Formulation Development and Optimization of Press Coated Tablets of Ranitidine HCl by using 3^2 Factorial Design

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ABSTRACT

The main aim of the present work is to formulate and evaluate a chronotherapeutic drug delivery system of ranitidine hydrochloride using suitable mucoadhesive polymers by press coating technique. For elucidating the effect of formulation factors of press coated tablets a 3^2 full factorial design was employed. The effect of two factors, ratio of hydroxy propyl methyl cellulose (HPMC) K4M to ethyl cellulose (EC) in the core (X_1) and ratio of HPMC K4M to carbopol 934P in the coat(X_2) as independent variables. Y_1 (drug release lag time), Y_2 (% drug release after 6 hours) and Y_3 (mucoadhesion strength) were selected as dependent variables. Thirteen formulations were formulated and subjected to various physiochemical evaluations like weight variation, friability, hardness, drug content, *in vitro* drug release and kinetic studies, swelling index and *ex vivo* mucoadhesion studies. The optimum formulation consists of ranitidine HCl 150mg, HPMC K4M: EC (0.72:1) in the inner core and HPMC K4M: carbopol 934P (1:1) in the outer coat with drug release lag time 1.89 hrs, cumulative % drug release after 6 hrs 41.15% and mucoadhesion strength 43.67 g. Ranitidine HCl tablets exhibited zero order release kinetics, resulting in regulated and complete release until 11 hrs.

Keywords: Chronotherapy, Factorial design, Mucoadhesion, Press coating technique, Ranitidine hydrochloride.

1. INTRODUCTION

The most common chronic, relapsing condition which is a risk of significant mortality and potential morbidity mortality from resultant complications is gastro esophageal reflux disease (GERD). The National Ambulatory Medical Care Survey (NAMCS) found that 38.53 million annual adult outpatient visits were due to GERD, being more prevalent in pregnant women and elderly people. Normal gastric acid secretion follows a circadian rhythm, when gastric pH level goes far below for at least 1 hour in the midnight results in a sudden raise of gastric acidity[1]. The common symptoms are being heartburn, coughing or choking due to fluid in the throat, breathlessness, wheezing and morning phlegm. This pathophysiological condition is termed as nocturnal acid breakthrough (NAB) and is even more prolonged and clinically critical for *H. pylori*-negative patients on proton pump inhibitor (PPI) therapy. NAB is one of the foremost reasons of treatment failure of gastro esophageal reflux disease (GERD) compromising therapeutic goals in patients[2].

Histamine-H_2 receptor antagonists (H_2RAs) and proton pump inhibitors (PPIs) are the most commonly prescribed regimens for treating moderate to severe heartburns. It begins with simple treatments, such as antacids or over-the-counter H_2RAs for mild symptoms, and steps up to high dose H_2RAs or PPIs, for more severe symptoms. H_2RAs are the historical mainstay in the treatment of GERD, particularly for the symptomatic treatment of heartburn[3]. A randomized study conducted revealed that almost 70% patients were found to be resistant to high doses of PPIs even taken twice daily; and thus indicating

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forth failure in providing necessary nocturnal acid suppression with PPI[4]. It is demonstrated that nocturnal recovery of gastric acid secretion can be achieved by adding a bed-time dose of H_2 antagonist to an evening dose of proton pump inhibitor provided[5-6]. However, the possible development of tolerance on regular dosing makes the long-time efficacy of the combination therapy is debatable[7]. This limitation can be overcome by a chronotherapeutic approach which will ensure that the maximum blood levels of the drug are achieved together with the peak symptoms in early morning hours. By this approach limited exposure of the drug to the biological system is made possible; in this manner it will diminish the chances of development of tolerance[8-9]. Hence, a bed-time dosing of H_2 antagonist with a pulsatile drug delivery system united with normal twice daily PPI dosing would be a promising therapeutic regimen.

One of the most challenging H_2RA is ranitidine hydrochloride (HCl) with maximum absorption from the stomach and upper part of the gastro intestinal tract (GIT) and is rapidly metabolized in the intestine due to colonic bacteria[10]. Hence gastro-retentive dosage forms are appropriate for the delivery of ranitidine HCl which reside only in stomach and are not affected by variability of pH, local environment or gastric emptying rate. These considerations led to the development of pulsatile release dosage forms possessing gastric retention capabilities[11]. Previously many research works were done based on combining floating and pulsatile principles to develop drug delivery system, intended for chronotherapy in nocturnal acid breakthrough[12-13]. The present investigation conceptualizes a specific technology to ascertain the gastro retentivity of ranitidine HCl using suitable mucoadhesive polymer for designing press coated tablets (PCT).

Press-coating, also referred to as double compression coating/ compression coating/ dry coating is an old technique first proposed and patented by Noyes[14]. This process has a relatively short manufacturing process without use of solvents and achieves a greater increase in mass of the core tablet than solvent-based methods[15]. Even though it is an old concept, press-coating is a novel technology for the formulation of modified drug delivery systems, through isolation of incompatible drugs, protection of hygroscopic, light sensitive, oxygen labile and acid-labile drugs, and sustained drug release and modification of the drug release profile[16-17]. As this technique provides the delivery of a drug from a solid dosage form at predetermined times and sites following oral administration and in a pulsatile manner rather than continuously, can be classified as a chronopharmaceutical technology. A press coated tablet consists of an inner core tablet and an outer coating shell[18].

In the present investigation, the inner core tablet consists of hydroxypropyl methyl cellulose (HPMC K4M) and ethyl cellulose (EC) as drug carriers for sustaining the drug release and to enhance the bioavailability[19]. Gastro retentive drug delivery can be achieved using this technique by employing mucoadhesive polymers such as HPMC and carbopol 934P in the outer coating shell of the press coated tablet which improve the component swelling and bio adhesive characteristics. This timed pulsatile release of ranitidine HCl (H_2 antagonist) with delayed "burst" release will attenuate midnight acidity and will provide relief from the peak symptoms in the early morning hours. A 2-factor, 3- level, 13 run 3^2 full factorial design (FFD) was developed using design expert software (DoE) to study the effect of formulation variables on the drug delivery system[20-21]. All the 13 formulations prepared were evaluated for weight variation, hardness, thickness, diameter, friability, drug content, *in vitro* drug release kinetics, swelling index and *ex vivo* mucoadhesion strength. The formulation with maximum desirability was chosen as the optimized formula and the model was further cross validated.

2. Materials and Methods

2.1 Materials

Ranitidine HCl, HPMC K4M and carbopol 934P were purchased from Yarrow chemicals, Mumbai. Ethyl cellulose (EC) was obtained from Oxford laboratories, Mumbai. Talc was procured from Otto chemicals, Mumbai. Magnesium stearate was purchased from LOBA chemicals, Mumbai. All other ingredients used in the present investigation are of HPLC and analytical grade and

generally regarded as safe. This article does not contain any studies with human or animal subjects performed by any of the authors.

2.2 Drug–excipient compatibility studies using FTIR

The drug-excipient compatibility studies were carried out by using FTIR spectroscopy. The IR spectral studies emphasized on the active functional groups of the drug molecule which are more susceptible for chemical interaction with other active functional groups of the excipient /polymer. The IR spectrums of pure drug were interpreted for its functional and structural features of the drug based on the characteristic absorption bands in cm^{-1}. The appropriate absorption band for the vibrational frequency of functional group/ structural fragment of the pure spectrum is compared with its spectrum of formulation for the presence of characteristic functional group in the same wave number[22]. FTIR spectra of ranitidine HCl, 1:1 physical mixture of drug and HPMC K4M: carbopol 934P (1:1) and 1:1 physical mixture of drug and HPMC K4M: EC (1:1) were obtained by the conventional KBr disc/pellet method. 100mg of each sample was grounded gently with anhydrous KBr and compressed to form pellet. The scanning range was 400 and 4000 cm^{-1}. cm.

2.3 Preparation of press coated tablet of ranitidine HCl

Experimental design for preparation of press coated tablets of ranitidine HCl was constructed using Design-Expert® Software (Stat-Ease, Inc., Minneapolis, MN). A two level, full factorial 3^2 design was developed to evaluate the interaction and effect of two factors namely, ratio of HPMC K4M and EC in the core (X_1) and ratio of HPMC K4M and carbopol 934P in the coat (X_2) as independent variables[23]. Experimental range and levels of independent variables are represented in Table 1. Y_1 (drug release lag time), Y_2 (% drug release for 6 hours) and Y_3 (mucoadhesive strength in grams) were selected as dependant variables.

Table 1. Experimental ranges and coded values of factors X_1 and X_2

Coded values	Actual values	
	X_1[a]	X_2[b]
-1	1:1	1:1
0	2:1	1:3
+1	3:1	1:5

a- Ratio of HPMC K4M: EC in the core tablet

b- Ratio of HPMC K4M:Carbopol 934P in the coating shell

2.3.1 Preparation of core tablet

The core components consist of a drug (ranitidine HCl 150 mg per tablet); HPMC K4M and EC (Table 2) were weighed and taken into a clean mortar and then blended and granulated using isopropyl alcohol as granulating agent. Then the dried coarse granules were sifted through sieve 24 to get fine uniform sized granules. To the above granules around 1% W/W of magnesium stearate and talc were added as lubricant and glidant, respectively to adjust the total weight of core tablet. Then the granules were subjected to compression in a single station tablet press into tablet (diameter 8 mm; flat; hardness 5 Kg/cm^2; average weight of the tablet is 220 mg). A total of 13 formulations were prepared as per the 3^2 factorial design.

2.3.2 Press coating of core tablet of Ranitidine HCl

Then the polymer blend of outer hydrophilic barrier layer (HBL) coat (Table 2) was separated into 100mg and 200mg for top layer (HBL_T) and bottom layer (HBL_B) layers respectively. The mixture was directly compressed by taking 200 mg of coating mixture ($HBL_{B)}$ and spread uniformly to form a polymer bed, each of the 13 core tablet was placed in the centre of die carefully, and then the 100 mg of the coating mixtures ($HBL_{T)}$ was poured and compressed into a tablet (diameter 12 mm; biconvex; hardness 6.5 Kg/cm^2; average weight of the tablet is 520

mg) using biconvex-faced plain punches on a 16-station rotary compression machine.

2.4 Evaluation of press coated tablets of ranitidine HCl

2.4.1 Post-compression parameters

All the thirteen formulations prepared were evaluated for weight variation (n=10), hardness (n=3), thickness (n=6), diameter (n=6) and friability (n=6) using an electronic balance (Shimadzu, Mumbai), hardness tester (Pfizer, Mumbai), digital caliper (Vernier, Mumbai) and friabilator (Electrolab, Mumbai), respectively.

Table 2. Formulation of experimental formulations of press coated tablet

Formulation code	Coded values		Drug	Core		Coat			
	Core	Coat		HPMC k4M	EC	HPMCk4M		Carbopol 934P	
						HBL_T	HBL_B	HBL_T	HBL_B
PCT1	-1	-1	150	32.5	32.5	50	100	50	100
PCT2	0	-1	150	43.3	21.6	50	100	50	100
PCT3	+1	-1	150	48.75	16.25	50	100	50	100
PCT4	-1	0	150	32.5	32.5	25	50	75	150
PCT5	0	0	150	43.3	21.6	25	50	75	150
PCT6	+1	0	150	48.75	16.25	25	50	75	150
PCT7	-1	+1	150	32.5	32.5	16.66	33.32	83.33	166.66
PCT8	0	+1	150	43.3	21.6	16.66	33.32	83.33	166.66
PCT9	+1	+1	150	48.75	16.25	16.66	33.32	83.33	166.66
PCT10	0	0	150	43.3	21.6	25	50	75	150
PCT11	0	0	150	43.3	21.6	25	50	75	150
PCT12	0	0	150	43.3	21.6	25	50	75	150
PCT13	0	0	150	43.3	21.6	25	50	75	150

2.4.2 Drug content uniformity

Around five tablets were randomly sampled and peeled off to remove the outer coat. The core tablets were crushed to powder by using mortar and pestle. Then 73.33 mg of the crushed powder which is equivalent to 50 mg of ranitidine HCl was weighed and transferred into a clean and dry volumetric flask. Then the contents were made to dissolve by using 3 mL of ethyl alcohol then the volume was made up to the mark by using 0.1 N HCl and this was named to be stock solution(500 µg/mL). An aliquot of 1 mL from the stock solution was withdrawn and transferred to 100 mL volumetric flask and then volume made to the mark with 0.1 N HCl (5 µg/mL). Then the optical density was taken from UV-Visible spectrophotometer (model SL210, Elico, Hyderabad), in a 1 cm quartz cell, at 227 nm for all the 13 batches. Each drug content estimation procedure was done in triplicate.

2.4.3 In vitro drug release and kinetic studies

The *in vitro* dissolution study was conducted as per the United States Pharmacopoeia (USP) XXIV. The rotating paddle method was used to study the drug release from the tablets. The dissolution medium consisted of 900 ml of 0.1 N HCl (pH 1.2). The release was performed at 37°C ± 0.5°C, at a rotational of speed of 50 rpm. 5 mL samples were withdrawn at predetermined time intervals up to 12 h and the volume was replaced with fresh medium and analyzed for ranitidine HCl after appropriate dilution by UV spectrophotometer at 227 nm. The mean cumulative % drug release of six tablets was calculated using the

calibration curve of the drug in 0.1 N HCl (pH 1.2). By mathematical modeling, the release data was fitted into different kinetic models[24].

2.4.4 Percent swelling index

Tablet was weighed (W_1) and placed in a petridish containing 25mL of 0.1N HCl, at 37 ± 0.5^{0}C. At different time intervals of, the tablets were removed and the outer surface was wiped by a tissue paper to remove the excess water. The study was carried out for 3 h in triplicate and the tablet was then reweighed (W_2) and the swelling index were determined by the following formula[25]. All the tablets were taken out after completion of the respective stipulated time span as mentioned above.

$$\%\ Swelling\ index = \frac{W2 - W1}{W1}\ X\ 100$$

2.4.5 Ex vivo mucoadhesion strength

In the present study, sheep gastric mucosa was used as a model mucosal surface for mucoadhesion testing. Immediately after slaughter, the gastric mucosa of sheep was transported to laboratory placing in tyrode solution at 40ºC[26-27]. An assembly was fabricated to determine the *ex vivo* mucoadhesion strength of press coated tablets by means of modified physical balance (Figure 1). The sheep gastric mucosa was cut into strips/pieces and washed with tyrode solution. At the time of testing a section of sheep gastric mucosa (Figure 1, C) was secured keeping the mucosal side out, on the upper glass vial (Figure 1, B) using rubber band and aluminum cap. The diameter of each exposed mucosal membrane was 1 cm. The vial with the sheep gastric mucosa was stored at 37°C for 10 min. Then vial with section of sheep gastric mucosa and another vial were fixed on height adjustable pan (Figure 1, E). To the lower vial, a tablet (Figure 1, D) was placed with the help of bilayered adhesive tape, adhesive side facing downward. The height of the lower vial was adjusted so that a tablet could adhere to the sheep gastric mucosa on the upper vial. A constant force was applied on the upper vial for 2 min, after which it was removed and the upper vial was then connected to the balance. Then the weight on right side pan was slowly added by pouring water into the beaker in the right side pan drop by drop, till the two vials just separated from each other. The total weight (Figure 1, G) of water required to detach two vials was taken as a measure of mucoadhesive strength. The test was conducted in triplicate.

A-scale; **B**-glass vial; **C**-sheep gastric mucosa; **D**-mucoadhesive tablet; **E**-adjustable pan; **F**-weight

Figure 1: Schematic diagram of modified physical balance for measurement of mucoadhesion strength

2.5 Statistical analysis of the data and cross validation of the model

Statistical analysis and evaluation of the quality of fit of the model for the current study were performed employing Design Expert® software (Version 7.1.2, Stat-Ease Inc., Minneapolis, MN). Polynomial models including interaction and quadratic terms were generated for all the response variables using multiple linear regression analysis. 3D response plots were constructed using Design-Expert® software. The targeted response parameters were statistically analyzed by applying one-way analysis of variance (ANOVA), at 5% significance level and the significance of the model was estimated using the statistical package Design-Expert. The individual parameters were evaluated using *F*-test and mathematical relationship was generated between the factors (independent variables) and responses (dependent variables) using multiple linear regression analysis, for determining the levels of factors which yield optimum dissolution responses.

The final optimized formulation corresponding to the predicted optimum independent variables was formulated. Subsequently, the resultant experimental data of the response properties were quantitatively compared with those of the predicted values by calculating percent prediction error.

2.6 Preparation of optimized press coated tablet

Optimized formulations were prepared with the optimal values of levels (X_1 and X_2) and evaluated for uniformity of weight, hardness, friability, thickness, diameter, uniformity of drug content, *in vitro* dissolution, percent swelling index and mucoadhesion strength as described. The optimized formulation of press coated tablet (PCT_{opt}) is shown in the Table 6. The granules of the core tablet of PCT_{opt} containing 150 mg of ranitidine hydrochloride, 27.2 mg of HPMC K4M and 37.8 mg of EC were evaluated for their pre compression parameters. Finally the coating of core tablet of PCT_{opt} was done with 150mg of HPMC K4M & 150mg of carbopol 934P in the coating layer.

3. Results and Discussion

3.1 Drug-excipient compatibility studies using FTIR

There was no disposition/disappearance in the FTIR spectra of ranitidine HCl in combination with HPMC K4M, carbopol 634P and EC polymer mixtures as observed in Figure 2. The characteristic S=C stretch, aliphatic N=O stretch and C-H bend in plane of ranitidine HCl observed at 1235, 1390 and 1439 cm^{-1} respectively, were not shifted/disappeared in the polymer mixtures; indicating the absence of solid-state interactions between ranitidine and polymer matrix blend. The characteristic absorption bands of N-H and C-H stretch of ranitidine HCl observed at 3418 cm^{-1} and 2973 cm^{-1} showed no disposition/disappearance in the spectra of its polymer mixtures indicating the drug-excipient compatibility.

3.2 Post compression parameters

All the post compression parameters such as weight variation (0.45-2.2%), friability (0.22%), hardness (6.5-8.0 kg/cm^2), diameter (12mm), thickness (2.9-3.0 mm) and drug content uniformity (98.90% - 101.40%) were found to be within the limits as per I.P. specifications, indicating uniformity and effectiveness of the prepared granules (Table 3).

3.3 *In vitro* dissolution studies

The *in vitro* drug release profiles of formulations PCT1- PCT13 were shown in Figure 3. From the results it can be concluded that the maximum delayed drug release drug release profile of ranitidine HCl in the formulated press coated tablets was achieved in PCT3 containing 150mg of ranitidine HCl, HPMC K4M & ethyl cellulose in the ratio of 3:1 in the core and HPMC K4M & carbopol 934P and in the ratio of 1:1 in the coat of press coated tablet. A lag time of two hours was achieved sustaining the drug release up to eleven hours, attenuating the midnight gastric acidity.

Table 3. Post compression parameters of press coated tablets

Formulation	Weight variation (mg)[a]	Hardness[b] (kg/cm^2)	% Friability[c]	Thickness (mm)[c]	Diameter (mm)[c]	% Drug content[b] (mg)
PCT1	514±3.6	6.75±0.2	0.26±0.3	2.9±0.5	12.3±0.4	99.8±0.9
PCT2	515±6.8	7.25±0.2	0.26±0.1	2.9±0.5	11.8±0.6	100.6±0.6
PCT3	520±1.8	8.00±0.2	0.12±0.1	3.0±0.1	11.7±0.6	100.3±0.4
PCT4	518±4.7	6.50±0.5	0.06±0.2	2.9±0.2	12.4±0.6	100.3±0.7
PCT5	522±4.2	7.75±0.2	0.06±0.4	3.0±0.4	11.6±0.3	99.6±0.3
PCT6	525±6.5	8.00±0.1	0.06±0.6	3.0±0.5	11.7±0.2	98.9±0.9
PCT7	522±5.1	7.50±0.1	0.38±0.2	2.9±0.2	12.1±0.2	100.5±0.5
PCT8	519±4.7	8.00±0.3	0.26±0.2	2.9±0.2	11.9±0.0	100.0±0.1
PCT9	520±7.7	8.00±0.1	0.19±0.3	2.9±0.1	11.7±0.2	99.6±0.7
PCT10	522±4.2	7.75±0.2	0.06±0.4	3.0±0.5	11.6±0.3	99.7±0.6
PCT11	523±2.4	7.72±0.3	0.06±0.4	3.0±0.2	11.9±0.2	98.9±0.8
PCT12	522±4.2	7.57±0.2	0.06±0.2	2.9±0.5	12.4±0.3	99.8±0.3
PCT13	512±4.3	7.46±0.5	0.06±0.4	3.0±0.2	11.6±0.1	98.9±0.8

a - mean ±% devition, n=10
b - mean± s.d, n=3
c - mean, n=6

The drug release was sustained up to 9 h from the formulation PCT1 containing HPMC K4M: EC in the ratio of 1:1 in the core and HPMC K4M: carbopol 934P in the ratio of 1:1 in the coat, respectively with a lag time of 2 h. Both the formulations PCT4 and PCT6 containing HPMC K4M: carbopol 934P in the ratio of 1:3 in the coat and HPMC K4M: EC in the ratio of 1:1 and 3:1 in the core, respectively have shown a sustained drug release profile up to 9 h with a lag time of 1 h. All the other formulations PCT2, PCT5, PCT8, PCT10, PCT11, PCT12 and PCT13 containing HPMCK4M and EC in the ratio of 2:1 in the core attenuated the drug release profile up to 8 h only. This decrease in drug release was due to increased permeability and hydrophilicity of the core because of the lower concentration of hydrophobic polymer (ethyl cellulose). With increase in concentration of erodible polymer (HPMC), a more tortuous diffusional path length results in decreased release profile. However, the effect of weight ratio of HPMC: EC in the core seems to be much more pronounced as compared with that of coating level of HPMC: carbopol. This is in agreement with Equation (3) as well as Figure 6(B).

On the other hand, the effect of coating level of HPMC: carbopol seems to be more pronounced as compared with that of weight ratio of HPMC: EC in the core. This receives confirmation from the mathematical model generated for response Y1 (Equation (2) and Figure 6(A)). The formulations PCT1 - PCT3 have shown a release lag time of more than two hours when compared to all other formulations PCT4 – PCT13, which showed a lag time of one hour due to more pronounced hydration or swelling characteristics of the hydrophilic polymer carbopol in the outer coat[28]. This decrease in lag time was due to decreased permeability and increased hydrophobicity of the coating

membrane because of the lower concentration of insoluble polymer (HPMC) in the coating shell. With increase in concentration of HPMC K4M with respect to EC in the core the drug release was more sustained in all the formulations PCT1(1:1) to PCT3 (3:1). By fitting in the Design Expert software, it can be concluded that an optimum ratio of 1:1 of both HPMCK4M: EC and HPMC K4M: carbopol 934P was sufficient to delay the drug release for a desired period of time. Hence, PCT1 was further considered for optimization of the best formula that could attenuate the mid night acidity.

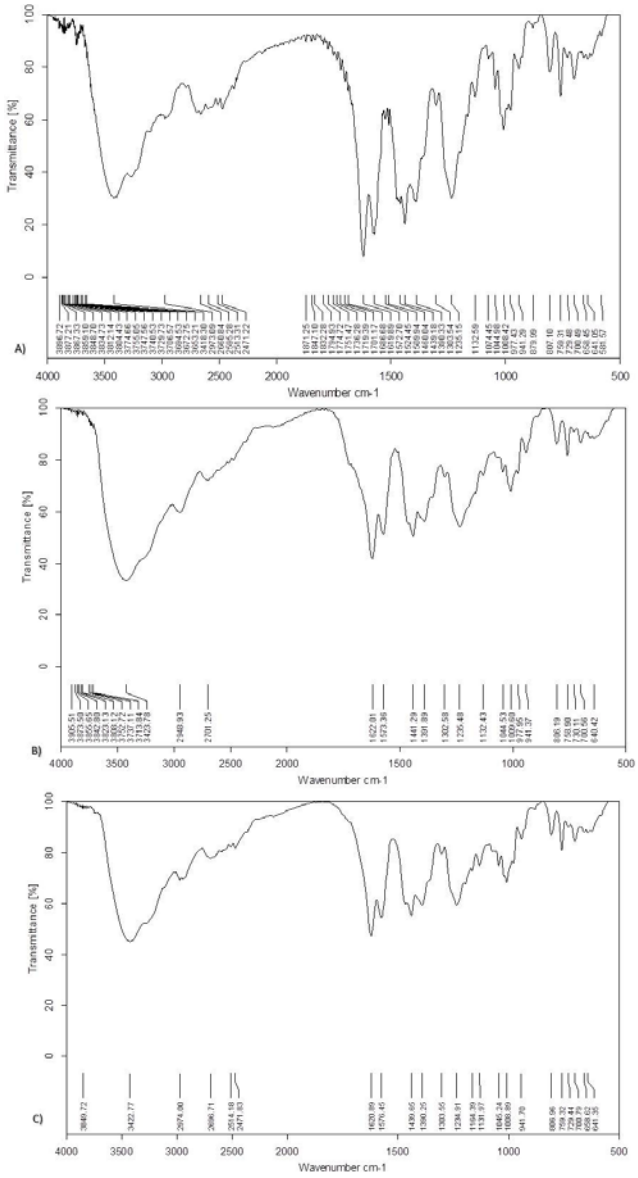

Figure 2: FTIR spectras of FTIR spectra of (A) ranitidine HCl, (B) 1:1 physical mixture of drug and HPMC K4M: carbopol 934P (1:1) and (C) 1:1 physical mixture of drug and HPMC K4M: EC (1:1)

3.4 Drug release kinetics and mechanisms

The drug release kinetics was determining by fitting the dissolution data to zero order and first order equations. It was observed that all the press coated tablets followed zero order release kinetics i.e., the drug release is independent of its initial concentration. The correlation coefficients (r) of zero order plot were in the range of 0.959- 0.991 as given in Table 4.

Table 4. Drug release kinetics of ranitidine HCl in PCTs

Formulation	Zero order		First order		Higuchi	Korsmeyer-Peppas	
	k_0	r	k_1	r	R	r	n
PCT1	10.82	0.973	0.35	0.816	0.888	0.808	1.387
PCT2	11.32	0.959	0.440	0.758	0.865	0.794	1.376
PCT3	9.19	0.973	0.203	0.843	0.900	0.857	1.287
PCT4	10.4	0.976	0.373	0.882	0.950	0.861	1.239
PCT5	12.92	0.991	0.419	0.867	0.939	0.859	1.336
PCT6	11.51	0.986	0.495	0.831	0.956	0.872	1.436
PCT7	24.21	0.966	1.393	0.780	0.863	0.852	1.790
PCT8	15.21	0.975	0.477	0.789	0.911	0.850	1.527
PCT9	17.09	0.991	0.820	0.774	0.932	0.878	1.511
PCT10	12.22	0.990	0.419	0.861	0.938	0.854	1.337
PCT11	12.93	0.991	0.415	0.868	0.936	0.857	1.338
PCT12	12.89	0.989	0.417	0.865	0.939	0.855	1.336
PCT13	12.21	0.990	0.418	0.869	0.937	0.859	1.339

The drug release mechanism was determined by fitting the dissolution data to Higuchi and Korsmeyer-Peppas equations. It was found that all the prepared press coated tablets followed Higuchi's diffusion mechanism with correlation coefficients in the range of 0.863-0.956. Korsmeyer-Peppas plots of log fraction of ranitidine hydrochloride released versus log time of the all press coated tablets were found to be linear with release exponent 'n' value greater than 1.0, indicating super –case II transport mechanism[29]. The rate controlling step in this kind of mechanism corresponds to the relaxation process of the macromolecules upon water imbibition into the system, exhibiting linear time dependence in both the amount diffused and in the penetrating swelling front position[30]. Thus the formulated ranitidine HCl press coated tablets obeyed zero order release kinetics through polymer matrix relaxation mechanism (super case II).

3.5 Percent swelling index

The swelling studies were conducted for all formulations i.e. PCT 1 to PCT13 and the results were shown in Figure 4. The formulations containing HPMC K4M: carbopol 934P in the ratio of 1:1 (PCT1 to PCT3) had shown a slow and greater extent of swelling when compared to other formulations containing HPMC K4M: carbopol 934 P in the ratio of 1:3 and 1:5 (PCT4 to PCT13). So it can be concluded that with increase in the concentration of carbopol 934P, the degree of hydration was more rapid influencing its gastroretention[20]. Among the three formulations containing optimum ratio of 1:1 of HPMC K4M: carbopol 934 P, PCT1 had shown higher percent swelling index of about 120% when compared to

PCT2 and PCT3 showing 112 and 106%, respectively. This can be ascribed to decreased drug permeability from the core tablet with lesser number of channels/ pores available for the effective diffusion of the drug as the proportion of HPMC increases.

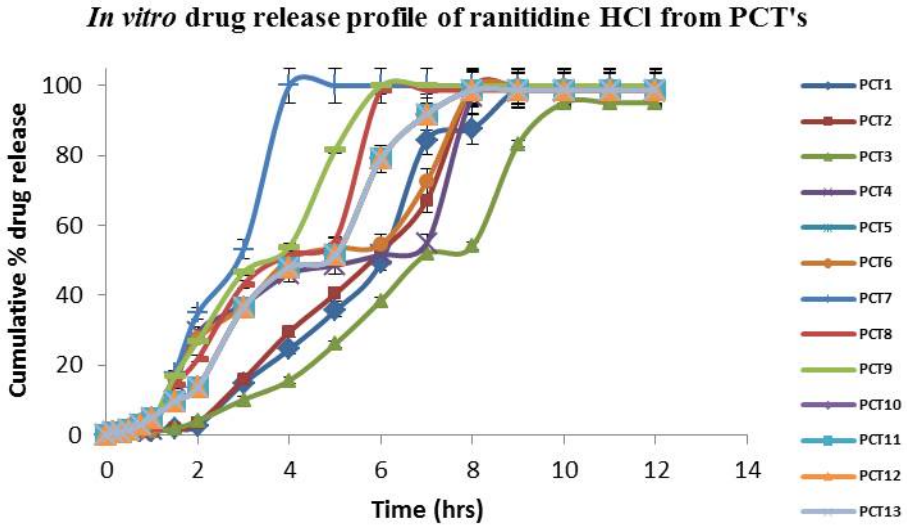

Figure 3: *In vitro* drug release profile plot of ranitidine HCl from prepared press coated tablets PCT1-PCT13

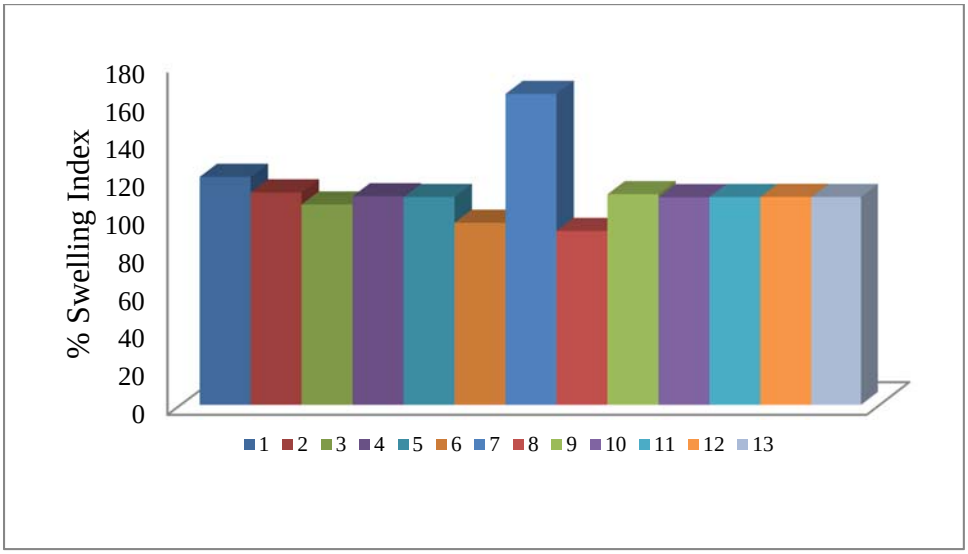

Figure 4: Swelling index of press coated tablets

3.6 *Ex vivo* mucoadhesion strength

The mucoadhesion characteristics were affected by the concentration of the mucoadhesive polymer carbopol 934P in the coating membrane. Increase in concentration of bio adhesive polymer increases the hydrophilicity and mucoadhesive strength of formulation. From the results it can be concluded that the mucoadhesive strength was increasing as the proportion of carbopol 934P was

increasing from PCT1-PCT9 (Figure 5). In addition, the weight ratio of HPMC: carbopol in the coating shell was the only linear factor that seems to effect the mucoadhesion as confirmed by Equation (4) as well as Figure 6(C).

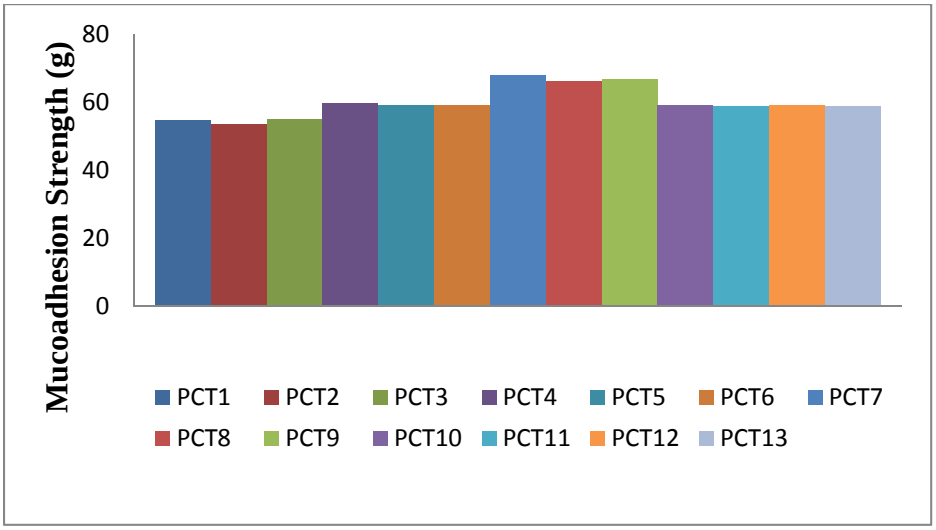

Figure 5: Mucoadhesion strength of PCT1-PCT13

3.7 Statistical optimization by using 3^2 factorial designs

3.7.1 Data analysis

The summary of statistics along with comparative R^2, adjusted R^2, predicted R^2, PRESS, s.d., F-values and p-values are presented in Table 5. A suitable model for describing the data was selected based on coefficient of determination (R^2) and PRESS values. Response Y_1, Y_2 and Y_3 were found to follow *quadratic*, *quadratic* and *linear model*, respectively for press coated tablets of ranitidine HCl. These models showed higher R^2 and F-values and lower PRESS and p-values. Hence these models were selected for further optimization.

Table 5. Summary of model statistics for responses Y_1, $Y_2$and Y_3

Model	R^2	Adjusted R^2	Predicted R^2	PRESS	s.d	F-value	p- value	Remarks
Response Y_1 = Lag time i.e., time for drug release up to 4% (h)								
Linear	0.6101	0.5321	0.1663	2.92	0.37	-	-	
Interactive	0.6280	0.5040	-0.7241	6.03	0.38	-	-	
Quadratic	0.9817	0.9687	0.8555	0.51	.096	75.24	<0.0001	**suggested**
Response Y_2 = Cumulative % drug released in 6 h								
Linear	0.6022	0.5227	0.2703	3538.77	13.89	-	-	
Interactive	0.6085	0.4780	0.0813	4454.95	14.32	-	-	
Quadratic	0.8945	0.8192	-0.0333	5010.80	8.55	11.87	0.0026	**suggested**
Response Y_3 = Mucoadhesion strength (g)								
Linear	0.9965	0.9958	0.9927	5.59	0.52	1421.41	<0.0001	**suggested**
Interactive	0.9972	0.9963	0.9927	5.62	0.49	-	-	
Quadratic	0.9986	0.9975	0.9899	7.75	0.40	-	-	
s.d.: Standard deviation; F: Fischer ratio;								

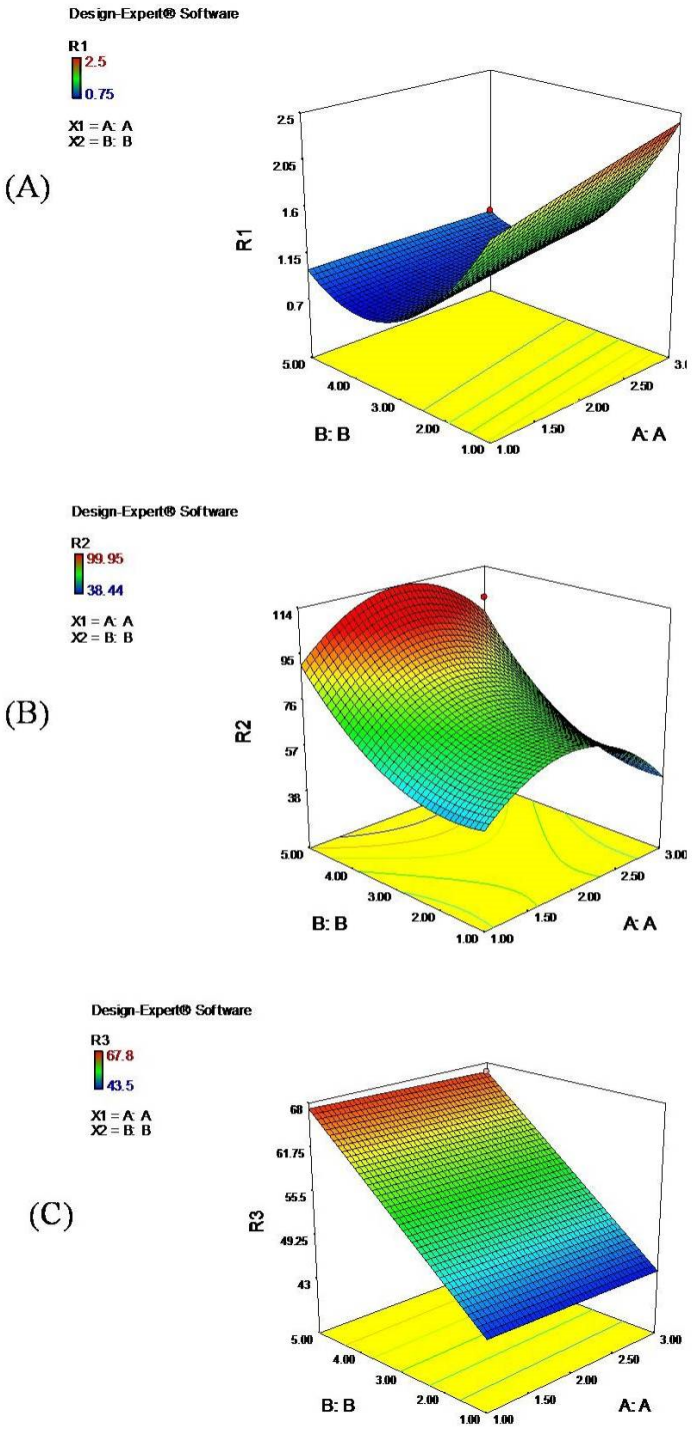

Figure 6: Response surface plot for (A) drug release lag time, (B) % drug release for 6 hours and (C) mucoadhesion strength of press coated tablets

3.7.2 Multiple regression and mathematical model building

A second-order polynomial regression equation that fitted to the data is as follows:

$$Y = b_0 + b_1 X_1 + b_2 X_2 + b_{12} X_1 X_2 + b_{11} X_1^2 + b_{22} X_2^2 \quad \textbf{(1)}$$

Where b_0 is the intercept representing the arithmetic averages of all the quantitative outcomes of 13 runs; b_1, b_2, b_{12}, b_{11} and b_{22} are the coefficients computed from the observed experimental values of Y; and X_1 and X_2 stand for the main effects. The terms X_1X_2 and X_i^2 (i = 1 and 2) represent the interaction and quadratic terms, respectively used to simulate the curvature of the designed sample space. In table 6, factor effects of 3^2 FFD model and associated p-values for the responses Y_1, Y_2 and Y_3 are presented. A factor is considered to influence the response if the effects significantly differ from zero and the p-value is less than 0.05. significant factors affecting the response Y_1 by antagonistic effect of the linear contribution of factor X_2 and cross product contribution (interaction), synergistic effect of quadratic contribution of main factors X_1 and X_2. The response Y_2 was significantly affected by the synergistic effect of linear contribution of factor X_1 and quadratic contribution of the factor X_2 along with antagonistic effect of quadratic contribution of the factor X_1. The response Y_3 was significantly affected by the synergistic effect of the linear contribution of factor X_2.

A backward elimination procedure was adopted to fit the data into different predictor equations. The final equations of the responses are given below:

$$R_1 = 2.59 - 1.10 X_2 - 0.062 X_1 X_2 + 0.16 X_2 2 \quad (2)$$

$$R_2 = 1.53 + 80.40 X_1 - 21.47 X_1 2 + 3.53 X_2 2 \quad (3)$$

$$R_3 = 39.37 + 5.63 X_2 \quad (4)$$

3.7.3 Response surface analysis

The quadratic models generated by regression analysis were used to construct 3D response surface plots in which response parameter Y was represented by a curvature surface as a function of X. Figure 6(A), 6(B) and 6(C) show the effect of two factors on the three responses namely, drug release lag time, cumulative percentage drug release for 6 hours and mucoadhesion strength (Table 7).

Table 6. Summary of each factor effect and its *p*-values for, response Y_1, Y_2 and Y_3

Factor effect	Y_1 (Drug release lag time in hours)		Y_2 (%drug release for 6 hours)		Y_3 (mucoadhesion strength in g)	
	Factor effect	p- Value	Factor effect	p- Value	Factor effect	p- Value
Intercept	2.59	<0.0001*	1.53	0.0026*	39.37	<0.0001*
X_1	0.33	0.2187**	80.40	0.0078*	-0.30	0.1862**
X_2	-1.10	<0.0001*	-12.94	0.1933**	5.63	<0.0001*
$X_1 X_2$	-0.062	0.0346*	1.38	0.5397**	-	-
X_1^2	-1.310	0.9423**	-21.47	0.0042*	-	-
X_2^2	0.16	<0.0001*	3.53	0.0286*	-	-

* Significant ($p<0.05$)

** Not significant ($p>0.05$)

Table 7. Formulation of optimized PCT_{opt} and its characteristics

Ingredient	mg/tablet
Ranitidine hydrochloride	150.0
In the core	
HPMC K4M	27.2
EC	37.8
Talc	2.5
Magnesium stearate	2.5
In the coat	
HPMC K4M	150.0
Carbopol 934P	150.0
Total	520.0
Characteristics	
Drug release lag time (hours)	1.84
Drug release after 6 hours (%)	40.03
Mucoadhesion strength (g)	44.79

Figure 6 (A) depicts a curvilinear relationship between the two independent variables (factors) on response Y_1 (drug release lag time). This can be attributed to the potential occurrence of interaction between the two independent variables at the corresponding factor levels, construing that each independent variable is tending to modify the effect of another towards the release lag time. This receives confirmation from the mathematical model generated for response Y_1 (Equation 2).

Figure 6(B) depicts a curvilinear relationship for Y_2 (% drug release for 6 hours) between the two independent variables (factors). This can be attributed to the potential occurrence of quadratic relationship within the two independent variables at the corresponding factor levels, construing that each independent variable is tending to modify the effect of itself towards the release of ranitidine hydrochloride in 0.1N HCl. This receives confirmation from the mathematical model generated for response Y_2 (Equation 3).

Figure 6(C) depicts a linear relationship between the two independent variables (factors) on response Y_3 (mucoadhesion strength). This increase in mucoadhesion strength was due to increased swelling and hydrophilicity of hydrophilic polymers due to increase in the concentration of carbopol 934P in the coating membrane. This receives confirmation from the mathematical model generated for response Y_3 (Equation 4).

3.8 Design of statistically optimized formulation

Optimization was carried out by both numerical optimization and graphical optimization techniques. The desirability and overlay plots are shown respectively in Figure 7. The desirability function was found to be 0.942 which is effective for the optimized formula indicating the suitability of the formulations.

A numerical optimization technique using the desirability approach was employed to develop a new formulation with the desired responses. In this study optimization was performed with constraints for Y_1 (Y_1=2 h), Y_2 (30% < $Y2$ < 50%) and Y_3 (40g < Y_3 < 50g) set as goals to locate the optimum settings of the independent variables in the new formulation. The independent variables X_1(HPMC K4M: EC) and X_2 (HPMC K4M: carbopol 934P) were found to be optimum with 0.72: 1 and 1:1 respectively to achieve the desired pulsed release profile after a programmed lag time for formulating gastro-retentive solid dosage form of ranitidine HCl in the chronotherapeutic management of nocturnal acid

breakthrough. The formulation of optimized press coated tablet based on the optimum independent variables and the responses were shown in Table 7.

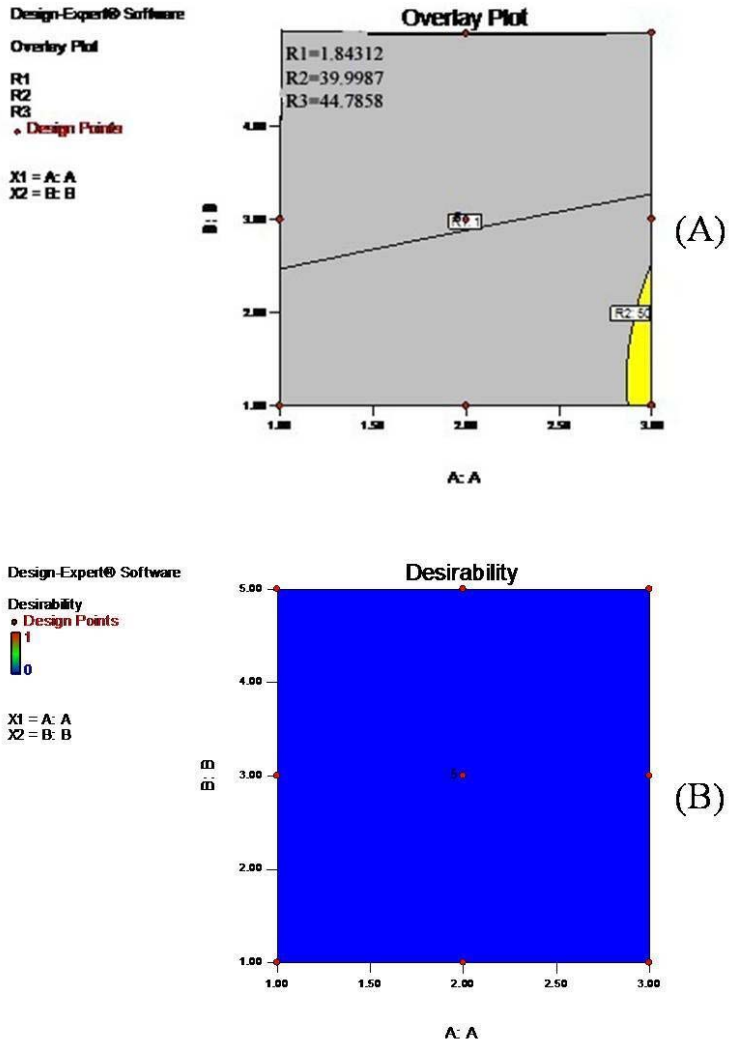

Figure 7: (A) Overlay plot and (B) Desirability plot of PCTopt

3.8.1 Evaluation of pre compression parameters of granules of core tablet

The pre compression parameters of granules of core tablet of PCT_{opt} were evaluated. All the parameters were found to be within the limits of official standards with angle of repose 24^0, Carr's index 10% and Hausner's ratio1.23, exhibiting good flow properties of the powdered blend.

3.8.2 Evaluation of post compression parameters of PCT_{opt}

The post compression parameters of PCT_{opt} were evaluated. All the post compression parameters such as weight variation, hardness, thickness, diameter, % friability and drug content were found to be within the official limits of IP specifications with low % CV, confirming the uniformity and effectiveness of compression coated tablet.

The inter day variability of formulation of PCT_{opt} was

carried on and the drug release profile was observed with 0.374 average standard deviation of dissolution profile. The % swelling index of PCT_{opt} for 0, 0.5, 1, 2, and 3 hours are 44.8, 63, 94, 108 % respectively and their digital images were shown in Figure 8. The mucoadhesion strength of optimized formulation was found to be 44.7mg. The response characteristics of the formulated PCT_{opt} were complying with that of theoretical response characteristics given in the optimization.

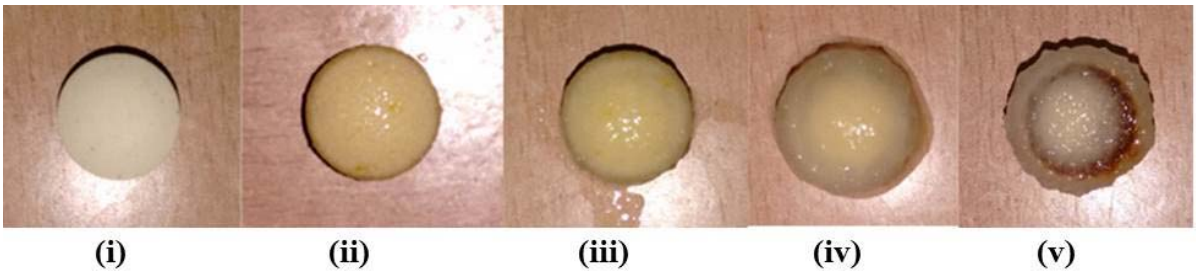

Figure 8: Digital images depicting swelling of PCTopt (i) 0, (ii) 0.5, (iii) 1 (iv) 2, (v) 3 hours respectively

3.8.3 Cross validation of model

A reasonable agreement between predicted and experimental values was observed as indicated by low values (<5%) of the prediction error (Table 8). This proved the validity of model and ascertained the effects of ratio of HPMC K4M and EC (0.72:1) in the core and the ratio of HPMC K4M and carbopol 934P (1:1) on drug release and mucoadhesion strength. As desired, the tablets prepared according to optimum formulation achieved a lag time of 2h, followed by complete drug release within next 10 h with sufficient mucoadhesive strength.

Table 8. Percent prediction error of responses

Response	Predicted value	Experimental value	% Prediction error[#]
Lag time (h)	1.89	1.84	2.64
Drug release in 6 h (%)	41.15	40.03	2.72
Mucoadhesion strength (g)	43.67	44.79	-2.55

$$\#\text{ - }\%\,Prediction\ error = \frac{Predicted\ value - Experimental\ value}{Predicted\ value}\ X\ 100$$

4. Conclusions

The present research proves and provides a novel pulsatile chronotherapeutic formulation of ranitidine HCl, a non-imidazole blocker of histamine receptors, naturally having absorption maxima in stomach and upper part of GIT and predominantly being metabolized by the colonic bacteria of the intestine. So as to overcome these drawbacks associated with the conventional dosage forms, the better way is to develop a press coating tablet to deliver the highest blood levels of the drug at predetermined times and sites of the gastrointestinal tract following oral administration. By controlling the critical processing parameters, especially the polymeric carrier concentration in the inner core and outer coat, systematic design of ranitidine HCl press coated tablets can be readily achieved. The optimum formulation contains ranitidine HCl 150mg, HPMC K4M: EC in the ratio 0.72:1 in the inner core and HPMC K4M: carbopol 934P in the ratio 1:1 in the outer coat with drug release lag time of 1.89 hours, cumulative percentage drug release after 6 hours 41.15% and mucoadhesion strength of 43.67g. By observing the characterizations, the results provoke that the development of delayed press coating formulations based on erodible (hydroxypropyl methylcellulose), rupturable (ethyl

cellulose), and mucoadhesive (carbopol) polymers could achieve the desired pulsed release profile after a programmed lag time. Thus the designed approach can be considered as one of the promising technique for formulating gastro-retentive solid dosage form of ranitidine HCl and can be applicable in the chronotherapeutic management of nocturnal acid breakthrough by delivering the drug in a pulsatile fashion rather than continuously.

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صياغة التنمية والتحسين للصحافة مغلفة ألواح من رانيتيدين HCl باستخدام 3^2 "تصميم مضروب"

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ملخص

الهدف الرئيس لهذا العمل هو صياغة وتقييم نظام إيصال المخدرات تشرونوثيرابيوتيك هيدروكلوريد رانيتيدين من خلال استخدام البوليمرات موكوادهيسيفي مناسبة بتقنية طلاء الصحافة. لتوضيح أثر العوامل وضع الصحافة مغلفة بأقراص كان يعمل على تصميم مضروب الكاملة .32 أثر هذين العاملين، ونسبة هيدروكسي بروبيل الميثيل السليلوز K4M (HPMC) إلى إيثيل السليلوز (EC) في نسبة HPMC K4M إلى كاربوبول ف 934 في coat(X2) كمتغيرات مستقلة وجوهر) Y1 .(X1) المخدرات الإفراج عن الفارق الزمني (، %) Y2 المخدرات الإفراج بعد 6 ساعات (ونعم) 3 قوة موكواديسيون (واختيرت كمتغيرات تعتمد على .الصيغ الثلاث عشرة صيغت ويتعرضون لمختلف التقييمات الفيزيائية مثل اختلاف الوزن وتنفسها وصلابة، والمحتوى المخدرات، الإفراج عن المخدرات في المختبر والدراسات الحركية، تورم الفهرس والسابقين فيفو موكواديسيون الدراسات .وضع أمثل يتكون من رانيتيدين 150 HCl ملغ، :HPMC K4M المفوضية الأوروبية (0.72:1) في النواة الداخلية و :HPMC K4M كاربوبول ف (1:1) 934 في معطف الخارجي مع المخدرات الإفراج عن تأخر الوقت 1.89 ساعة، % التراكمية المخدرات الإفراج بعد أن سجلت ساعات 41.15% وقوة 43.67 موكواديسيون زاي HCl رانيتيدين أقراص الصفر أمر الإفراج عن حركية، أسفرت عن الإفراج عن التنظيم وكاملة حتى 11 ساعة.

وكاربوبول ف 934 على قوة المخدرات الإفراج وموكواديسيون هيدروكلوريد رانيتيدين.

الكلمات الدالة: تشرونوثيرابي، تصميم مضروب، موكواديسيون، تقنية طلاء الصحافة، هيدروكلوريد رانيتيدين.

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