V_b$$

❖ **Tapped density[12]:**

The tapped density is an increased bulk density attained after mechanically tapping a container containing the powder sample. The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (ρ_t) was calculated by using formula.

$$\rho_t = M / V_t$$

❖ **The angle of repose[13]:**

The angle of repose or critical angle of repose of a granular material is the steepest angle of descent or dip relative to the horizontal plane to which a material can be piled without slumping. The angle of repose was determined by using the funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. The radius of the heap(r) was measured and the angle of repose (Θ) was calculated using the formula.

$$\Theta = \tan^{-1} (h/r)$$

❖ **Compressibility Index (I) [14]:**

The Carr's Compressibility Index is an indication of the compressibility of a powder.

The Carr index is calculated by the formula

$$C = 100 [(V_b - V_t) / V_b]$$

Where, V_b is the volume that a given mass of powder would occupy if let settled freely, and V_t is the volume of the same mass of powder would occupy after "tapping down".

❖ **Hausner ratio (H_R) [15]:**

The Hausner ratio is a number that is correlated to the flowability of a powder or granular material. The Hausner ratio is calculated by the formula.

$$H_R = \rho_t/\rho_b$$

Where ρ_b is the freely settled bulk density of the powder and ρ_t is the tapped density of the powder.

➢ **Post-compression parameters**

❖ **Physical appearance[16]:**

The shape of the tablet can be dimensionally described, monitored and controlled.

❖ **Organoleptic properties[17]:**

It includes the color and odour of the prepared tablet.

❖ **Weight variation [18]:**

Weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weight to the average weight.

❖ **Hardness test[19]:**

The hardness of the tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under the condition of storage, transportation, and handling before usage depends on its hardness.

The Pfizer tester compresses tablet between a holding anvil and a piston connected to a force-reading gauge when its plier-like handles are gripped.

The force required to break the tablets is measured in kilograms

❖ **Thickness and diameter[20]:**

Tablet thickness is an important characteristic in reproducing appearance and in counting by using the filling equipment. The thickness and diameter of the tablets were measured using Vernier callipers. It is expressed in mm.

❖ **Friability[21]:**

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets has determined by using Roche friabilator. It is expressed in percentage (%).

$$F = [(W_i - W_f) / W_i] 100$$

Where; F = friability, W_i = initial weight, W_f = final weight

❖ ***In vitro* Mucoadhesive Strength[22,23]:**

The mucoadhesive strength of the tablet was measured on the modified physical balance.

Figure 1: Modified double beam physical balance for *in vitro* mucoadhesion study

The apparatus consists of a modified double beam physical balance in which the right pan has been balanced with left pan by adding additional weight. Goat gastric mucosa was used as the model substrate and 0.1N HCl of pH 1.2 was used as the moistening fluid. Freshly excised goat gastric mucosa was obtained from the local slaughterhouse used within 3 hr of slaughter and kept in a Krebs buffer during transportation. The underlying mucous membrane was

separated using a surgical blade and wash thoroughly with buffer media 0.1N HCl of pH 1.2. It was then tied over disc using a thread. The disc was then kept in a glass beaker containing 0.1N HCl of pH 1.2 as buffer media in such a way that buffer just reaches the surface of the mucosal membrane and kept it moist. The tablet to be tested was stuck on the mucous membrane. A preload of 10 mg was placed over the left pan for 5 min (preload time) to established adhesion bonding between mucoadhesive tablet and goat stomach mucosa. The preload and preload time were kept constant for all formulations. After the completion of preload time, preload was removed from the pan. Then the weight on the right-hand side was slowly added in an increment of 0.5g until the tablet separated from the membrane. The weight required to detach the mucoadhesive tablet from stomach mucosa was noted as a mucoadhesive strength in grams. From the mucoadhesive strength following parameter was calculated.

Force of adhesion (N) = Mucoadhesive strength / 1000 × 9.81

Bond strength (N/m2) = Force of adhesion (N)/ Surface area of tablet (m^2)

❖ **Measurement of the *invitro* Residence Time/ Wash - off test [24]:**

Figure 2: Modified disintegration apparatus

The *ex vivo* residence time was determined using a modified USP disintegration apparatus, which gave an idea about *in vivo* retention time and provide quantitative information on their mucoadhesive properties. Pieces of goat stomach mucosa were mounted on the glass slides provided with suitable support. After fixing of tablets under test to this glass slide, it was tied to the arm of USP tablet disintegration test apparatus and was run at 37°C. Time of detachment of tablets from the mucosal surface was noted down as the mucoadhesion time.

❖ **Swelling index[25]:**

Swelling of tablet excipients particles involves the absorption of a liquid resulting in an increase in weight and volume. The extent of swelling can be measured in terms of % weight gain by the tablet. For each formulation batch, one tablet was weighed individually (W0) and placed separately in Petri dishes containing 20 ml 0.1N HCl of pH 1.2 solution. At regular intervals of time (1, 2, 3, 4, 5, 6, 7, and 8 hrs.), the tablets were removed from the Petri dishes, and excess surface water was removed carefully using the filter paper.

The swollen tablet was then reweighed (Wt), and swelling index (SI) was calculated using the following formula,

Swelling Index (S.I.) = (Wt-Wo) / Wo

Where, S.I. = Swelling index

Wt = Weight of tablet at time t

W0 = Weight of the tablet before placing in the beaker

❖ **Drug Content Estimation[12]:**

Ten tablets were accurately weighed and the average weight was calculated. Then the tablets were grounded in a glass mortar with a pestle to get a fine powder. An amount equivalent to 10 mg of drug was accurately weighed and was extracted with 100 ml of 0.1N HCl of pH 1.2. The solution was filtered through a filter paper (Whatman 0.22-µm pore size). Then pipetted out 1 ml of sample from the filtered solution and properly diluted with 0.1N HCl to get a concentration of 10 µg /ml and the absorbance was determined by UV spectrophotometer at a wavelength 315 nm and the percentage drug content was calculated.

❖ ***In Vitro* Release Study[26,27]:**

The release rate of Ranitidine HCl from mucoadhesive tablets was determined using USP Dissolution Testing Apparatus II (Paddle type). The dissolution test was performed using 900 ml of 0.1 N HCl buffer of pH 1.2 at 37 ± 0.5°C. The rotational speed of the paddle was 50 rpm. Aliquots of 1 ml were withdrawn at specific time intervals up to 10 hrs and replaced with 1ml fresh dissolution medium. The withdrawn samples were diluted with dissolution medium (0.1 N HCl buffer of pH 1.2) and then filter it with Whatman filter paper. The

absorbance of the samples was measured by UV spectrophotometer (Shimadzu UV 1800) at 315 nm. The % release of drug was calculated.

❖ **Kinetics of in-vitro drug release[28]:**

The results obtained from in-vitro release studies were attempted to fit into various mathematical models as follows:

1) Cumulative percent drug released Vs. Time (Zero order kinetics)

2) Log cumulative percent drug retained Vs. Time (First order kinetics)

3) Cumulative percent released Vs. The square root of Time (Higuchi model)

4) Log cumulative percent drug released Vs. Log Time (Korsmeyer- Peppas model)

In the Peppas model, the value of 'n' characterizes the release mechanism of the drug as described in Table 2.

Table 2: Interpretation of diffusional release mechanism

Release exponent (n)	Diffusion release mechanism
<0.45	Quasi – Fickian diffusion
0.45	Fickian diffusion
0.45 <n<0.89	Anomalous(Non-Fickian) diffusion
0.89 - 1.0	Case II transport (Zero order release)
>1.0	Super case II transport

❖ **Stability studies[29,30] :**

The success of an effective formulation can be evaluated only through stability studies. According to ICH Q1A (R2), "the purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light". The selected formulations were subjected to stability studies up to 3 months under different storage conditions. The tablets were sealed in airtight aluminum foil packets and stored at controlled room temperature condition (25 ± 2 °C and 60 ± 5% RH) in a desiccator and at accelerated condition (40 ± 2 °C and 75 ± 5% RH) instability chamber. The stored formulations were evaluated for drug content, *in vitro* mucoadhesive strength, *in vitro* retention time and *in vitro* drug release at a predetermined time interval.

RESULTS AND DISCUSSIONS

➢ Preformulation studies

❖ Determination of Organoleptic properties

The organoleptic properties of Ranitidine HCl were found to be pale yellow, odourless and crystalline state.

❖ Determination of Melting point

The melting point of Ranitidine HCl was found to be 69^0C.

❖ Solubility

The solubility of Ranitidine HCl in various solvents such as (Distilled water, Chloroform, Ethanol) was studied and found that it is freely soluble in distilled water while it is slightly soluble in ethanol and insoluble in chloroform.

❖ Compatibility studies

- **FT-IR spectroscopy of Ranitidine HCl**

The FT-IR spectrum of Ranitidine HCl is shown in figure 3, complies with standard functional group frequencies.

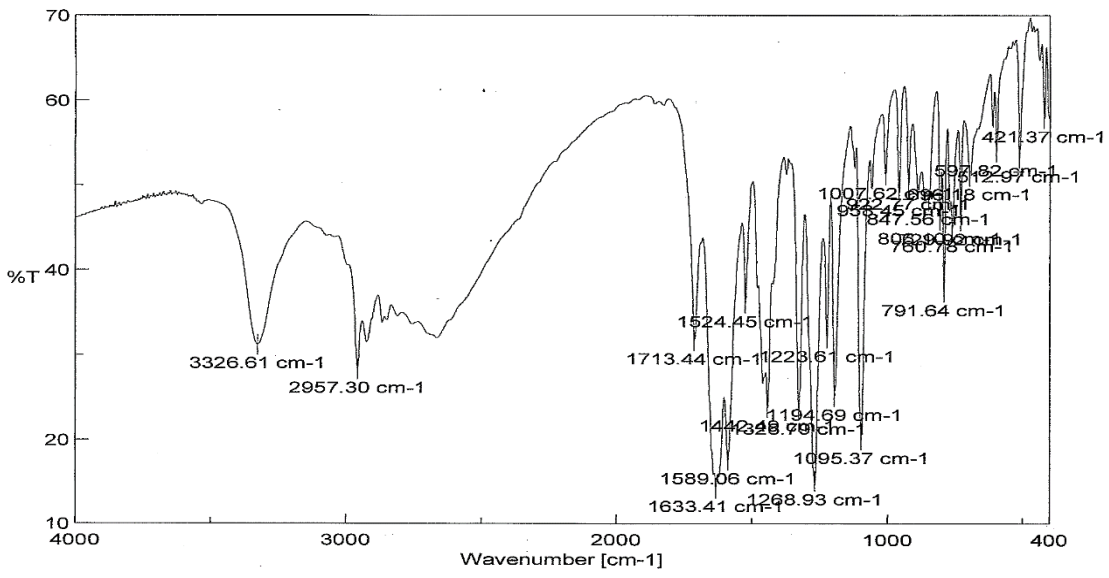

Figure 3: FT-IR spectrum of Ranitidine HCl

Table 3: IR frequencies of Ranitidine HCl

Functional group	Characteristic Wavenumber(cm^{-1})	Ranitidine HCl observed wave number(cm^{-1})
N-H Stretching	3140-3500	3326.61
C-H Stretching	2800-3100	2957.30
C=C Stretching	1680-1620	1633.41
C-S Stretching	705-570	597.82

The peaks analyzed in Table 3 indicate the most characteristic frequencies of the functional group of Ranitidine HCl which are N-H, C-H, C=C, C-S etc. were confirmed compared to the reported frequencies.

- **Compatibility between drug and polymer**

The FT-IR spectrum of Ranitidine HCl is shown in figure 3 and the combination of Ranitidine HCl with excipients are shown in figure 4

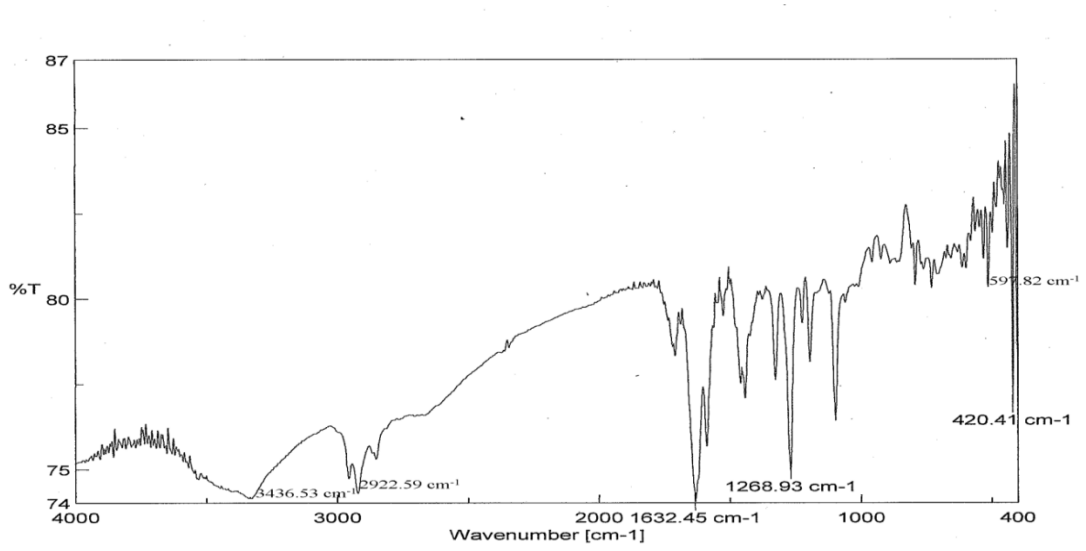

Figure 4: FT-IR Spectrum of Ranitidine HCl with HPMC K100M, Carbopol 934P, Xanthan gum.

Table 4: IR frequencies of Ranitidine HCl with HPMC K100M, Carbopol 934P, Xanthan gum.

Functional group	Characteristic Wave number(cm^{-1})	Ranitidine HCl observed wave number(cm^{-1})	HPMCK100M, Carbopol934P, Xanthan gum (cm^{-1})
N-H Stretching	3140-3500	3326.61	3436.53
C-H Stretching	2800-3100	2957.30	2922.59
C=C Stretching	1680-1620	1633.41	1632.45
C-S Stretching	705-570	597.82	597.82

The compatibility between drug and polymer were carried out by using FT-IR peak matching method. All major peaks present in the spectrum of the pure drug were observed in the spectrum of the drug-polymer mixture. This suggests that the drug remains in its normal structure and hence this confirmed the absence of any chemical interaction or complexation between drug and polymers.

➢ PREPARATION OF CALIBRATION CURVE OF RANITIDINE HCl

- **Preparation of simulated gastric fluid**

The gastric fluid was prepared and pH measured using a digital pH meter and was found to be 1.2.

- **Preparation of a standard calibration curve of Ranitidine HCl**

Table 5: Standard calibration curve for Ranitidine HCl at 315 nm

Concentration (µg/ml)	Absorbance (nm)
5	0.050
10	0.094
15	0.151
20	0.201
25	0.245

The calibration curve was found to be linear in the range of 5-25 µg/ml at λ max 315nm

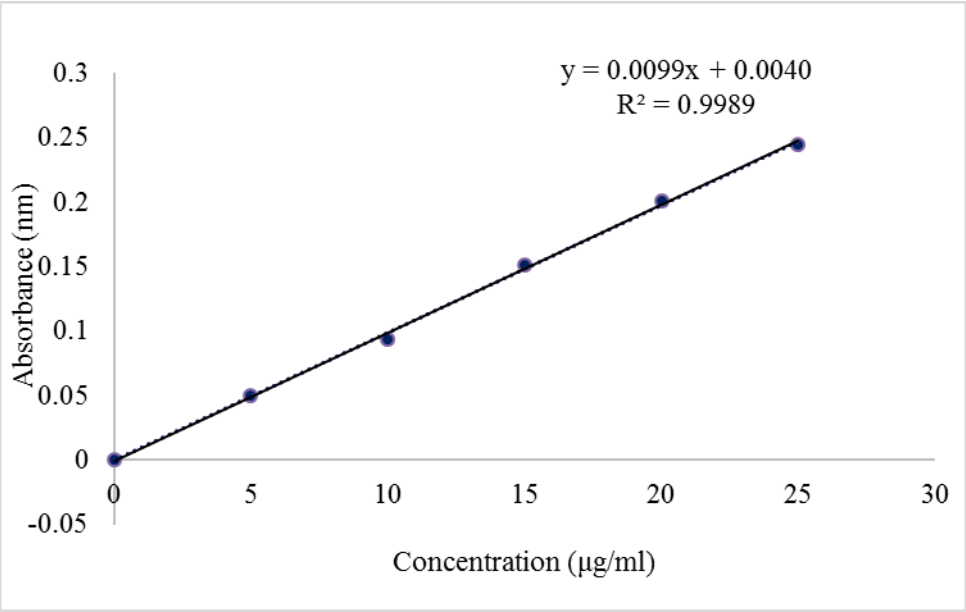

Figure 5: Calibration curve of Ranitidine HCl

➢ **FORMULATION OF MUCOADHESIVE GASTRORETENTIVE MATRIX TABLETS**

- **Method of Formulation of mucoadhesive matrix tablets**

The mucoadhesive matrix tablets were prepared by using the polymers such as HPMC K100M, Carbopol 934P, and Xanthan gum in different ratios. Microcrystalline cellulose was used as diluent. Talc and Magnesium stearate was used as lubricants.

➢ **Pre-compression parameters**

Table 6: Pre-compression parameters of formulations F1 – F8

Formulation code	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Angle of repose	Compressibility index	Hausner's ratio
F1	0.49 ± 0.021	0.58 ± 0.013	31.21° ± 1.53	15.51 ± 1.36	1.18 ± 0.34
F2	0.48 ± 0.014	0.56 ± 0.019	30.83° ± 1.44	14.28 ± 1.41	1.16 ± 0.21
F3	0.43 ± 0.027	0.49 ± 0.013	27.55° ± 1.03	12.24± 0.61	1.13 ± 0.18
F4	0.47 ± 0.013	0.53 ± 0.011	26.36° ± 0.73	11.32 ± 0.71	1.12 ± 0.17
F5	0.41 ± 0.017	0.47 ± 0.019	28.72° ± 1.18	12.76 ± 0.58	1.14 ± 0.25
F6	0.40 ± 0.025	0.45 ± 0.016	30.46° ± 1.40	11.98 ± 0.48	1.13 ± 0.19
F7	0.45 ± 0.014	0.52 ± 0.014	28.14° ± 1.15	13.46 ± 1.21	1.15 ± 0.22
F8	0.42 ± 0.016	0.50 ± 0.018	29.72° ± 1.34	15.00 ± 1.44	1.17 ± 0.30

➢ **Post-compression parameters**

❖ **Physical appearance**

All the formulations F1-F8 were compressed in the round and standard convex shape

❖ **Organoleptic properties:**

All the prepared formulations showed pale yellow in color without specific odour.

Table 7: Post-compression parameters of formulation F1 – F8

Formulation code	Average weight (mg)	Average Hardness ($kg/cm^{2)}$	Thickness (mm)	Diameter (mm)	% Friability
F1	0.249 ± 0.61	5.6 ± 0.152	4.5 ± 0.04	8.20 ± 0.05	0.816 ± 0.05
F2	0.251 ± 0.40	5.2 ± 0.113	4.6 ± 0.05	8.16 ± 0.03	0.787 ± 0.07
F3	0.248 ± 0.48	4.2 ± 0.212	4.4 ± 0.04	8.20 ± 0.04	0.833 ± 0.06
F4	0.249 ± 0.45	4.6 ± 0.113	4.5 ± 0.04	8.20 ± 0.04	0.826 ± 0.03
F5	0.245 ± 0.38	5.4 ± 0.145	4.3 ± 0.06	8.13 ± 0.05	0.813 ± 0.08
F6	0.249 ± 0.60	4.8 ± 0.214	4.4 ± 0.04	8.20 ± 0.04	0.829 ± 0.01
F7	0.246 ± 0.41	4.4 ± 0.149	4.5 ± 0.05	8.13 ± 0.05	0.806 ± 0.04
F8	0.247 ± 0.45	5.8 ± 0.119	4.6 ± 0.06	8.13 ± 0.04	0.819 ± 0.06

Table 8: Post-compression parameters of formulation F1 – F8

Formulation code	Mucoadhesive strength (gm)	Force of adhesion (N)	Bond strength (N/m^2)	Retention time (hrs)
F1	20.66 ± 0.87	0.2026	4.94	8.25 ± 0.16
F2	23.00 ± 1.08	0.2256	5.24	9.40 ± 0.15
F3	28.30 ± 0.82	0.2776	6.77	10.10 ± 0.09
F4	29.60 ± 0.78	0.2903	7.08	10.55 ± 0.11
F5	9.00 ± 0.87	0.0882	2.16	2.20 ± 0.21
F6	11.33 ± 1.16	0.1110	2.70	4.15 ± 0.15
F7	14.00 ± 0.92	0.1373	3.37	5.40 ± 0.11
F8	19.66 ± 0.89	0.1929	4.82	6.35 ± 0.20

Table 9: Post-compression parameters of formulation F1 – F8

Formulation code	Swelling index (%)	Content uniformity (%)
F1	92 ± 0.78	94.45 ± 0.10
F2	116 ± 0.25	96.07 ± 0.13
F3	136 ± 0.32	98.72 ± 0.15
F4	180 ± 0.31	99.99 ± 0.11
F5	144 ± 0.63	97.50 ± 0.19
F6	164 ± 0.28	98.52 ± 0.09
F7	108 ± 0.32	97.20 ± 0.10
F8	112 ± 0.28	97.75 ± 0.12

❖ ***In vitro* dissolution studies :**

In vitro dissolution studies of all formulations were carried out in dissolution test apparatus using 0.1N HCl of pH 1.2 as the dissolution medium for 10 hrs. Percentage cumulative drug release at each time interval as shown in the table and the data represented graphically.

Table 10: Percentage cumulative drug release data for Formulations F1-F4

Time (min)	%CDR			
	F1	F2	F3	F4
0	0	0	0	0
0.5	27.30	31.55	29.12	30.94
1	29.12	33.37	33.97	33.97
2	35.79	40.65	41.25	40.65
3	43.07	44.29	52.78	46.71
4	49.14	47.32	60.06	54.60
5	56.42	52.17	65.52	63.70
6	61.88	58.24	74.62	71.59
7	66.74	60.06	81.30	78.87
8	76.44	63.70	85.54	86.76
9	80.08	66.74	91.01	90.40
10	84.33	68.56	97.07	94.04

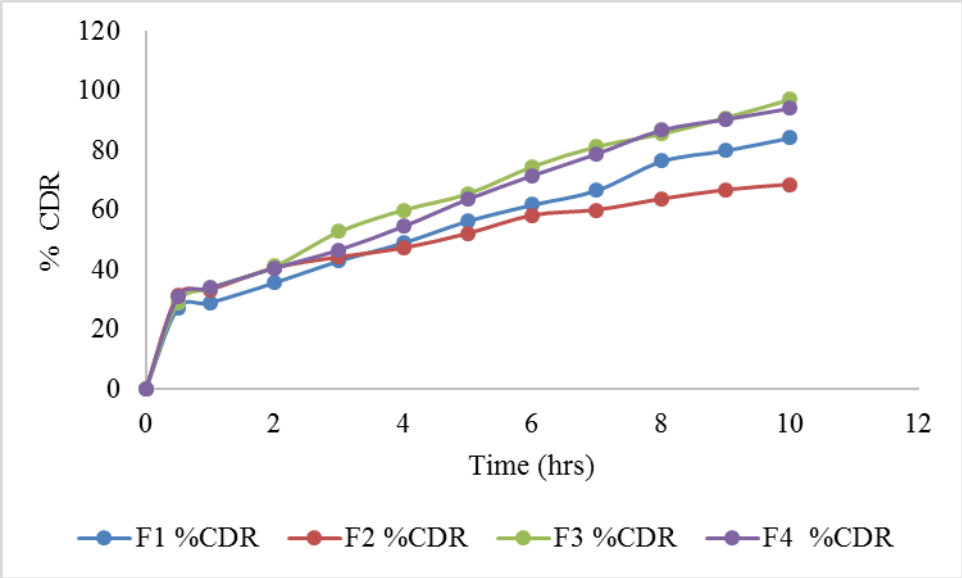

Figure 6: *In vitro* dissolution studies for Formulations F1-F4

Table 11: Percentage cumulative drug release data for Formulations F5-F8

Time (min)	% CDR			
	F5	F6	F7	F8
0	0	0	0	0
0.5	35.79	32.76	32.76	29.72
1	49.14	37.61	37.01	31.55
2	66.13	44.29	44.29	38.83
3	76.44	55.81	49.75	41.25
4	83.72	67.95	57.03	47.32
5	90.40	78.26	66.13	54.60
6	95.86	88.58	72.80	58.85
7	-	93.43	75.84	63.70
8	-	98.29	80.69	67.34
9	-	-	84.33	69.77
10	-	-	89.18	75.23

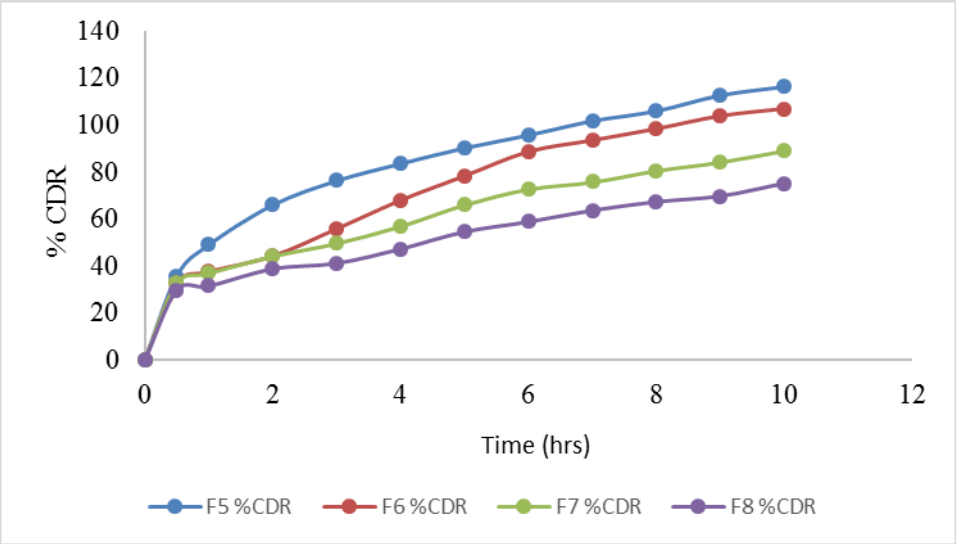

Figure 7: *In vitro* dissolution studies for Formulations F5-F8

From the *in-vitro* drug release data of mucoadhesive gastro retentive matrix tablet of Ranitidine HCl, it was observed that the percentage cumulative drug release of Ranitidine HCl decreased as the concentration of polymers increased. The formulation F4 was optimized formulation based on its sufficient *in vitro* mucoadhesive strength, maximum *in vitro* residence time and better *in vitro* drug release profile up to 10 hrs. The combination of

HPMC K100M and Xanthan gum in the ratio of 1:2 and 2:1 respectively were able to prolong the drug release for more than 10 hrs as compared to that of Xanthan gum alone.

❖ Kinetics of *in vitro* drug release

The results obtained from *in vitro* release studies were attempted to fit into various mathematical models.

Table 12: Kinetic study of formulations F1-F8

Formulation code	Release Kinetics				
	Zero-order R^2	First order R^2	Higuchi R^2	Peppas	
				R^2	N
F1	0.9914	0.9746	0.9734	0.9802	0.4818
F2	0.9819	0.9329	0.9891	0.9829	0.3205
F3	0.9887	0.8945	0.9903	0.9888	0.4734
F4	0.9928	0.9416	0.9705	0.9687	0.4786
F5	0.9580	0.9469	0.9915	0.9976	0.3657
F6	0.9731	0.9327	0.9831	0.9795	0.4984
F7	0.9845	0.9814	0.9876	0.9799	0.4018
F8	0.9911	0.9905	0.9796	0.9736	0.3867

The *in vitro* drug release data was subjected to the goodness of fit by linear regression analysis, according to zero order, first-order kinetic equation, Higuchi and Korsmeyer models to ascertain the mechanism of drug release.

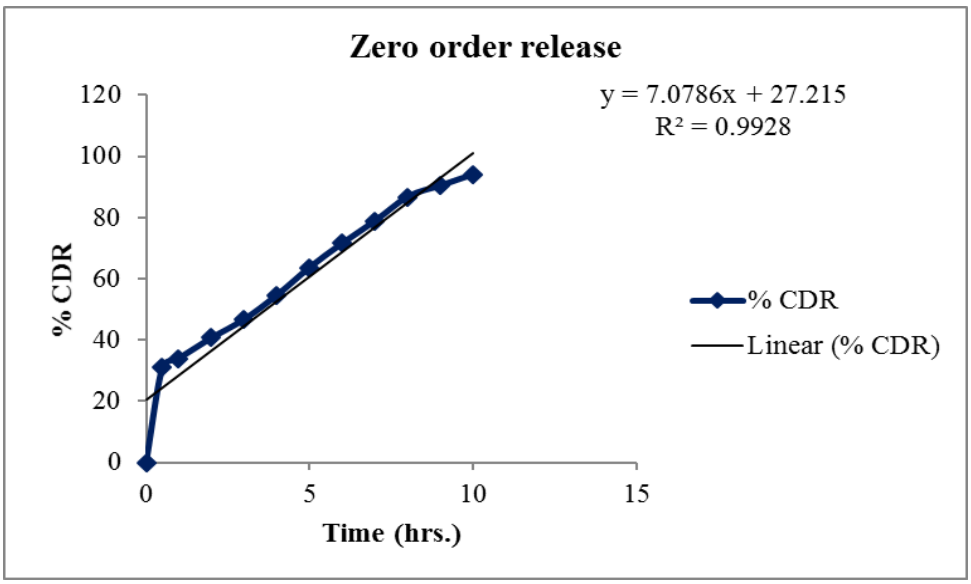

Figure 8: Zero order plot of F4

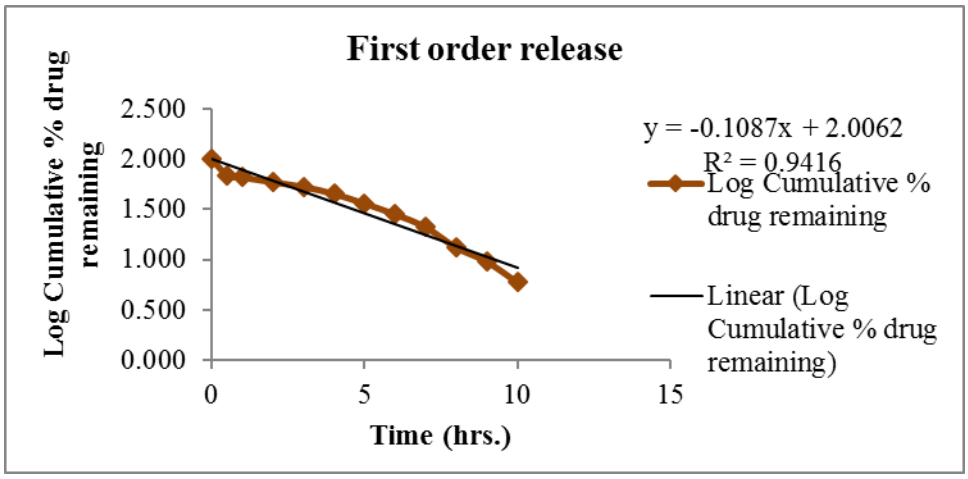

Figure 9: First order plot of F4

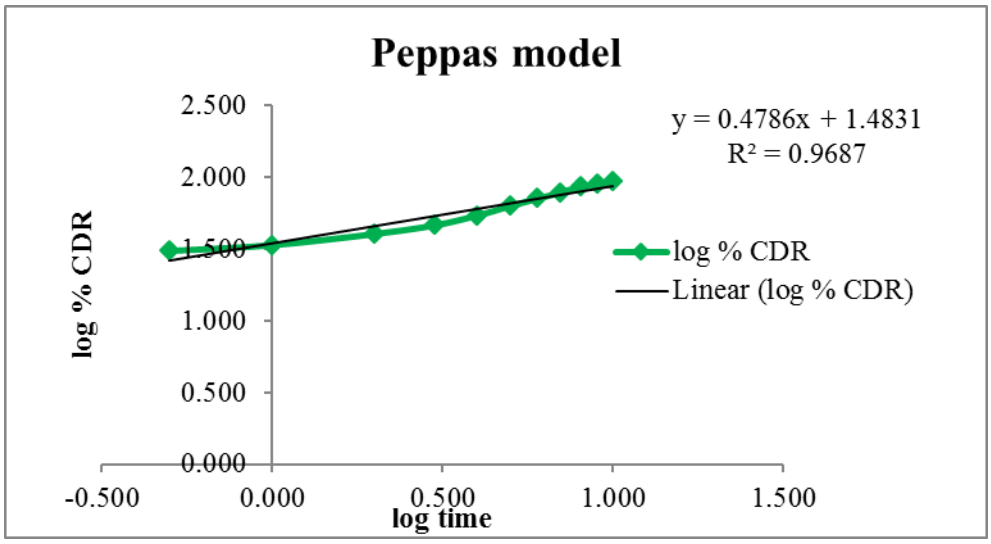

Figure 10: Peppas plot of F4

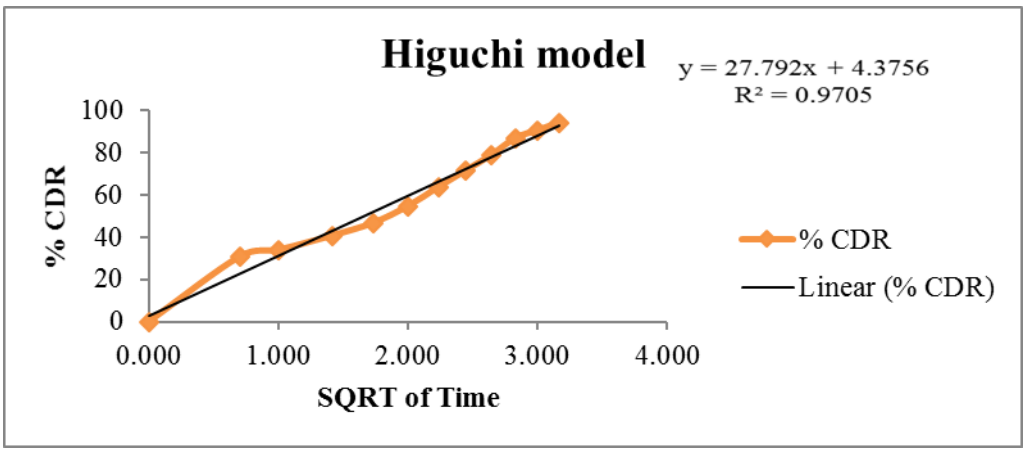

Figure 11: Higuchi plot of F4

From the above graphs, it was concluded that the formulation F4 follow zero order kinetics. The *in vitro* drug release data as log % CDR versus time were fitted to Korsmeyer equation in order to understand the mechanism by which Ranitidine HCl was released from this formulation. Value of exponent 'n' was found to be 0.3205-0.4984.The Korsmeyer Peppas model yields 'n' values >0.45 indicating that the diffusion mechanism from the formulation followed Non- Fickian diffusion.

❖ **Stability studies:**

Stability studies were carried out on formulation F4 for a period of 3 months and comparison of the parameters before and after stability studies was represented in table 13 and 14.

Table 13: Comparison of parameters before and after stability

Parameters	Before stability studies	After stability Studies (1 month)	After stability Studies (3 months)
Physical changes	Pale yellow, Round, standard convex	No changes	No changes
%drug content	99.99	99.87	99.23
***In vitro* Mucoadhesive strength**	29.6	29.4	29
Retention period	10.55	10.40	10.30

Table 14: Drug release determination after stability

Time (hrs)	Before stability % CDR	After stability %CDR (1 month)	After stability %CDR (3 month)
0	0	0	0
0.5	30.94	30.24	29.72
1	33.97	33.16	32.15
2	40.65	39.44	38.83
3	46.71	45.90	45.50
4	54.60	53.77	52.78
5	63.70	61.28	60.67
6	71.59	71.02	69.77
7	78.87	78.18	77.05
8	86.76	85.87	83.72
9	90.40	89.92	87.97
10	94.04	93.97	93.43

The stability of the optimized formulation was known by performing stability studies for 3 months at accelerated conditions of 40^{0} C ± 75 % RH. The formulation was found to be stable with no physical changes and shows the slight decrease in mucoadhesive strength and retention time and also shows a slight decrease in drug content and *in vitro* drug release pattern after the stability period. From the stability studies, it was confirmed that the formulation remains stable at accelerated stability conditions.

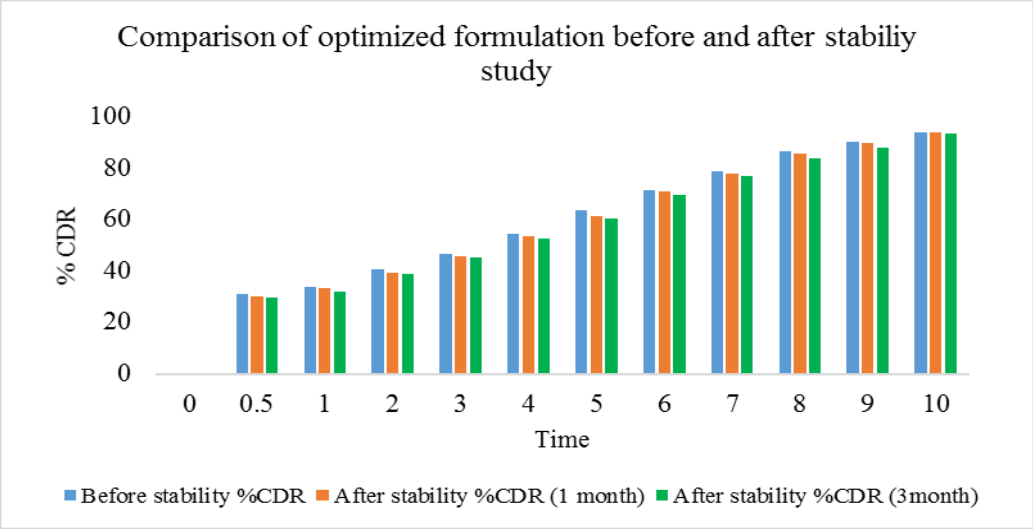

Figure 12: Release pattern of the optimized formulation before and after stability study

CONCLUSION

Oral drug delivery remains the most preferred route for administration of various therapeutic agents. The oral route is considered the safest and easiest route of drug administration. The reasons for selection of oral route include ease of administration, well known gastrointestinal physiology offering flexibility in dosage form design, requires least aseptic constraints and their easy manufacturing. Gastro retentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the stomach for local or systemic effects. These dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time of the drugs. It will release the drug in the stomach in a controlled manner so that the drug could be supplied continuously to absorption site in GIT i.e. stomach**.** Prolonged gastric retention improves bioavailability, increases the duration of drug release, reduces drug waste, and improves the drug solubility that is less soluble in a high pH environment. Also, prolonged gastric retention time (GRT) in the stomach could be advantageous for local action in the upper part of the small intestine e.g. treatment of peptic ulcer.

Ranitidine HCl is a histamine H2 receptor antagonist used for the treatment of peptic ulcer disease (PUD), dyspepsia, stress ulcer prophylaxis, and gastroesophageal reflux disease (GERD), Zollinger Ellison syndrome, Erosive Esophagitis. They suppress histamine-mediated the normal secretion of acid by parietal cells and the meal-stimulated secretion of acid by the act as an antagonist to histamine receptors.

Polymers like HPMC K100M, Carbopol 934P, Xanthan gum were chosen as mucoadhesive polymers for the formation of mucoadhesive gastro-retentive matrix tablets. In this study, 8 formulations were prepared by direct compression method using different mucoadhesive polymers at varying ratios. MCC was added as diluent. Talc and Magnesium stearate was added as lubricants.

The compatibility of the drug in the formulation was performed by FT-IR spectroscopy. Each batch of the formulations was subjected to Precompression and post-compression evaluation techniques and stability study of the optimized formulation. The mucoadhesive strength and retention time of the prepared formulations depends upon the number of polymers used.

Based on the physicochemical, drug release characteristics, *in vitro* mucoadhesive strength, *in vitro* retention time the present study conclude that the formulation F4 containing carbopol 934P with the highest concentration was the optimized one due to its *in vitro* mucoadhesive

strength of 29.6 gm, *in vitro* retention time of 10 hrs and 55 min and promising drug release of 94.04 % up to 10 hrs. The formulations F7 and F8 containing a combination of HPMC K100M and Xanthan gum in the ratio of 1:2 and 2:1 respectively were able to provide good mucoadhesive strength and sustain the drug release when compared to that of formulations (F5 & F6) containing xanthan gum alone.

The findings of the result revealed that Ranitidine HCl administered in the form of mucoadhesive gastro-retentive matrix tablets will be a potential novel drug dosage form for treatment of peptic ulcer disease (PUD), dyspepsia, stress ulcer prophylaxis, and gastroesophageal reflux disease (GERD), Zollinger Ellison syndrome, Erosive esophagitis due to its good mucoadhesive properties and retention time and are also able to sustain the drug action for prolonged periods thus improves the bioavailability of the drug.

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