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RESEARCH ARTICLE

Design, Development, and *In vitro* Evaluation of Single Unit Hydrodynamically Balanced System of Captopril

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Abstract:

Background:

This study investigated the use of *in situ* polyelectrolyte complex formation by using two oppositely charged polysaccharides [Chitosan (cationic), Sodium Alginate (anionic)]. It forms 3-D intercalation and interpenetrating network helping in controlling the release of highly acid-soluble Captopril.

Objective:

To develop a polyelectrolyte complex based single unit gastroretentive tablet by using optimization based 3 (2) Taguchi factorial design for controlled delivery of Captopril.

Materials and Methods:

Gastroretentive Captopril tablets were prepared by the direct compression technique. Total 09 batches were prepared as per 3 (2) Taguchi factorial design studies of 100 tablets each.

Results:

Thermal analysis method revealed that there is a formation of PEC between chitosan and sodium alginate. *In vitro* buoyancy and $T_{60\%}$, drug release studies revealed that due to complex formation, formulation remains stable and remains buoyant. From factorial design studies, it was interpreted that for buoyancy time (Y_1) chitosan desired effect value was found higher. For 60% drug release ($T_{60\%}$; Y_2) both chitosan and sodium alginate have a synergistic effect. Durbin Watson's statistical model and residual data suggested that the model is statistically validated. All formulations follow the zero-order kinetics. Stability studies revealed that formulations F5 and F9 remain stable for long-term stability studies without showing any significant changes. The fit analysis studies indicated that the prepared formulation was different from the innovator product indicating low f_1 and f_2 values.

Conclusion:

From the result generated it was concluded that chitosan-sodium alginate polyelectrolyte complex has sufficient potential to retard the release of CPT.

Keywords: Polyelectrolyte complex, Factorial design, Buoyancy time, 60% drug release, Thermal studies, Gastroretention.

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1. INTRODUCTION

Captopril (CPT) [log p=0.34, water solubility at 37°C =4.52 mg/ml] is an excellent candidate for the medication of hypertension and congestive heart failure therapy, because of its extreme clinical effectiveness and low toxicity. Nowadays, the popularity of CPT is decreasing continuously due to the requirement of high doses and multiple doses regimen. This high dosing frequency leads to an adverse effect of CPT as compared to the other Angiotensin converting enzyme inhibitors [1]. The required dose of CPT that is clinically effective is 12.5-150 mg a day in divided doses of two or three. After a single oral administration of CPT helps to regulate hypertension for 6-8 hours. The short half-life of CPT of about

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2 hours indicates the requirement of high dosing frequency for therapeutic effect. It leads to fluctuations in levels of drug concentration in the systemic circulation, therefore, increasing the side effect of the drug [2, 3].

These all above properties of CPT indicate that there is a need to develop novel controlled-release formulations. The need of gastroretentive tablet formulations help to maintain a relatively steady concentration of CPT in blood for an extended time, hence reduction in dosing frequency. The formulation aids in the retention of the drug in the upper part of the stomach for a longer time and protects the CPT from degradation in the harsh intestinal or colonic environment [4, 5].

Chitosan (CH) generally dissolves at low pH while it is insoluble at alkaline and neutral pH. On the other hand, Sodium Alginate (SA) get dissolves at neutral pH and shrinks at gastric pH. These properties of both polymers restrict their use alone. When these polymers are used together, the positively charged amino groups of CH and the negatively charged carboxylate groups of SA interact with each other *via* electrostatic interaction in 0.1 M HCl (pH 1.2) forms *in-situ* CH-SA polyelectrolyte complex (PEC) [6, 7]. This complex overcomes the limitations encountered in CH and SA alone, where the dissolution of CH at gastric pH and the dissolution of SA at neutral pH are reduced by SA and CH, respectively when used in combination. Considering the above facts our objective was to develop, optimize, and evaluate the gastroretentive CH-SA based single unit PEC matrix tablets for sustained stomach delivery of CPT.

2. METHODS

2.1. Drug, Chemicals, and Reagent

Captopril (CPT) was procured from Yarrow Chem Products, Mumbai. Chitosan (CH), Sodium Alginate (SA) was procured from Sigma-Aldrich, Hydroxypropyl Methylcellulose (HPMC K 100 M) was obtained as a gift sample from Colorcon Asia, India. All the excipients used were of USP grade and other chemicals used were of analytical grade.

2.2. Development of Gastroretentive PEC Matrix Tablets of CPT

The direct compression method was selected for the preparation of gastroretentive matrix tablets using a tablet punching machine (Shakti Pharmtech, India). All ingredients of each formulation were passed through mesh screen 80. The required amount (Tables **1** and **2**) of CPT, CH, SA, and HPMC K100M was weighed and transferred into the double cone tumbler (Shakti Pharmtech, India) and this mixture was mixed for 20 minutes. After mixing, the remaining excipients (Sodium Bicarbonate, Citric Acid Magnesium Stearate, and Talc) were added and again mixed in a double cone tumbler for 15 minutes at 35 rpm to obtain a homogenous physical blend. The required amount for a single tablet was weighed and the tablets were compressed at the compression force of 8kg/cm^2, by using a tablet punching machine.

The obtained data was transformed into various mathematical models by fitting into the Minitab- 18. Response surface graphs, contour plots and main effect plots were drawn to study the effect of CH, SA responsible for the development of PEC.

Table 1. Coded and actual values of the CPT-PEC gastroretentive matrix tablets as per 3(2) Taguchi factorial design.

Formulation Code	SA (A)		CH (B)	
	Coded Level*	Actual Quantity (mg)	Coded Level*	Actual Quantity (mg)
F1	-1	60.00	-1	60.00
F2	0	72.50	-1	60.00
F3	+1	85.00	-1	60.00
F4	-1	60.00	0	72.50
F5	0	72.50	0	72.50
F6	+1	85.00	0	72.50
F7	-1	60.00	+1	85.00
F8	0	72.50	+1	85.00
F9	+1	85.00	+1	85.00

Note: *Coded transition levels of polymers at three levels *e.g.*, low, medium, and high (-1, 0, +1) were selected based on initial trial studies for $T_{60\%}$ drug release and buoyancy time.

Table 2. Composition of various CPT PEC gastroretentive matrix tablets prepared as per 3(2) Taguchi factorial design.

Ingredients	Quantity (mg); Per Tablet
CPT	25
CH	60-85
SA	60-85
HPMC K100M	100
SB	20
CA	5
MS	2.5
Talc	2.5

Note: SB: Sodium Bicarbonate, **CA:** Citric Acid, **MS:** Magnesium Stearate.

2.3. Drug polymer Compatibility Studies and Confirmation of PEC Formation

While designing any formulation it is very important to investigate any polymer-polymer, polymer-drug interaction that occurs or not. Therefore, in the current research investigation, it is necessary to confirm whether the drug is interacting with polymers under experimental condition and during the shelf life. So, in the current investigation polymer-polymer, polymer-drug interaction studies were performed by using the thermal analysis method (EXSTAR TG/DTA 6300) by Differential Scanning Calorimetry (DSC), Derivative Thermogravimetry (DTG) and Thermal gravimetry analysis (TG) [8, 9].

2.4. Characterization of Gastroretentive CPT-PEC Tablets

Prepared tablets were evaluated for various parameters as per USP like drug content, weight variation, friability, and *in vitro* drug release. Tablets were also evaluated for in-house parameters of thickness, and tablet hardness. All the parameters were evaluated in triplicate [9].

2.5. Lag and Buoyancy Time Estimation

The buoyancy time and the lag time were determined by USP type II apparatus (Electrolab dissolution tester TDT -08L). The tablet was placed in a dissolution vessel containing 900 ml of 0.1N HCl at 50 rpm. The time required for the tablet to reach the surface of dissolution media after placing was taken as lag time and the entire time on which the tablet remained buoyant was noted as buoyancy time [10].

2.6. *In-vitro* Drug Release and Release Kinetic Study

An *in-vitro* drug release study was performed by using USP Type II apparatus. The study was performed in 900ml of 0.1N HCl (pH 1.2) at 50 rpm speed at 37±0.5ºC. The 1ml of the sample was withdrawn at different time intervals of one hour and the same quantity of 0.1 M HCl was added to the dissolution vessel to maintain the sink condition. The withdrawn sample was analyzed in a UV-visible spectrophotometer (Shimadzu UV 1800) at a wavelength of 204.70 nm. To explain the drug release kinetics from the formulation of various kinetics models like Zero, First, Higuchi and Korsmeyer-Peppas equations were used. All the equations were applied in the KinetDS version 3.0 software [8].

2.7. Statistical Optimization and Analysis of Data

Response surface methodology (RSM) optimization study was performed by using the Minitab-18 software. Statistical second-order model, including polynomial equations, was used. It includes independent variables and their interactions for various measured responses (Y_1 and Y_2). The general form of the model is depicted as:

$$\mathbf{Y} = \beta_o + \beta_1 A + \beta_2 B + \beta_3 AB + \beta_4 A^2 + \beta_5 B^2 + \beta_6 A^2 B + \beta_7 AB^2 + \beta_8 A^2 B^2 \quad \textbf{(1)}$$

Where β is the intercept and it is the arithmetic means of all the quantitative outcomes of nine experimental runs, β_1-β_8 is the regression coefficients computed from the observed experimental values of Y; A and B are the coded levels of independent variables; AB is the interaction between variables; A^2 and B^2 are polynomial terms. The main effect of SA (A) and CH (B) represent the average result of changing one factor at a time from low to high value (the desired effect). The polynomial equation was used as an interpretation tool and used to draw a conclusion after considering the intensity of the coefficient from the mathematical sign it carries which may be positive or negative. The positive sign represents the synergistic action. One-way ANOVA was used for the statistical validity of the hypothesized model. The level of significance was considered at $p < 0.05$ [8, 11].

2.8. Validation of Statistical Model for Response Y_1 and Y_2

Response Y_1 and Y_2 were validated by using the Durbin – Watson statistic and residual data were determined using Minitab-18 software. The value of ≤ 2.0 was considered as there is a chance of a low degree of error in the response and the models are validated [8, 12].

2.9. Stability Studies of Optimized Formulations

Optimized formulations (F5 and F9) were packed in blister packaging and stored in a stability chamber for one year (25°C, 60% RH). After each interval of three months, the formulations were evaluated for percent buoyancy, percent drug release, and percent drug content [13].

2.10. Estimation of Fit Factors

Moore and Flanner have developed a model for independent approximation using fit factors [14]. These fit factors signify the difference between the percent drug dissolved per unit time of a test compared with reference formulation. Nowadays fit factors have been widely accepted by FDA Centre for Drug Evaluation and Research (CDER) [15] and has also been adopted by the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) [16] and World Health Organization (WHO) [17, 18] as a rating criterion of similarity between two *in vitro* dissolution profiles. Here, fit factors were determined for PEC gastroretentive formulation F8 and marketed innovator product Aceten 25 mg tablet manufactured by Wockhardt Limited, India.

3. RESULTS AND DISCUSSION

3.1. Drug Polymer Compatibility Studies and Confirmation of PEC Formation

Fig. (**1a**) represents the DSC thermal characterization of CPT under experimental conditions. The DSC data was plotted against Temperature (ºC) on x-axis and mW (heat flow) on y-axis. The thermogram of DSC of CPT represents a sharp endothermic peak at 108ºC (enthalpy 88.5 mJ/mg) and it represents the melting point of CPT. Fig. (**1b**) represents a broad exotherm peak at 290 ºC (enthalpy -237 mJ/mg) in the DSC thermogram could be indicative of the slow degradation of CH under experimental conditions. Fig. (**1c**) represents DSC thermogram of SA which indicates the two exothermic peaks at 241 ºC (enthalpy -219 mJ/mg) and at 338 ºC (enthalpy -931 mJ/mg) which is attributed to the degradation of SA resulting in the carbonized residue. Fig. (**1d**) represents DSC thermogram of physical mixtures which indicates the endothermic peak of the drug at 105 ºC (enthalpy 4.76 mJ/mg) three exothermic peaks at 252 ºC, 291 ºC (enthalpy -394 mJ/mg) and at 361 ºC (enthalpy -165 mJ/mg), which attributed to the degradation of the physical mixture. Fig. (**1e**) represents the DCS thermogram of LSIF (Formulation F5), the sharp endothermic peak of CPT at 108 ºC (enthalpy 88.5 mJ/mg) disappeared in the DSC of LSIF. The changes could probably indicate changes occurring in some physical properties after PEC formation such as crystalline, dehydration, or melting point. The disappearance of the CPT endothermic peak might indicate the amorphization of the CPT and/or its inclusion in the formed complex of SA-CH [19]. The exothermic peak at 300 ºC (enthalpy -391 mJ/mg) was not present in the individual thermogram of SA and CH and this new exothermic peak could be suggestive of PEC formation between SA-CH.

The DTG data was plotted against Temperature (ºC) on x-axis and µg/Celsius (heat flow) on y-axis. Fig. (**2a**) represents the thermogram of CPT under experimental conditions. The thermogram of DTG represents that the CPT was stable up to 200ºC. Fig. (**2b**) The DTG thermogram represents that CH was stable up to temperature 284ºC. (Fig. **2c**) The DTG thermogram represents that SA was stable up to 237 ºC. (Fig. **2d**) The DTG thermogram represents that physical mixtures were stable up to 280 ºC. (Fig. **2e**) DTG thermogram represents that the dried gel of LSIF was stable up to a temperature of 298 ºC.

The TG data was plotted against Temperature (ºC) on x-axis and TG% (weight loss) on y-axis. Fig. (**3a**) represents the TG thermal characterization of CPT under experimental conditions. The total weight of CPT was 10.52 mg during thermal characterization. TGA thermogram of CPT represents that between temperatures 32-300ºC, 73.4% loss of mass occurred from CPT. TGA thermogram suggests the single-stage decomposition of CPT occurs under experimental conditions. Fig. (**3b**) represent the TG thermal characterization of CH under experimental condition. The total weight of CH was 10.56 mg during analysis. The TGA thermogram represents that 45.6% loss of mass from CH occurred between temperature 33-300 ºC and it suggests the single-stage decomposition. Fig. (**3c**) represents the TG thermal characterization of SA under experimental conditions. The total weight of the sample during the analysis was 10.54 mg. The 52.14% mass loss occurs at a temperature between 30-252 ºC. TGA thermogram also represents the single-stage decomposition process. Fig. (**3d**) represent the TG thermal characterization of physical mixtures under experimental condition. The total weight of the sample during analysis was 10.54 mg. There is a 47.48% mass loss at temperatures between 30-300 ºC. TGA thermogram also represents the single-stage decomposition process of physical mixtures. Fig. (**3e**) shows the TG thermal characterization of LSIF under experimental conditions. The total weight of the sample during the analysis was 10.61 mg. The TGA thermogram represents that LSIF that 54.58% mass loss occurs at a temperature between 34-315 ºC. TGA thermogram also represents the single-stage decomposition process.

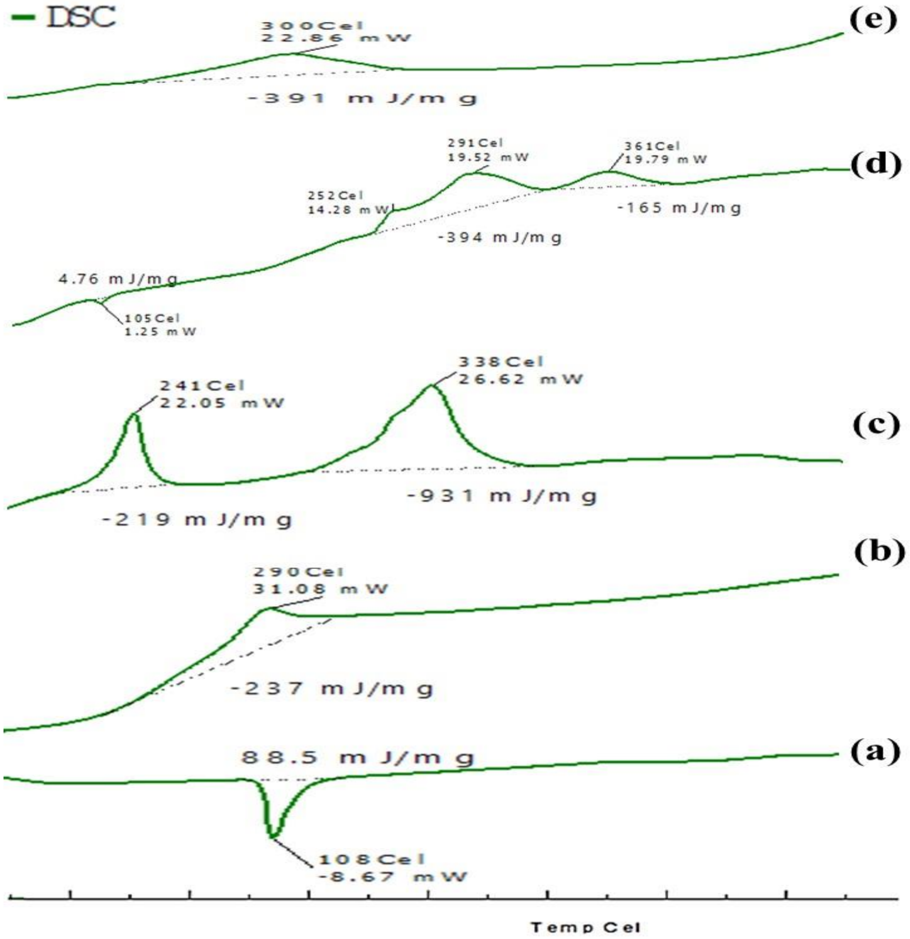

Fig. (1). (**a**) DSC Thermogram of CPT (**b**) DSC thermogram of CH (**c**) DSC thermogram of SA (**d**) DSC thermogram of physical mixtures of CPT, CH & SA (1:1:1) (**e**) DSC thermogram of Liquid State Interaction of formulation F5 (LSIF).

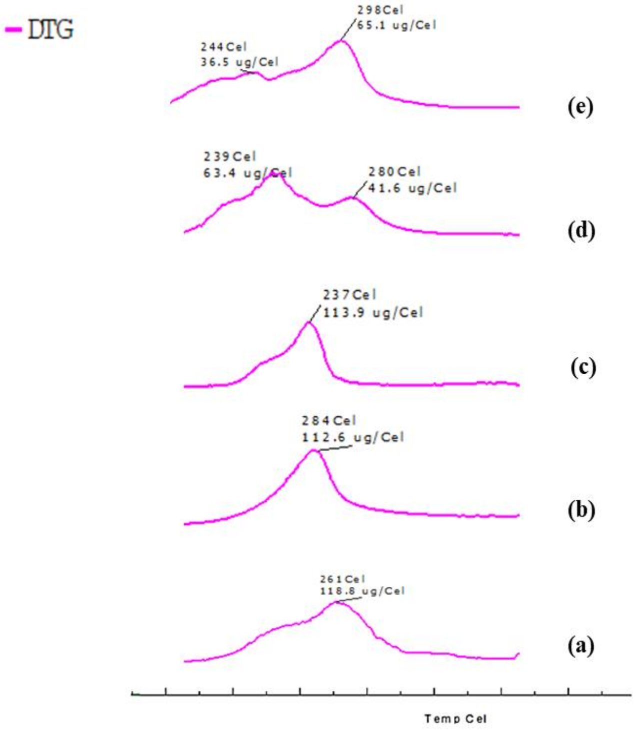

Fig. (2). (**a**) DTG thermogram of CPT (**b**) DTG thermogram of CH (**c**) DTG thermogram of SA (**d**) DTG thermogram of physical mixtures of CPT, CH & SA (1:1:1) (**e**) DTG thermogram of Liquid State Interaction of formulation F5 (LSIF).

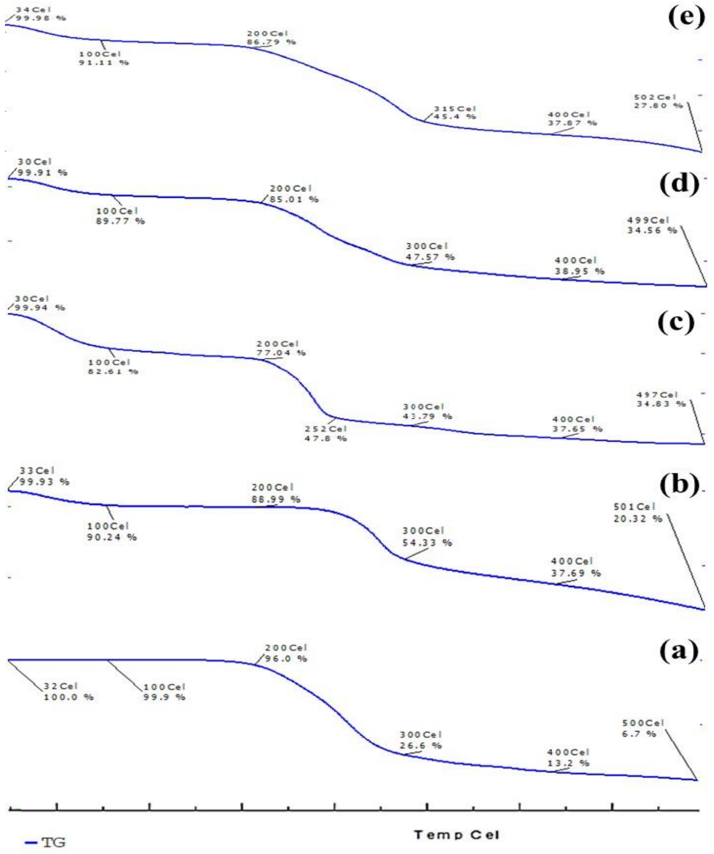

Fig. (3). (**a**) TG thermogram of CPT (**b**) TG thermogram of CH (**c**) TG thermogram of SA (**d**) TG thermogram of physical mixture of CPT, CH & SA (1:1:1) (**e**) TG thermogram of Liquid State Interaction of formulation F5 (LSIF).

3.2. Physico-chemical Evaluation of CPT Gastroretentive PEC Matrix Tablets

All the formulations F1-F5 comply the weight variation test as per USP [20]. The hardness of all the formulation batches was found to be in the range of 5.3 to 6.8 kg/cm^2. The drug content of all the 09 batches was found to be 93.47 to 98.63, which is within the mentioned limits. The friability of all the batches was found to be less than 1%, which indicates the good mechanical strength of the PEC tablet formulations (Table **3**).

3.3. Effect of Formulation Variable on Buoyancy (Y_1) for Formulation F1-F9

The constant and regression coefficients for Y_1 (Buoyancy time) represented as

$$Y_1 = 9.889 + 0.500A + 0.833B + 0.167A*A + 0.167\,B*B + 0.250\,A*B \quad \textbf{(2)}$$

The polynomial equation was found to be significant with an *F* Value of 1.42 ($p = 0.010$). The above polynomial equation signifies that the AB, A^2, B^2 were significant model terms (Equation II). From the main effects plot for means, we can say that the high level of CH and SA was responsible for achieving buoyancy in PEC tablet formulation. The main effects plot (Fig. **4**) for means indicated that the high level (+1) of the CH and SA is more effective for imparting buoyancy as compared to the -1 and 0 levels, respectively. The desired effect of response was maximum for buoyancy time 12 hours at a high level (+1) *i.e.* 0.979 and lower for buoyancy time 08 hours 0.137 for the contour plot (Fig. **5**). From the Response Surface Plot (RSP), we can say that CH had a comparatively more pronounced effect than SA (Fig. **6**) and changes in buoyancy time were attributed to the adding/selection of the levels of CH and SA. As the levels are added to A and B or *vice versa* the contour area was also increased which corresponds to an increase in buoyancy time in PEC formulations. Formulations F5 and F9 were found to be optimized.

Table 3. Physico-chemical evaluation of CPT Gastroretentive PEC matrix tablets.

Formulation	Weight Variation Test	Hardness* (kg/cm^2)	Friability * (%)	Drug Content * (%)
F1	Complies	6.8±0.36	0.52	95.67±0.04
F2	Complies	6.2±0.26	0.63	96.16±1.43
F3	Complies	5.9±0.26	0.71	97.18±0.98
F4	Complies	6.3±0.55	0.58	94.74±1.67
F5	Complies	5.6±0.36	0.89	95.48±1.82
F6	Complies	5.4±0.63	0.96	93.47±2.04
F7	Complies	5.7±0.45	0.86	98.63±1.74
F8	Complies	5.5±0.18	0.96	96.51±1.68
F9	Complies	5.3±0.36	0.92	94.34±1.02

Note: *All determinations were carried out in triplicate n=3, ± S.D.

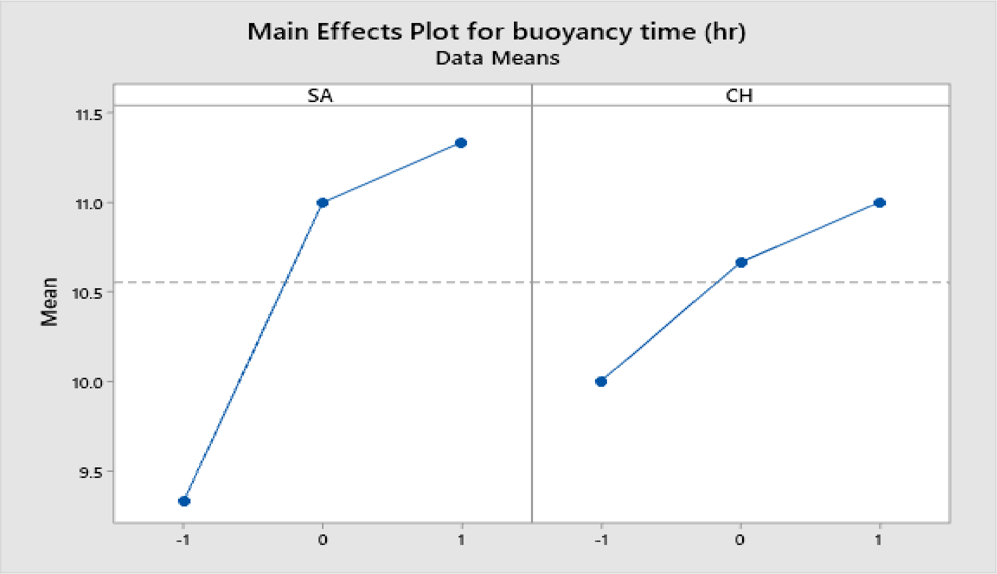

Fig. (4). Main effect plot for buoyancy time (Y_1).

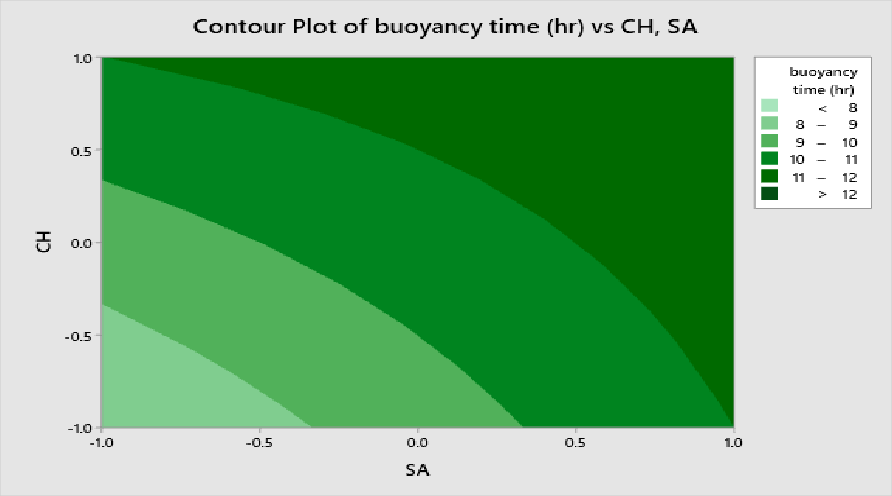

Fig. (5). Contour plot for buoyancy time (Y_1).

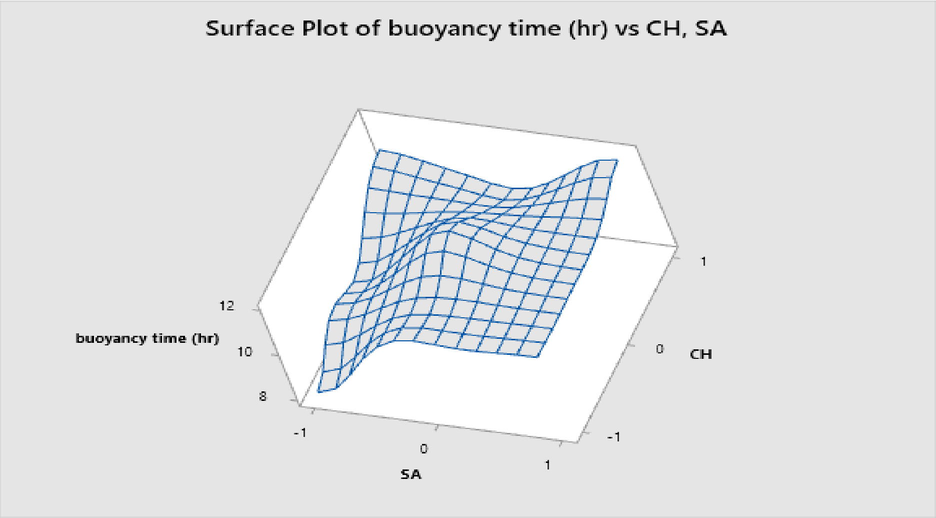

Fig. (6). Response Surface Plot for buoyancy time (Y_1).

3.4. Effect of formulation variable on $T_{60\%}$ (Y_2) for formulation F1-F9

The constant and regression coefficients for Y_2 ($T_{60\%}$) drug release represented as

$$Y_2 = 6.68 + 0.957\ A + 0.624\ B - 0.42\ A*B + 0.56\ B*B + 0.580\ A*B \quad (3)$$

The quadratic polynomial equation was found to be significant with an *F* Value of 4.53 ($p = 0.011$). The above equation/model signifies that the AB, A^2, B^2 were significant model terms (Equation III). The main effects plot for means indicated that the high level of CH and SA (+1) has a more pronounced effect as compared to the lower (-1) and middle (0) levels respectively. From the main effect plot, SA has a more pronounced effect for retardation of CPT (Fig. **7**) The contour plot (Fig. **8**) revealed that the desired effect was maximum (0.8421) for the $T_{60\%}$ drug release in 08 hours and lower in 06 hours 0.0494. Furthermore, the contour plot also revealed that increasing the levels of SA and CH from low level to high level leads to the retarded rate of CPT from the PEC inter and intra polymeric matrices (Fig. **9**). Formulations F5 and F9 were found to be optimized.

3.5. Validation of Statistical Optimization

For formulations, F1-F9 Durbin –Watson statistical model was applied by using Minitab-18 software. Durbin –Watson value was found to be 1.52 and 1.29 for Y_1 and Y_2, respectively (Figs. **10** and **11**). A low value ≤ 2.0 suggests that the statistical model is validated, and the degree of error between the factors, variables and responses is negligible. Actual values and predicted values were also calculated by using Minitab software (Table **4**). The finding suggests that statistical models for response Y_1 and Y_2 are highly validated and the degree of error in the studied statistical model is less [12].

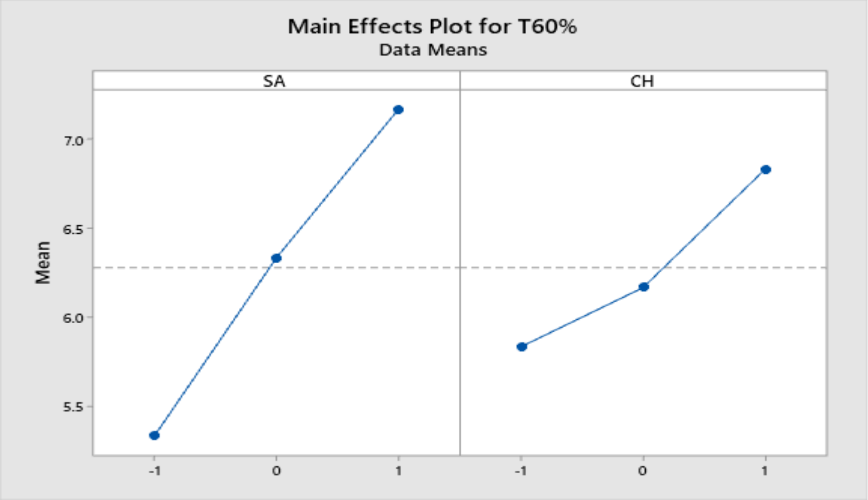

Fig. (7). Main effect plot for $T_{60\%}$ drug release (Y_2).

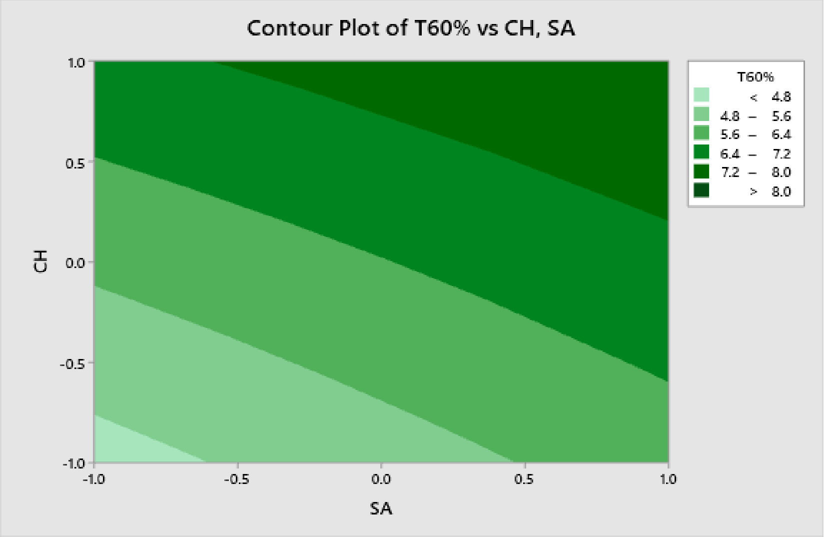

Fig. (8). Contour plot for $T_{60\%}$ drug release (Y_2).

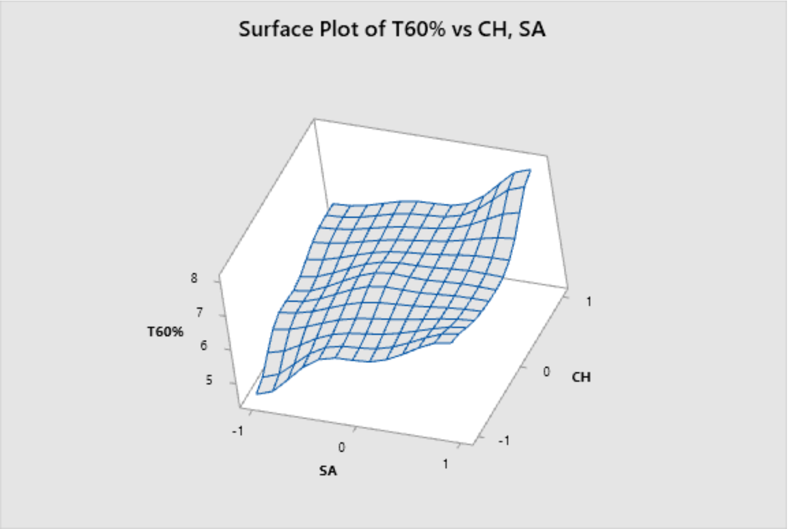

Fig. (9). Response surface plot for $T_{60\%}$ drug release (Y_2).

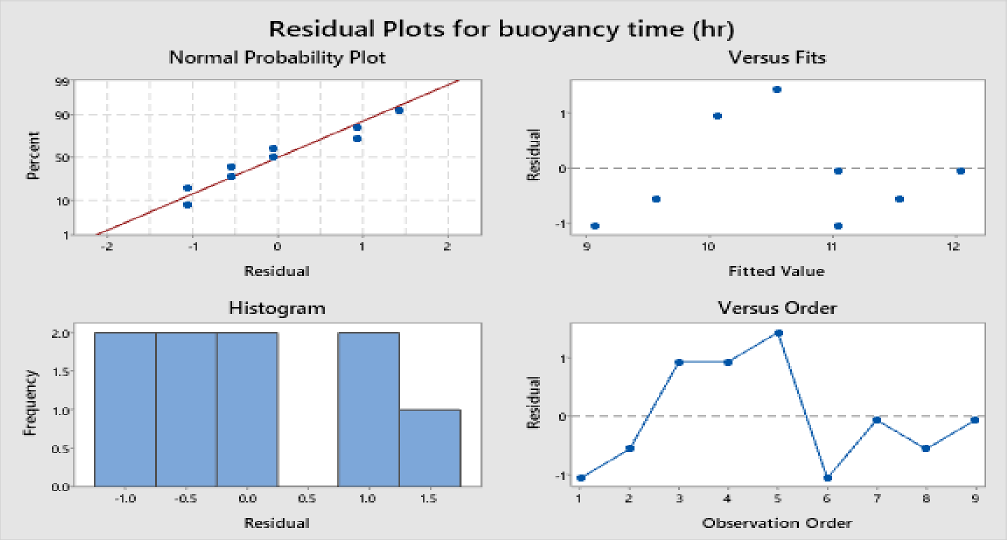

Fig. (10). Durbin-watson residual plots for buoyancy time (Y_1).

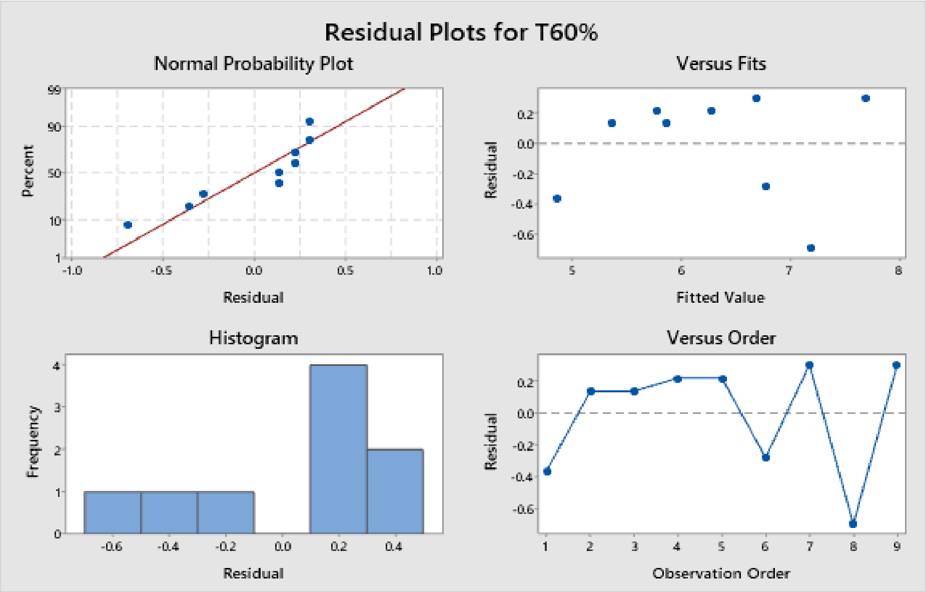

Fig. (11). Durbin-Watson residual plots for $T_{60\%}$ drug release (Y_2).

Table 4. Residual data for Y_1 and Y_2 responses.

Formulation Code	Actual Buoyancy (Y_1) (Hours)	Predicted (Hours)	Residual	Actual $T_{60\%}$ (Y_2) (Hours)	Predicted (Hours)	Residual
F1	8.00	8.75	-0.75	4.50	4.75	-0.25
F2	9.00	9.75	0.75	5.50	6.00	-0.50
F3	11.00	11.50	-0.50	6.00	6.75	-0.75
F4	11.00	11.75	-0.75	6.00	6.00	0.00
F5	12.00	12.25	-0.25	6.50	6.25	0.25
F6	10.00	10.50	0.50	6.50	6.75	-0.25
F7	11.00	11.75	0.75	7.00	6.75	0.25
F8	11.00	11.50	-0.50	6.50	7.00	-0.50
F9	12.00	12.25	-0.25	8.00	7.75	-0.25

Table 5. Formulation Parameters for Gastroretentive PEC Matrix Tablets of CPT as per Taguchi 3(2) Factorial Design for F1-F9.

Formulation Code	Buoyancy Time *(Y_1) (Hours)	Lag Time* (min: sec)	$T_{60\%}$ *(Y_2) (Hours)	$T_{90\%}$* (Hours)
F1	8.00±1.12	4.00±0.50	4.50±0.52	8.00±1.71
F2	9.00±0.89	4.26±0.76	5.50±0.69	9.00±1.96
F3	11.00±1.12	4.30±0.57	6.00±0.67	11.00±0.89
F4	11.00±0.91	6.50±0.50	6.00±1.76	11.00±1.02
F5	12.00±0.73	6.33±0.28	6.50±0.99	12.00±0.92
F6	10.00±1.73	7.83±0.76	6.50±0.64	10.00±0.89
F7	11.00±1.40	5.50±0.50	7.00±0.89	11.00±0.74
F8	11.00±1.64	6.10±0.28	6.50±0.76	11.00±0.99
F9	12.00±1.02	9.10±1.75	8.00±0.73	12.00±0.69

Note: *n=3, mean ± SD.

3.6. Study of Lag and Buoyancy Time Estimation

Buoyancy time for formulations F1-F9 ranges from 8-12 hours (Table **5**). The possible reason for buoyancy to the formulation is the nature of the biopolymer used. HPMC leads to the early hydration of the formulation which causes the development of hydrogel on the outer layer of the PEC tablet. Further, the addition of CH and SA leads to the expansion of the polymeric structure after exposure to the dissolution medium (0.1 M HCl; pH 1.2). Sodium bicarbonate reacts with HCl and leads to the alkali-acid reaction which ultimately leads to the development of porosity at the outer surface. This whole phenomenon leads to the lower density of the formulation and remains buoyant at the upper surface of the dissolution medium. The lag time ranges from 4-9 minutes, a low lag time is very important for achieving gastro retention.

3.7. Drug Release Studies using USP type II Dissolution Apparatus

In vitro drug release was performed in 0.1 M HCl (pH 1.2) using USP type II apparatus. From formulation F1 there was a burst release of CPT, about 39%, 57%, and 93% of CPT was released at the end of the 1st, 4th, and 8th hour (Fig. **12**). From formulation F2, the release of CPT was sustained and about 27%, 41%, 62%, and 96% of CPT was released at the end of 1st, 3rd, 6th, and 9th hr. This difference in drug release from formulations F1 and F2-was significant ($p<0.05$) and could be attributed to the presence of SA (-1) in the PEC formulation (F2). SA provides facilitation of gelation between CH and HPMC K100M by providing them adequate exposure to an acidic dissolution medium (0.1 M HCl). This has resulted in increased gelation in the case of formulation F1 leading to retarded CPT release. HPMC K100M was kept constant in all the formulations. The possible reason behind this concept is to bring the initial stage of hydration to the formulation. This leads to the development of a gelatinous structure at the outer surface which retards the diffusion of CPT before the development of *in situ* PEC between SA and CH after interacting with the dissolution medium (0.1 M HCl; pH 1.2) [8].

Formulations F3 and F4 showed 71% and 80% retardation of CPT release, respectively from the PEC matrices at the end of the 9th hour (Fig. **12**). The release profile of F3 and F4 formulations was significantly different from formulations F1 and F4 (p=0.00012 and p=0.00016 respectively). This type of release pattern is attributed to the ratio of CH: SA used in the formulation. As the levels of CH increase (formulation F4) a number of amino groups also increases and binds to the anionic carboxyl group of SA. This leads to intra and interchain hydrogen bonding formation of PEC which retards the release of CPT from PEC polymeric matrix. Formulations F5 showed 23%, 59%, and 98% release of CPT at the end of the 1st, 6th, and 12th hour, respectively. In this case, the retardation of CPT release was increased up to 12th hour. This type of phenomenon is attributed to the increased level of CH and SA (-1 and -1) as compared to formulation F4. Formulation F6 showed 34%, 53%, and 95% release of CPT at the end of 3rd, 6th, and 10th hour, respectively (Fig. **13**). Increasing the levels of CH and SA leads to the increased thickness of the hydrogel layer at the outer surface of formulation and retards the CPT release. Formulation F6 was statistically different from formulation F5 (p=0.00011).

In the case of formulations F7, F8 & F9, +1 level of CH was used in comparison to formulations F1, F2 & F3. From formulations F7, F8 and F9, CPT release was retarded from the PEC matrix and was comparable to formulations F1, F2, and F3. From formulations F7-F9, there was no burst release of CPT was observed (Fig. **14**). This could be attributed to an increase in the concentration of CH in the polymer matrix which results in more interaction with SA and may form hydrogen bonds that would retard the release of CPT [21]. In all the formulations the concentration of HPMC K100M was kept constant. The concept of keeping concentration constant is attributed to the bringing of early hydration over the PEC-CPT tablet and initially prevents burst release of the CPT.

As the pH increases/intestinal pH degradation of CPT takes place from the formulations (F1-F9) (Fig. **15**). The similar concept was also reported by authors Anaizi *et al.*, 1993 [22]. The possible reason behind this is being a weak base (pKa=9.55) due to its thiol-containing group. When it comes in contact with the basic environment (intestinal pH; small- large intestinal pH 6.8-7.4) the pseudo degradation process takes place and affects bioavailability [22 - 24]. Complete degradation (approximately 95-99%) of CPT from the formulation takes place within 3 hours of the study. %

Dissolution efficiency was calculated at 95% CI (with respect to the total area) (Table **6**) in formulations F1-F9 which was carried out in 0.1 M HCl (pH 1.2) it was found that increasing the levels of polymers helps in retardation and slow diffusion of CPT from the matrices.

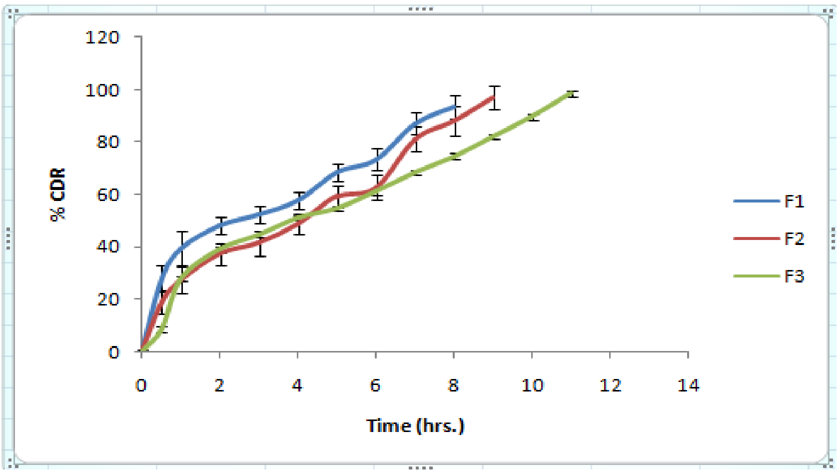

Fig. (12). Drug release profile of formulation F1-F3 (n=3 ± S.D).

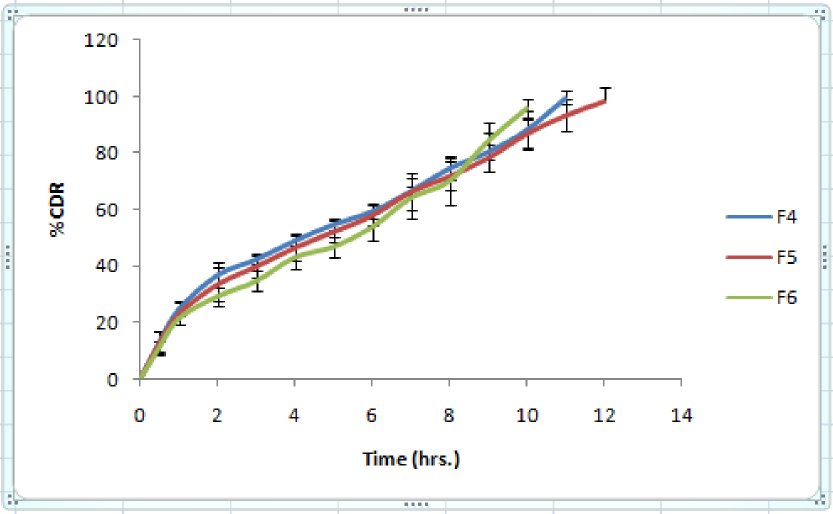

Fig. (13). Drug release profile of formulation F4-F6 (n=3 ± S.D).

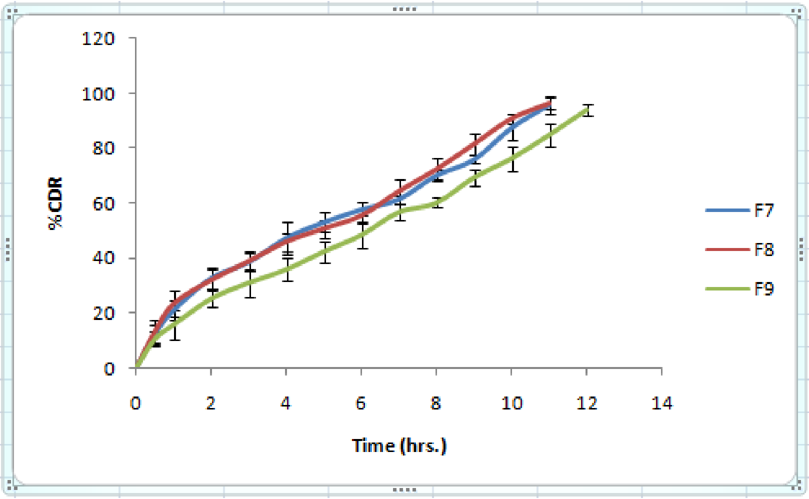

Fig. (14). Drug release profile of formulation F7-F9 (n=3 ± S.D).

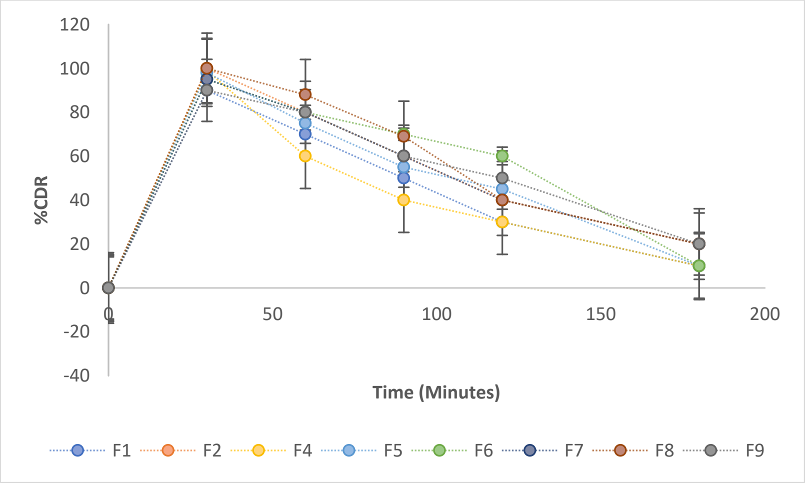

Fig. (15). Drug release profile of formulation F4-F6 at intestinal pH 6.8 (n=3 ± S.D).

Table 6. Determination of % dissolution efficiency for formulation F1-F9.

Formulation Code	Total Area	% Dissolution Efficiency ($DE_{60\%}$) *	Std. Error	95% Confidence Interval	%Area
F1	301.0	98.17	8.196	284.9 to 317.1	100.0
F2	529.8	99.76	31.11	468.8 to 590.7	100.0
F3	622.2	94.13	39.96	543.9 to 700.5	100.0
F4	270.2	99.56	5.958	258.5 to 281.8	100.0
F5	395.7	99.34	6.608	382.7 to 408.6	100.0
F6	320.3	96.78	5.809	308.9 to 331.7	100.0
F7	259.5	99.10	5.050	249.6 to 269.4	100.0
F8	311.8	99.50	6.564	299.0 to 324.7	100.0
F9	431.3	99.01	6.035	419.5 to 443.2	100.0

Note: *Significant difference in cumulative percent drug release, applied *vs.* each formulation by univariate ANOVA, $p<0.05$.

Table 7. Determination of R^2 and AIC value.

Formulation Code	R^{2*}		n value	AIC*	
	Zero Order	First Order		Zero Order	First Order
F1	0.9124	0.4571	1.84	13.07	74.13
F2	0.9705	0.5588	1.92	38.89	44.90
F3	0.9519	0.5635	1.98	23.56	35.89
F4	0.9663	0.5626	1.92	32.93	43.15
F5	0.9767	0.5783	1.91	34.65	38.92
F6	0.9791	0.6257	1.97	47.89	73.89
F7	0.9725	0.5868	1.93	34.71	65.89
F8	0.9794	0.5870	1.92	38.90	58.83
F9	0.9908	0.6519	1.95	42.44	48.25

Note: *Determined for first 60% CPT release.

3.8. Drug Release Kinetics and AIC Value Determination

The R^2 values of all the formulations F1 to F9 were analyzed by fitting the dissolution data into various kinetic models. The R^2 value was found to be higher for formulations F1-F9, which indicated a zero-order release (Table **7**). Obtained results of zero-order kinetics indicate drug release is independent of drug concentration in the PEC-CPT formulations. The zero-order mechanism suggests that formulation will have minimal side effects [8]. On the other hand, formulations F1-F9 follow the super case II transport mechanism which is described by the movement of solvent penetration into the CH-SA matrix. The speed of solvent penetration in the matrix is much greater than the swelling of the CH-SA-HPMC K100M matrix, with this being the rate-limiting factor in the CPT release.

Table 8. Stability data of optimized formulations.

Formulation Code	Drug Content (%) *	Drug Release (%) *	Time of Drug Release (Hour)	Buoyancy Time (Hour)	Lag Time (min: sec)	Similarity Factor (f_2)
F5						
0 Months	97.89±1.21	98.45±1.77	12	12	6.00	78.90
03 Months	98.99±1.00	99.81±1.88	12	12	6.33	79.90
06 Months	97.43±1.89	97.89±1.78	12	12	6.54	77.89
09 Months	98.51±1.76	98.23±1.99	12	12	6.98	78.19
12 Months	99.88±1.87	98.67±0.87	12	12	6.44	79.54
F9						
0 Months	95.66±0.99	93.54±1.55	12	12	9.01	84.63
03 Months	95.89±1.88	94.00±1.27	12	12	9.89	83.92
06 Months	96.31±1.33	93.39±1.79	12	12	8.99	85.90
09 Months	95.78±1.25	93.65±1.65	12	12	9.00	84.73
12 Months	95.11±0.87	93.51±1.55	12	12	9.05	84.90

Note: *All determinations were carried out in triplicate n=3, ± S.D.

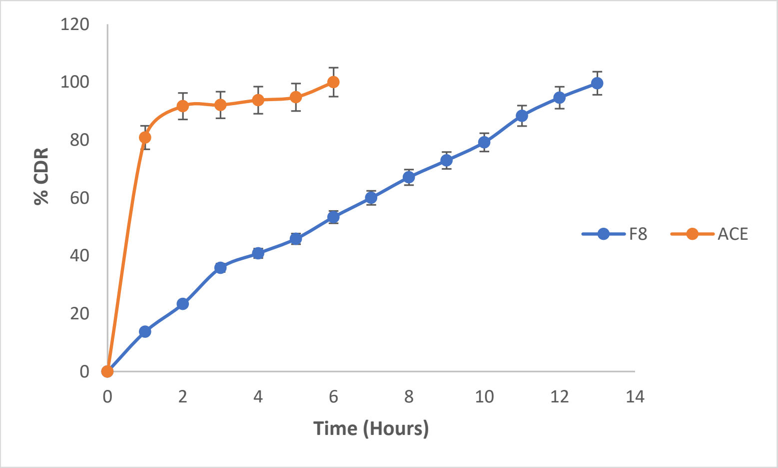

Fig. (16). Comparison of dissolution profile of formulation F8 *vs.* innovator product.

Apart from R^2 values determination AIC values were also determined by using Kinet DS v3.0 software. AIC values also depict that formulations F1-F9 follow the zero-order kinetics. The kinetics model with the smallest value AIC was regarded as a best-fit model.

3.9. Stability Studies of Optimized Formulations

After conducting the stability studies as per ICH guidelines, statistical analysis of the results for formulations F5 and F9 was carried out by using one-way ANOVA stored for different periods. No significant difference ($p > 0.05$) was observed in the drug release and drug content for stability studies formulations F5 and F9 when compared with initial formulations (F5 and F9). Similarity factor **(**$f2$**)** was also determined for comparison of dissolution profiles F5 and F9 for initial and aged formulations the value was found higher (≥ 50) (Table **8**). A higher similarity factor indicates more similarity between the initial sample and the aged sample dissolution curve. Above all finding suggests that CPT-PEC formulations were found stable during stability studies.

3.10. Estimation of Fit Factors

The observed values of f_2 and f_1 were found to be 26.25 and 20.94, respectively. Calculated t-value is greater than the tabulated value ($T_{cal.} = 4.50$, $T_{crit.} = 2.44$ and Degree of Freedom (DF) = 06). This indicates a significant difference between marketed products and optimized tablet formulations (Fig. **16**) (F8). From this, it can be considered that the developed formulation is better than the marketed product of CPT.

CONCLUSION

This research work is carried out to constitute the suitability and potential of polyelectrolyte complex as a promising technique for sustained-controlled release delivery of the highly aqueous soluble drug Captopril. Over the past few years, Chitosan-Sodium Alginate based PEC, has been gaining increased attention from the researcher. In the present study, CH-SA based *in situ* forming PEC were successfully optimized and developed to retard the Captopril release from gastroretentive CPT tablets. The prepared batch of PEC tablets showed good physical stability. The DSC studies confirmed the *in-situ* charge interaction between $NH3^+$ of Chitosan molecule and -COO$^-$ of Sodium Alginate is responsible for *in situ* PEC formation. The developed system exhibited a potential for sustaining the release of highly aqueous soluble drugs.

LIST OF ABBREVIATIONS

PEC = Polyelectrolyte Complex
IPN = Interpenetrating Network
CPT = Captopril
CH = Chitosan
SA = Sodium Alginate
HPMC K100 M = Hydroxypropyl Methylcellulose K100 M
TG = Thermo Gravimetric Analysis
DSC = Differential Scanning Calorimetry
DTG = Derivative Thermo Gravimetric Analysis
M = Molar
HCl = Hydrochloric Acid
S.D = Standard Deviation
AIC = Akaike Information Criteria
RSM = Response surface methodology
Rpm = Rotation per minute
LSIF = Liquid State Interaction of formulation

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No animals/humans were used in the study which is the base of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

All the data and supporting information is provided within the article.

CONFLICT OF INTEREST

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

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