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Research Article

PANTOPRAZOLE SUSTAINED RELEASE TABLETS: QBD-BASED STATISTICAL DEVELOPMENT AND IN VITRO INVESTIGATIONS

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ABSTRACT

Objective: The present study is an attempt to develop and evaluate the sustained release tablet formulations (oral) of pantoprazole sodium utilizing chitosan (CH) based *in situ* forming polyelectrolyte complex as retardant polymer.

Methods: The traditional method of wet granulation was used to create various formulations employing a 1% w/w solution of CH in 1% acetic acid (cooled to about 4°C and neutralized) as a binder. The formulation was optimized using a two-factor, three-level face-centered Central Composite Design. The Design-Expert software (Stat-Ease 360 trial version, Minneapolis, MN) was employed for further analysis of obtained results. For the study of effect of critical material attributes (CMAs) (independent variables) on Critical Quality Attributes (response variables) multiple liner regression analysis was performed through generation of second-order polynomial models using software. The analysis of variance was utilized for validation of generated models. To establish the interaction and main effects of CMAs software generated contour plots and 3D response surface plots were used. The optimized formulations were assessed for a number of characteristics, including thickness, hardness, uniformity of weight, drug content, friability, and *in vitro* drug release. The pharmacokinetic parameters were examined using various mathematical models to investigate and elucidate the mechanism of drug release from the various formulations.

Results: The drug release studies confirmed a zero-order sustained release of drug for 12 h. The polyelectrolyte complex formation (*in situ*) between anionic polymers and CH had been revealed by X-ray diffraction studies of polyelectrolyte complex gels.

Conclusion: The polyelectrolyte complex formed between CH and anionic polymer (sodium starch glycolate) had not only provided a sustained drug release but also prevent the initial burst release of hydrophilic drugs.

Keywords: Chitosan, Sodium starch glycolate, Critical quality attributes, Polyelectrolyte complex, Critical material attributes, Pantoprazole sodium.

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INTRODUCTION

It is very challenging to create sustained-release (single-unit) oral dosage forms for hydrophilic medicines, which are extensively soluble (10 mg/mL) in stomach fluids and also have high dose, due to the drug delivery system's burst release of the loaded medication and limitation on the number of rate-controlling excipients (due to high drug dosages) that can be utilized to create a formulation that has a size appropriate for oral administration [1]. A straightforward, yet incredibly efficient drug delivery method that can demonstrate a fairly steady rate of dissolution over a lengthy duration is therefore needed. After an examination of the literature, it was discovered that poly-electric complexes between polymers with opposing charges result in polymeric carriers that can be utilized to regulate the release of these medications from dosage forms, both initially and continuously. This may be explained by the resulting polymeric carriers' high degree of organization and dense, crystal-like shapes [2,3]. Thus, the current work aims to create sustained-release tablet formulations of pantoprazole sodium using chitosan (CH) solution as binder and sodium starch glycolate (SSG) as excipient. The *in situ* formation of polyelectrolyte complexes was expected when the tablet encountered the acidic dissolution medium (HCL + KCl buffer, pH – 1.5). It was anticipated that this strategy would maintain the drug's release sustained due to the high molecular organization and dense crystalline structure of the polyelectrolyte complexes formed between cationic polymer CH and anionic polymer SSG [4,5].

MATERIALS AND METHODS

Materials

Pantoprazole sodium (PPZ) was supplied by Saphinx Life Sciences, Vill. Barotiwala, Ponta Saib, Distt. Pantoprazole Sodium (PPZ) was procured from Well Treat Pharama (Rohtak, Haryana, India) as gift sample. The CH (Low molecular weight), SSG, Lactose, purified Talc, Magnesium stearate, and other excipients were purchased from Singhla Scientific Industries, 5309/27, Punjabi Mohalla, Ambala Cantt (Haryana). Every auxiliary chemical and excipient that was used was of the analytical and pharmaceutical grades, respectively.

Methods: Pre-formulation studies

Drug – polymer interaction studies

The drug – polymer interaction studies were performed using Fourier transform infrared spectroscopy (Spectrum BX, PerkinElmer, USA). Since it was anticipated that there would be no interaction, the Fourier transform infrared spectroscopy (FTIR) spectra of physical mixes of the drug and polymers were not recorded. Hence, to study the interactions, 1% w/v solution of the drug in distilled water was mixed with 1% w/v solution of polymers in a suitable medium (distilled water or 1% acetic acid). The mixture was kept at 37°C for 2 h. After that, the mixture was dried and FTIR spectra were recorded using KBr pellet technique.

Polymer – polymer interaction studies

"FTIR" and "differential scanning calorimetry" (DSC) were used in the polymer-polymer interaction investigations. Physical mixes of polymers

were not subjected to DSC thermograms and FTIR spectra because it was not anticipated that these would show any interactions between cationic and anionic polymers. There is a good chance that these interactions will occur, though, on exposure of the formulations to the acidic dissolution medium (0.1 M HCl, pH 1.5). Thus, to investigate how CH and SSG interact the polymers were mixed in ratio of 1:1 and packed in dialysis membrane (molecular weight cut – off - 1200) previously activated by boiling for 30 min in Phosphate buffer (pH 7.4). These sealed bags were kept at pH 1.5 (HCl+ KCl buffer) maintained at 37±2°C in a basket-type USP dissolution apparatus for 2 h. During the exposure, gel formation occurred. After being removed from the dialysis bags, the contents (gelled) were dried overnight at 60°C in an oven. For these dried samples (gels), DSC thermograms (DSC 25, TA Instruments, USA) and FTIR spectra were recorded.

Preparation of polymeric binder solution

Following the application of compression force, the binders are utilized to hold the various elements of a tablet together. The binder solution was prepared by dissolving CH in 1% acetic acid solution to produce desired concentration. The solutions were cooled to 4°C and then neutralized by 1M Sodium bicarbonate solution by maintaining the temperature at 4°C throughout the process [3].

Preparation of sustained-release tablets

Using a traditional wet granulation method, the sustained-release tablets were prepared. The binder solution prepared in 1% acetic acid was used to granulate the mixture of drug and excipients. The damp mass was passed through sieve no. 10 and dried at 60°C overnight in a hot air oven. Following their passage through sieve number 20, the dry granules were lubricated and compacted into tablets using a single rotating tablet compression machine [5].

Critical material attributes (CMAs) and critical quality attributes (CQAs) selection

Based on quality target product profile CQAs, that is, Critical Quality Attributes of developed system were selected through preliminary studies. First CQA selected was swelling index (SI) was because higher SI is desired for achieving the preferred therapeutic response. Other selected CQA was Cumulative Drug Release at 6th h (*in vitro*) to achieve sustained release and considerable drug absorption throughout the digestive tract. On the basis of risk assessment analysis and literature survey CMAs, that is, Critical Material Attributes were also selected [6,7].

Optimization of formulations/tablets using experimental design

The optimization study was performed by utilizing a two-factor, three-level face-centered Central Composite Design (CCD). The functional excipients such as concentration of CH and SSG were the two independent variables that were investigated. The investigation was performed to study the responses due to the impact of selected CMAs (independent variables) on the selected CQAs (dependent variables) such as SI and Cumulative Drug Release at 6th h. The used experimental variables in the design are shown in Table 1.

The functions of CMAs were expressed through the polynomial equations generated by software. For determining the effect of individual variables (main effects) and interaction among them with minimum experimentation the two factors, three levels Face centered CCD is the most efficient tool. The values of responses were unknown from older findings, so this tool was considered in the present study. Thus, for optimization of formulated tablets, this design was chosen [7-9].

Table 1: CQAs and CMAs used in face-centered central composite design (their coded and actual values)

S. No.	CMAs	Coded and actual values		
		Low (−1)	Medium (0)	High (+1)
1	Concentration of Chitosan (% w/v)	0.5	0.75	1
2	Concentration of SSG (% w/w)	1	1.5	2
	CQAs	Target		
1	Swelling index	Maximum		
2	Cumulative drug release at 6th h	Minimum		

Data analysis and validation of model

The Design-Expert software (Stat-Ease 360 -Trial version, Minneapolis, MN) was utilized for analysis of obtained results. For studying the effect of CMAs (independent variables) on selected CQAs (response variables) polynomial models were generated for performing multiple liner regression analysis using the software. The analysis of variance was utilized for the validation of models generated. To determine the relative effect of every CMA, the analysis of software-generated equations was performed. To ascertain the main and interaction effects of variables, software-generated 2D contour plots and 3D response surface plots were used. Based on the desirability approach of software, checkpoint batches were formulated and goals were set to get the optimum composition of CMAs to achieve the preferred target CQAs. The selected batch/formulation with the highest value of desirability (shown in Table 2) was further investigated and results observed were compared with predicted ones [6-9].

Evaluation of tablets

Pre-compression characterization

Moisture content

Moisture content of dried granules was determined using IR moisture balance [10].

Drug content

The assay of pantoprazole sodium was performed on high-performance liquid chromatography (HPLC) system (LC-2030 Plus, Shimadzu, Japan) with UV detector and auto-sampler, Phenomenex, C18 (4.6 × 250 mm i.d., 5 µm particle size) stationary phase and Lab-solution software. The mobile phase was prepared by mixing Solvent A, that is, a Buffer (0.525 g of Dipotassium Hydrogen Orthophosphate and 2.72 g Potassium Dihydrogen Orthophosphate in 1000 mL water, adjust the pH 7.4 with dilute potassium hydroxide) and solvent B, that is, Acetonitrile in a ratio of 60:40. During the process column temperature was maintained at 30°C, flow rate was 1.5 mL/min, injection volume used was 20 µL, runtime was 10 min and Isocratic mode elution was used. The sample solution was prepared by dissolving an amount of granules/powder equivalent to 40 mg of pantoprazole in 50 mL of methanol taken into 100 mL volumetric flask by sonication. The volume was adjusted with the methanol up to the mark. A 5 mL of stock solution was taken into 50 mL flask and mobile phase was added to make up the volume. The solution was filtered through a 0.22 µ nylon syringe filter, labeled and injected. The drug content was then ascertained using UV detector by absorbance measurement at λmax of pantoprazole sodium (i.e. 284 +5 nm) [11-14]. The drug content was determined using formula:

$$\text{Drug content} = \text{Concentration} \times \text{Dilution Factor}$$

$$\textit{Drug content} = \frac{\textit{Drug Content}\ (mg)}{\textit{Label Claim}\ (mg)} \times 100$$

Bulk density

The known weight of granules (20 g) was put in a graduated cylinder of bulk density apparatus gently and volume occupied was noted. The bulk density was calculated using the formula–

$$\text{Bulk density} = \text{Weight/Volume occupied}$$

Tapped density

The known weight of granules (20 g) was put gently in a graduated cylinder of bulk density apparatus and apparatus was operated for 100 tapings. After 100 tapings volume occupied by granules was noted, and tapings were repeated until no further change in volume was observed.

Table 2: Optimized parameters for formulations

S. No.	Formulation code	Pantoprazole sodium (mg)	Sodium starch glycolate (mg)	Lactose (mg)	Mg. stearate (mg)	Talc (mg)	Binder (Chitosan solution in 1% acetic acid)
1	PPZ 1	80 mg	---	100	27	9	1%w/v
2	PPZ 2	80 mg	50	50	27	9	1%w/v

The volume occupied after tapings is called tapped volume. The tapped bulk density was calculated using the formula–

Tapped density = Weight/Tapped volume.

Hausners' ratio

It is a number corresponds to the flow ability of granules/powder. The formula to determine Hausners' – Hausners' ratio = Tapped bulk density/Bulk density. This ratio determines the flow properties of granules. The ideal range for good flow properties should be 1.2–1.5.

Carr's consolidation index (Percent compressibility)

The percent compressibility or Carr's consolidation index was calculated using the formula – Percent compressibility = [(Tapped density – Bulk density) × 100]/Tapped density. Particle size, cohesiveness, and relative flow rate are all indirectly correlated with the Carr's consolidation index.

Angle of repose

The largest possible angle between surface of the powder or granules' pile and a horizontal plane is referred to as the angle of repose. This was measured by passing a known weight of granules through a funnel having 30 mm stem opening on a glass plate. When the granules were emptied from funnel, the piles' height (h) and piles' radius (r) were measured with ruler. The formula to determine the angle of repose – Angle of repose (Θ) = $\tan^{-1}$ h/r. The flow properties of powder or granules are measured by the angle of repose [10,15,16].

SI

To determine the swelling index each PPZ, CH, and SSG were mixed in ratio of 1:1 and packed in dialysis membrane (molecular weight cut – off - 1200), previously activated by boiling for 30 min in Phosphate buffer (pH 7.4). The previously weighted sample was first kept in HCL + KCl buffer (having pH 1.5) for 2 h and the sample was weighed after every 30 min. After that, each sample was transferred into a mixed phosphate buffer (having pH 7.4) for 8 h and each sample was weighed after every 1 h until three same consecutive readings were obtained. The formula for determining swelling index – Swelling index = [(Final weight – initial weight) × 100]/initial weight [15,16].

X-ray diffraction (XRD) studies

The XRD studies were conducted on X-ray diffractometer (Miniflex 600, Rigaku Corporation, Tokyo, Japan). These studies were conducted to ensure the formation of Poly Electric Complex by the interaction between CH and SSG when exposed to acidic environment. For the study, the samples were prepared by mixing each drug and polymers in ratio of 1:1 and packing in dialysis membrane (molecular weight cut – off - 1200) previously activated by boiling for 30 min in Phosphate buffer (pH 7.4) according to the experimental protocol shown below in Table 3. The XRD thermograms of test samples were also compared with that of pure compounds.

These samples in sealed bags were kept at pH 1.5 (HCl + KCl buffer) maintained at 37± 2°C in a basket-type USP dissolution apparatus for 2 h. During the exposure gel formation occurred. After being removed from the dialysis bags, the contents (gelled) were dried overnight at 60°C in an oven. To ascertain if the fine powder samples were crystalline or amorphous, they were continuously scanned at room temperature between 10° and 80° (2Θ) at 30 kV accelerating voltage, 15 mA current and at scanning speed of 10°C/min [17,18].

Table 3: Composition of polyelectrolyte complex gels for X-ray diffraction studies

S. No	Sample Code	Composition
1	G-1	Chitosan (CH)+Sodium starch glycolate (SSG)
3	G-8	Pantoprazole+CH+SSG

Post-compression parameters

Friability test

Required number of tablets (20) was weighed after dusting to find the initial weight. The sample was then put in Roche friabilator and machine was used for 4 min or 100 revolutions. The tablets were again weighted after dusting to note down the final weight. The % friability was determined using the formula – Friability = [(Initial weight – final weight)/initial weight] × 100. There should be <1% friability, ideally.

Uniformity of weight

For the test, 20 tablets of each formulation were used. The tablets (i.e. 20) were weighed and the average weight was calculated. Then each tablet was weighed individually and the difference in weight was determined by deducting the average weight from the individual weight of each tablet. The deviation from average weight was calculated by determining the percent weight variation using formula – Percent weight variation = [(individual weight – average weight) × 100]/ average weight. If no unit exceeds the double of the given limit and no more than two tablets fall outside the designated deviation limit, the sample passes the test [14,16,19].

Drug content

The drug content of tablets of each formulation was determined by performing assay mentioned in the pre-compression parameters under the drug content of granules [10-13].

Hardness testing

The Monsanto hardness tester was utilized to determine the hardness of formulated tables. Three tablets were arbitrarily selected from each formulation. The tablet was placed between anvil and spindle (diametrically) of tester and screw was rotated (clockwise) to hold the tablet. The scale was adjusted to coincide zero of the scale with pointer. The screw was again rotated (clockwise) until the tablet was broken. The reading on the scale give the hardness (force required to break the tablet) of tablet. Ideally, a tablet should have a hardness value 4–10 kg/cm^2.

Thickness testing

A vernier caliper was used to measure the thickness of formulated tablets. The thickness was determined for three tablets form each formulation (selected randomly). The tablet was placed between the larger jaws of caliper and jaws were tightened to hold the tablet. The tablet thickness was determined from readings of main scale and vernier scale [10,16].

In vitro dissolution studies

The test was conducted utilizing USP Type II apparatus (DS 8000, Lab India, Thane, India) at paddle speed of 100 rpm. A 500 mL of HCl + KCl buffer (pH 1.5) was used as dissolution media for the first 2 h, mixed phosphate buffer (pH 6.8) for next 8 h, and mixed phosphate buffer (pH 7.5) for the last 2 h. Samples of 3 mL were collected at various time points (after 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0,

10.5, 11.0, 11.5 and 12.0 h) until 12 h and the same amount of fresh media was added after each sample withdrawal. Reversed-phase HPLC (RP-HPLC) instrument equipped with UV detector (absorption maxima 280 nm) and auto-sampler was used to measure the concentration of free drug. Stationary phase used was C_{18}, 250 × 4.6 mm, 5 µm particle size, Sapphirus, and for the mobile phase Solvent A was buffer (0.525 g of Dipotassium Hydrogen Orthophosphate and 2.72 g Potassium Dihydrogen Orthophosphate in 1000 mL water, adjust the pH 7.4 with dilute potassium hydroxide) and solvent B was Acetonitrile in 60: 40 ratio. Injection volume used was 20 µL and runtime was 10 min. The drug content of each sample was determined against blank at 284 nm (pH 1.5) and at 289 nm (pH 6.8 and 7.4) [20-25].

Drug release kinetics

The various mathematical models were used to examine and test drug release data to determine the precise mechanism of drug release from different formulations were Zero – order equation, First – order equation, Higuchi square root law, Hixson – Crowell cube root law, and Korsmeyer – Peppas equation [5,26-28].

RESULTS AND DISCUSSION

Pre-formulation studies

Drug-polymer interaction studies

In the spectra (FTIR) of pure PPZ (Fig. 1a) characteristic peaks observed at 3422, 2934, 1590, 1492, and 1380 cm^{-1} corresponding to –CH aromatic stretching vibrations, C-H aliphatic stretching, C=N stretching, C=C stretching in aromatic ring and C-H bending of CH_2 and CH_3, respectively. The peaks observed at 1304 and 1071 cm^{-1} were due to CF_2 stretching and S=O stretching vibrations [29-31]. The spectra of CH (low molecular weight) (Fig. 1b) showed major absorption bands at 3423, 1632, and 1403 cm^{-1} because of amide I, II, and CH and OH bending respectively [3,5,32-34]. In the FTIR spectra of SSG (Fig. 1c) the prominent characteristic peaks were observed at 3377, 2932, 1616, 1567, and 1436 cm^{-1} due to -OH stretching, -CH_2 symmetrical stretching, carbonyl group, asymmetric and symmetric –COO vibrations respectively [34-36]. The spectra of the sample containing solution mixture of PPZ + CH (Fig. 1d) and PPZ + SSG (Fig. 1e) exhibited no interaction with drug due to the presence of intact major peaks of Pantoprazole sodium.

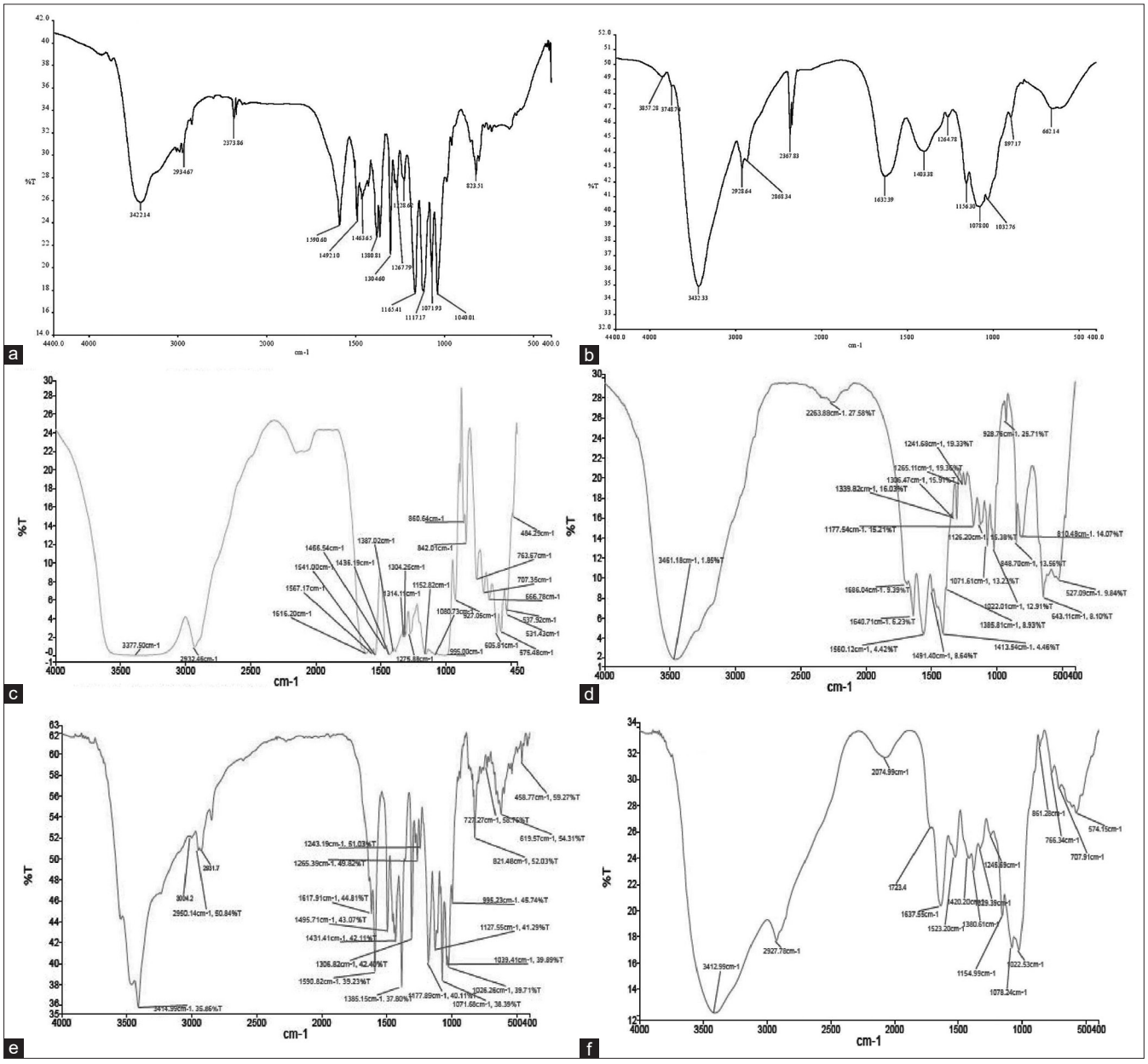

Fig. 1: Spectra (Fourier transform infrared spectroscopy) of: (a) Pantoprazole sodium (PPZ), (b) Chitosan (CH) (Low molecular weight), (c) sodium starch glycolate (SSG), (d) PPZ+CH (solutions), (e) PPZ+SSG (solutions), (f) CH+SSG (dried gel)

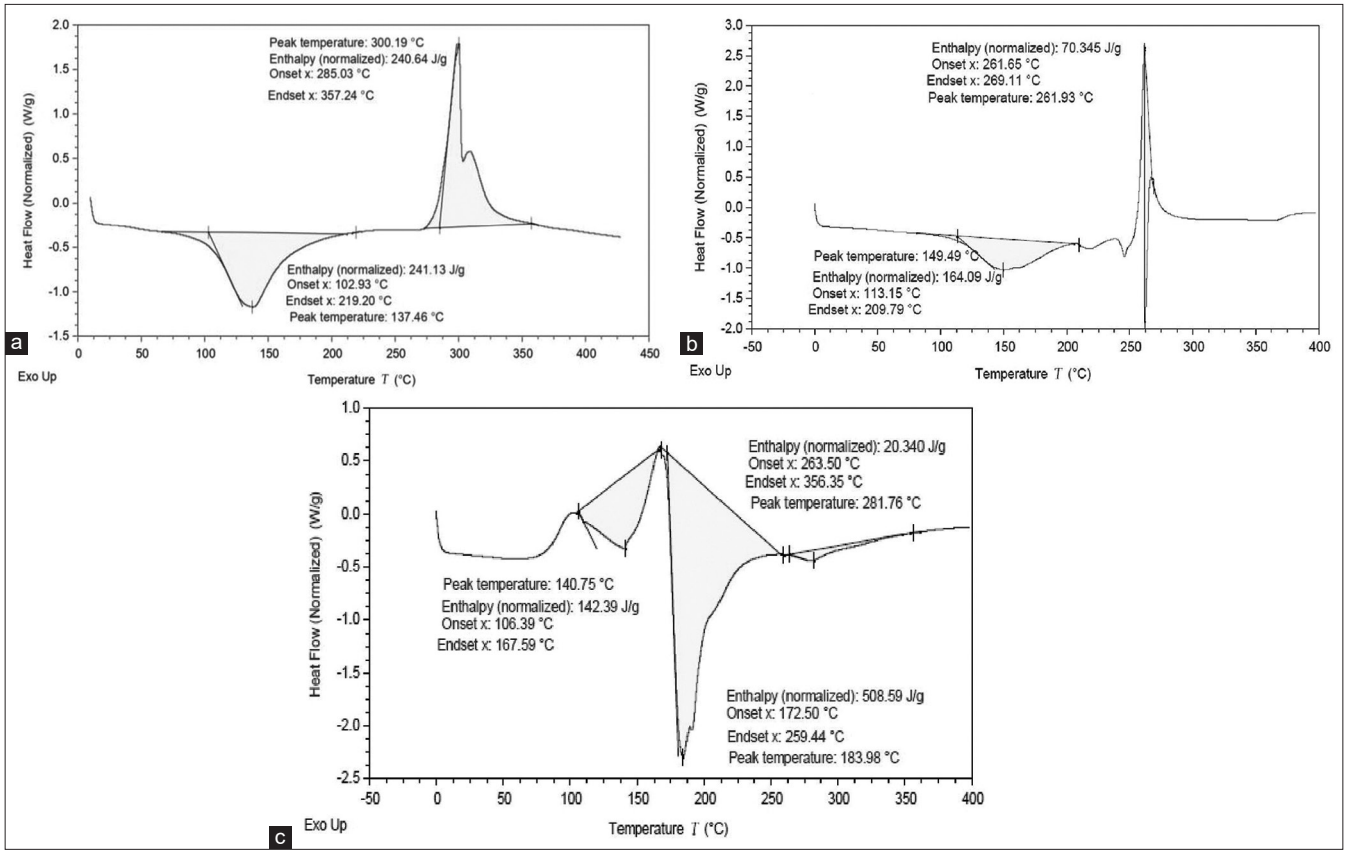

Fig. 2: Thermograms (differential scanning calorimetry) (exo up) of: (a) Chitosan (CH) (Low molecular weight), (b) sodium starch glycolate (SSG), (c) CH + SSG (dried PEC gel)

Polymer-polymer interaction studies

FTIR characterization

The spectra (FTIR) of PEC gel sample (dried) of CH + SSG (Fig. 1f) exhibited interaction between CH and SSG to form PECs. The peak at 1637 cm^{-1} due to –C=O stretching vibrations of –C=O group in SSG was shifted to a lower wavenumber (present at 1616 cm^{-1} in FTIR spectra of SSG) showed the interaction of amino group of CH with carboxylic group of SSG. The –NH bending vibration peak at 1523 cm^{-1} (was absent in pure polymers) indicates the formation of ionic bonds.

DSC characterization

The melting temperature, crystallinity change, and potential interactions between the polymers were all determined using DSC. Fig. 2 displays DSC thermograms of polymers and dried gels of polymer combinations. The DSC thermogram of pure CH (Fig. 2a) comprised of one endothermic peak at 137.46°C showing melting of CH and one exothermic peak 300.19°C exhibiting the thermal degradation of amine units [3,5,37-39]. In the DSC thermogram of SSSG (Fig. 2b) the dehydration of was exhibited by peak at 149.49°C and exothermic peak at 269.11°C is due to charing of SSG and is also related to thermal degradation of amine units [32,38]. In thermogram of CH + SSG dried gel (Fig. 2c) the interaction between polymers was confirmed by the presence of three endothermic peaks. The glass transition of PEC was shown by the first endothermic peak at around 140°C. The melting of PEC was exhibited by the second endothermic peak at 183°C. The third weak endothermic peak was observed at 281°C. The individual thermograms of CH and SSG do not have the endothermic peak at 183°C.

Response surface methodology

The response values of all experimental runs for various prepared batches are presented in Table 4.

The obtained range of responses was 142–298% for swelling index and 55.12±2.6–92.14±2.8% for cumulative drug release at 6^{th} h. To study the interaction effects of CMAs on CQAs, software-generated 2D contour plots, and 3D response surface plots along with polynomial equations used [6,7].

Interaction effect analysis of CMAs on individual CQA

The response surface analysis helped in enlightening the significant impact of both CMAs, that is, amount of CH and SSG on all the CQAs, namely, swelling index and cumulative drug release at 6^{th} h. Fig. 3a and b indicate that as the concentration of CH and SSG increases, the corresponding swelling index also increases. The higher swelling index indicates the formation of polyelectrolyte complex in acidic environment. In Fig. 3c and d with increase in the concentration of CH and SSG, the cumulative drug release at 6^{th} h decreases. This indicates the sustained or controlled release of drug from the formulation. The optimized formulation was further evaluated for other characteristics [6-9].

Optimization and validation of statistical model

The optimized formulation and validation check batch were evaluated for their CQAs and a comparison study was performed between the observed and predicted responses from statistical analysis (Table 5). The overlay plot was drawn using design expert software also confirms the results of optimized formulations (Fig. 4).

Evaluation of tablets

Pre-compression characterization

The observed values of all parameters were found within the limits specified (Table 6), showing that the powder blend is suitable for compression into tablets.

Table 4: Response values for all experimental runs

Formulation code	CMAs				CQAs	
	Actual values		Coded values		Swelling index (% w/w)	CDR at 6 h (%)
	Chitosan (% w/v)	SSG (% w/w)	Chitosan	SSG		
P1	1	2	1	1	298±2.8	60.45±2.1
P2	0.5	1.5	-1	0	230±3.2	88.32±3.4
P3	0.5	1	-1	-1	142±2.9	92.14±2.8
P4	0.75	1.5	0	0	260±3.2	75.26±2.9
P5	0.75	1.5	0	0	260±4.3	74.98±3.1
P6	0.5	2	-1	1	270±3.3	55.12±2.6
P7	0.75	2	0	1	290±3.9	68.75±3.0
P8	1	1	1	-1	240±4.8	79.83±2.5
P9	0.75	1.5	0	0	260±3.4	73.41±2.7
P10	0.75	1	0	-1	210±2.9	85.92±3.2
P11	1	1.5	1	0	260±3.4	69.28±2.9
P12	0.75	1.5	0	0	260±4.2	72.55±3.3
P13	0.75	1.5	0	0	260±4.1	73.10±3.0

All values are expressed as mean±SD, n=3

Table 5: Post-analysis solution using desirability approach with observed and predicted values of CQAs and % prediction error

Batch No.	CMAs		CQAs	
	Chitosan (% w/v)	SSG (% w/w)	Swelling index (%)	Cumulative drug release at 6 h
			Predicted values	
			307.676	59.713
			Observed values	
P1	1	2	330.400	54.798
% Prediction error			6.8	8.23

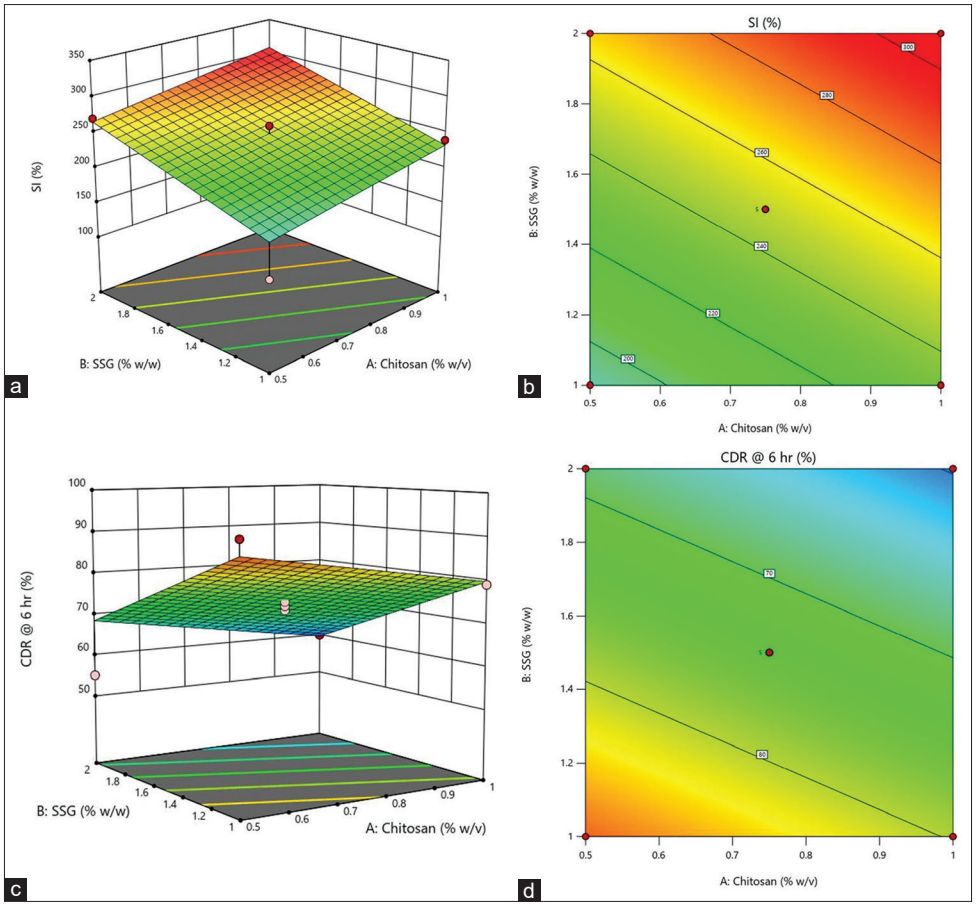

Fig. 3: Response surface methodology and contour plots of swelling index (a and b) and cumulative drug release at 6th h (c and d)

Swelling index
The swelling behavior of PEC gel (of PPZ 2) had showed more swelling in an acidic medium than alkaline medium due to formation of polyelectric complex in an acidic medium (Table 7).

XRD studies
The two broad peaks one at 2θ = 10° exhibiting the packing of glycosidic chains in the amorphous region and the second at 2θ=20° exhibiting crystalline packing of CH chains were observed in the XRD diffractogram of CH (Fig. 5a). The diffractogram also showed weak peaks at 2θ=11–13° attributed to inter-chain hydrogen bonding [40,41]. The XRD diffractogram of SSG (Fig. 5b) exhibited prominent peaks at 2θ=19–20° corresponding to the reflection from the crystalline planes of the starch molecule. The additional peaks at 2θ around 10–11° and 22–23° were also frequently observed and may be attributed to specific packing arrangements within the SSG structure. The less intense peaks at 2θ around 5–6°, 15–16°, and 27–28° may be seen depending on the preparation method and crystallinity of the SSG sample [42-44]. The XRD diffractogram of Pantoprazole sodium showed characteristic peaks at 2θ=6° and 22° due to crystalline nature (Fig. 5c) [17,18]. The XRD diffractogram of CH + SSG (Fig. 5d) dried PEC gel (G1) showed various peaks at 2θ=28.28°, 40.46°, 50.08°, 66.3° and 73.66° which were not present in pure compounds. There were numerous new peaks in the diffractogram of Pantoprazole sodium, CH and SSG dried PEC gel (G6) which were not present in the individual diffractograms of drug and polymers. Some characteristic peaks were showed 2θ=12.92°, 13.02°, 15.48°, 16.58°, 18.66°, 19.92°, 20.54°, 23.2°, 25.44°, 26.36°, 27.3°, 28.1°, 28.84° and 40.28° (Fig. 5e). The presence of numerous new peaks in the diffractogram which were not present in the individual diffractograms of drug and polymers, suggest the increase in crystallinity of dried gel due to formation of PECs.

Table 6: Pre-compression characterization

Parameters	PPZ 1	PPZ 2
Moisture content (% w/w)	1.7±0.58	1.3±0.58
Drug content (% w/w)	98.17±1.7	98.33±1.4
Bulk density (g/cm^3)		
Before lubrication	0.56±0.02	0.63±0.02
After lubrication	0.65±0.03	0.67±0.02
Tapped Density (g/cm^3)		
Before lubrication	0.68±0.02	0.66±0.02
After lubrication	0.81±0.02	0.81±0.02
Hausners' ratio		
Before lubrication	1.3±0.1	1.3±0.1
After lubrication	1.2±0.06	1.2±0.06
Carr's index (%)		
Before lubrication	17.6±0.6	28.8±0.6
After lubrication	17.6±0.4	15.2±0.4
Angle of repose (θ°)		
Before lubrication	23.4±0.8	22.6±1.3
After lubrication	29.4±1.4	30.0±1.5

All values are expressed as mean±SD, n=3

Post-compression parameters

All the batches of prepared tablets had a uniform smooth texture and structure confirmed by visual inspection. All the formulations had <1% friability and hence passed the test. The weight variation of all formulations was between 3% and 5% and individual deviations were found within the specified limits. Hence, the formulations also passed

Table 7: Swelling index of PEC gel in different mediums

S. No	Formulation code	Swelling index (% w/w)		
		In pH 1.5 (after 2 h)	In pH 7.4 (after 8 h)	Overall (after 10 h)
1	PPZ 2	293.1±1.5	16.2±2.2	330.4±2.3

All values are expressed as mean±SD, n=3

Table 8: Post-compression characterization of sustained-release tablets

Formulation code	Friability (%)	Weight* (mg)	Drug content (% w/w)	Hardness (kg/cm^2)	Thickness (mm)
PPZ 1	0.93±0.02	210.5±4.3%	97.9±1.5	4.9±0.2	4.2±0.1
PPZ 2	0.88±0.02	212.8±4.8%	98.6±1.0	5.2±0.2	4.2±0.1

All values are expressed as mean±SD, n=3;*n=20

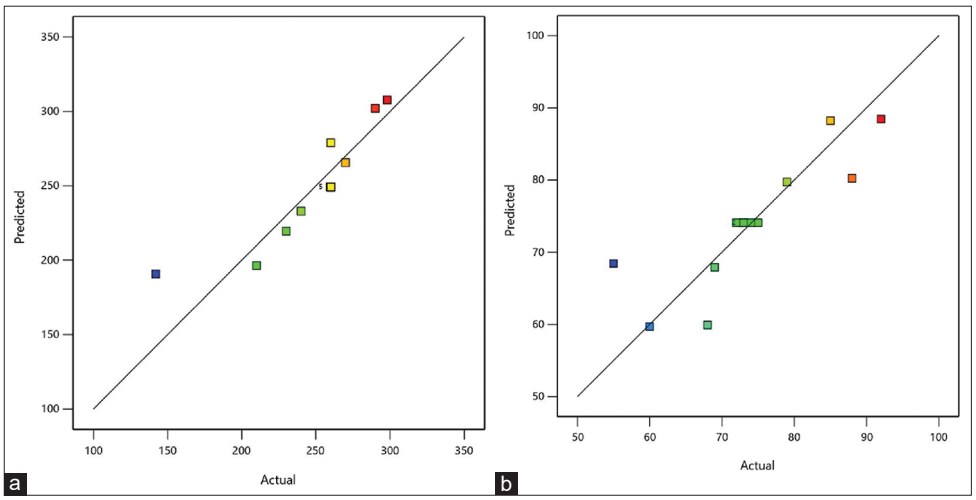

Fig. 4: Predicted versus actual graphs of (a) swelling index and (b) Cumulative drug release at 6 h

Table 9: Data of drug release kinetic study

Sr. No.	Formulation code	R^2 values					n (release exponent)
		Zero-order	First order	Higuchi	Hixson-crowell	Korsmeyer-Pepps	
1	PPZ 1	0.835	0.981	0.843	0.839	0.070	1.01
2	PPZ 2	0.979	0.838	0.866	0.898	0.823	0.38

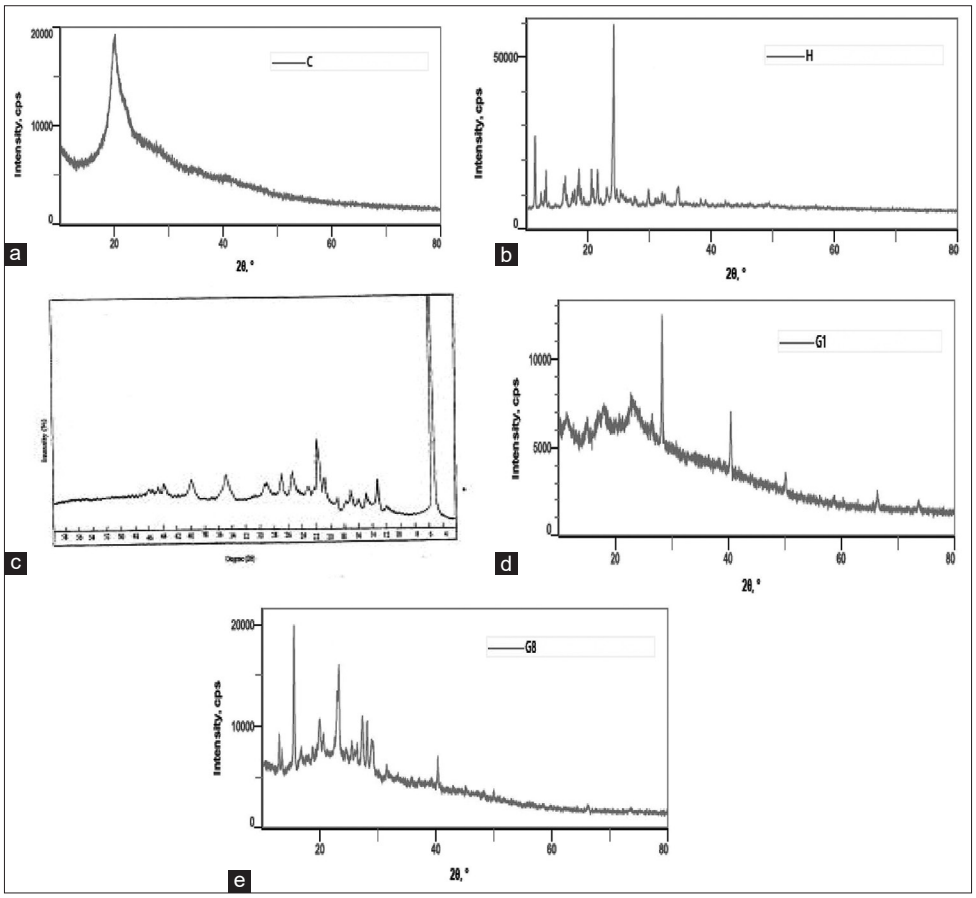

Fig. 5: X-ray diffraction diffractograms of: (a) Chitosan (CH), (b) sodium starch glycolate (SSG), (c) Pantoprazole sodium (PPZ), (d) CH+SSG, (e) PPZ+CH+SSG

the weight variation test. The drug content and hardness of formulation were found within the range of 96–99% and 4–5.5 kg/cm^2. The thickness of formulations was found between 4.1 and 4.3 mm (Table 8) [10].

In vitro drug release studies

A plot of % cumulative drug release versus time is shown in Fig. 6. It was observed that the formulation PPZ 1 showed 8% drug release within 2 h, indicating the degradation of about more than 90% drug in acidic medium (pH 1.5) and lesser or no degradation in alkaline medium. The formulation PPZ 2 exhibited 91% drug release in 12 h, indicating the sustained release for 12 h.

Drug release kinetics

After fitting the dissolution data into various kinetic models, it was observed that R^2 value of PPZ 1 was higher for the first-order equation, which exhibited that the drug release from the formulation depends on drug concentration and hence followed first-order release. The drug release from this formulation followed super Case II transport mechanism (n higher than 1) characterized by a higher speed of solvent penetration in the matrix. The formulation did not show the sustained release. Formulation PPZ 2 followed zero – order release. Regarding n values, formulation PPZ 2 followed Fickian release mechanism (n<0.5),

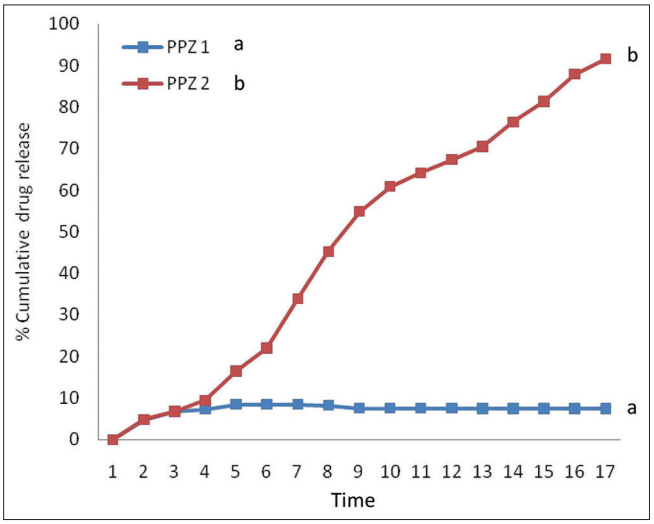

Fig. 6: Cumulative % drug release versus time graph of (a) Pantoprazole sodium (PPZ) 1 and (b) PPZ 2

indicating that the ordinary diffusion was the governing factor for drug release form the PECs (Table 9) [5,14,28,45,46].

CONCLUSION

The goal of the current study was to develop and assess pantoprazole sodium oral sustained release tablets using CH based *in situ* forming polyelectrolyte complex as retardant polymer. This study had successfully applied the QbD – approach for the development of sustained-release formulations of pantoprazole using CCD. The optimized formulation fulfills the desired requisite of CQAs. The results of this study had indicated that the polyelectrolyte complex formed between CH and anionic polymer SSG had proven an excellent excipient for designing sustained-release oral formulations of hydrophilic drugs. These PECs not only provide a sustained drug release but also prevent the initial burst release and degradation (in acidic medium) of drug. The formulated tablets were physically stable. The FTIR, DSC, and XRD analysis confirmed the formation of *in situ* PECs between CH and SSG. The formulations had shown sustained release up to 12 h with zero – order release kinetics.

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AUTHORS' CONTRIBUTION

Concept and study design were carried out by Dr. Vijay Sharma. Mr. Ajay Malik was responsible for data acquisition, data analysis and interpretation, drafting the manuscript, and performing statistical analysis. Critical revision of the manuscript and overall supervision were provided by Dr. Vijay Sharma and Dr. Navneet Verma. All authors have read and approved the final manuscript.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest, financial or otherwise.

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