ORIGINAL ARTICLE

Factorial Design Assisted pH-independent Delivery System of Poorly Soluble Drug Cinnarizine

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Abstract

Aim: This study aims to overcome pH-dependent solubility, a common problem observed in poorly soluble BCS (biopharmaceutics classification system) Class II drugs. **Materials and Methods:** A model drug, cinnarizine, was selected for the study to formulate oral multiunit pH-independent delivery system utilizing mucoadhesion as an intestine retention technique. Microenvironment pH modulation mechanism was utilized to ensure pH-independent delivery at varying gastric fluid pH conditions. The formulation was developed in the form of modified release capsule, comprising three components (i) fast dissolving granules, (ii) multilayer alginate beads (AB), and (iii) erodible capsule plug (EP). Fast dissolving granules were formulated by trial and error method. Other two components were optimized by applying 3 × 2 full factorial design. Independent variables selected for AB were HPMC K4M and Noveon® AA-1 while that of EP were HPMC K100LV and Polyox® 303 WSR. Dependent variables selected for AB were percentage drug release at 2 h (Q_{2h}), 4 h (Q_{4h}), 8 h (Q_{8h}) and mucoadhesion potential. For EP, dependent variables were erosion time, floating lag time and total floating time. Surface pH of multilayer AB was measured at regular time interval to ascertain acidic microenvironment. **Results and Discussion:** Optimized components were filled into Eudragit® L 100-55 coated hard gelatin capsule body. Optimized capsule formulation (OP) was characterized by relevant evaluation parameters, pH-independent drug release, and stability study. *In vitro* drug release profile of OP showed pH-independent release and followed Weibull release kinetic model. **Conclusion:** Drug delivery of pH-dependent poorly soluble drug to upper GI tract was successfully formulated to overcome problem of pH-dependent solubility.

Key words: Cinnarizine, intestine retention, microenvironment pH, pH-independent release, response surface methodology

INTRODUCTION

Oral drug delivery in the form of conventional dosage forms is being adopted since long. Formulating drug as conventional dosage forms is economical and patient compliant practice. Among them, solid oral dosage forms account to cover major market share owing to their versatility.[1,2] Formulating drug as immediate release dosage forms may face some pharmaceutical and clinical problems due to their different physicochemical properties. Hence, to attain optimum clinical performance of such drugs, they are formulated as modified release (MR) dosage forms. Besides, patient compliance and efficacy improvement also account for formulating such dosage forms.[3,4]

Biopharmaceutics classification system (BCS) classifies drugs according to their solubility and permeability.[5] Poorly soluble and highly permeable drugs fall under BCS Class II, which comprises major portion of the system.[6] Dissolution being rate limiting step for BCS Class II drugs,

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formulating them as MR dosage form produces many formulation and development challenges. Poor solubility, pH-dependent solubility, incomplete drug release to name a few.[7,8]

In this study, formulation and optimization of MR dosage form of poorly soluble BCS Class II drug cinnarizine (CNR) were carried out. CNR is an antihistamine, mainly prescribed to treat nausea and vomiting associated with motion sickness, vertigo, Meniere's disease or Cogan's syndrome.[9] It is marketed as immediate release dosage form which needs frequent administration due to short half-life (3-6 h). Besides it shows pH-dependent solubility, i.e. high solubility at low pH and *vice versa* and hence gastric acidity dependent bioavailability.[10] Considering its physicochemical properties, it should be delivered in stomach fluid (at lower pH). But being a weakly basic drug, it exists chiefly in ionized form at gastric pH (>99% at pH 1.2), which is not absorbed by passive diffusion according to the pH-partition theory.[11] Moreover, it precipitates out while transferring from stomach (low pH) to intestine (high pH), which are difficult to dissolve at higher pH.[12] An MR delivery system was developed to overcome these challenges by pH-independent sustained drug delivery targeted to the upper GI tract. Mucoadhesive alginate beads (ABs) with microenvironment pH (pH_M) modulation technique were filled in enteric coated capsule body separated by the erodible plug. Thus, delivering two sustained doses separated by an interval of approximate 10 h. Initial burst release to compensate slow sustained release up to 2 h was delivered by fast dissolving granules.

MATERIALS AND METHODS

Materials

Cinnarizine was gifted by FDC Ltd., Roha, India. HPMC K4M, HPMC K100LVand Polyox® 303 WSR were received as gift samples from Colorcon Pvt. Ltd., Goa, India. Noveon® AA-1 was received from Lubrizol Ltd., Mumbai, India. Citric acid, fumaric acid, and sodium bicarbonate were purchased from ASES chemical works, Jodhpur, India. Effer-soda® was obtained from SPI Pharma Inc. India. All other ingredients were of analytical grade.

Methods

Preparation of fast dissolving granules

Ingredients listed in Table 1 (except polyvinylpyrrolidone [PVP] K-30) were sifted (#40 mesh) and blended for 10 min in a double cone blender (Sheetal Scientific Industries: Mumbai, India). The blend was granulated using PVP K-30 solution in isopropyl alcohol. Granules were passed through #20 sieve.

Preparation of erodible capsule plug (EP)

Excipients listed in Table 2 were sifted (#40 sieve) and blended for 10 min in a double cone blender. Powder blend was compressed using 8 mm round shaped flat punches. Optimized formulation was derived by applying a 3 × 2 full factorial design on two independent factors $X1_{EP}$ (HPMC K100LV) and $X2_{EP}$ (polyox® 303 WSR). The layout of factorial batches EP1 - EP9 and corresponding checkpoint batches are presented in Table 3.

Preparation of multilayer alginate beads (AB)

Core sodium AB containing acidifier (30% w/w fumaric acid) was prepared by ionic gelation method using 20 G syringe. Core beads (#20 sieve) were layered using powder blend of solid components listed in Table 4 using a fabricated spheronizer [Figure 1]. The composition of powder blend

Table 1: Composition of fast dissolving granules

Ingredient	Amount
CNR	15
PVP K-30	2.5
SSG	5
Talc	1
Lactose	q.s. 40

CNR: Cinnarizine, PVP: Polyvinylpyrrolidone, SSG: Sodium starch glycolate

Table 2: Composition of EP

Ingredient	Amount
HPMC K100LV	40-60
Polyox® 303 WSR	30-50
Effer-soda®	28
Citric acid	20
Magnesium stearate	0.8
Ludipress®	q.s. 170

EP: Erodible capsule plug

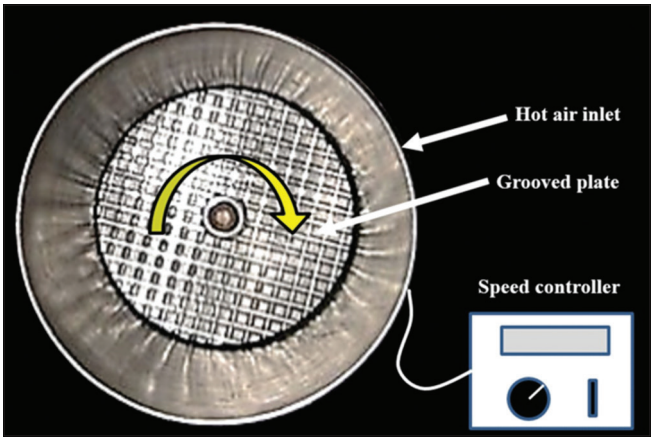

Figure 1: Fabricated spheronizer (groove size=2 mm, plate diameter=6 cm)

Table 3: Factorial batches layout and responses for EP and AB

Batch code	Coded values		Factorial responses (n=3)						
	$X1_{EP}/X1_{AB}$	$X2_{EP}/X2_{AB}$	$R1_{EP}$	$R2_{EP}$	$R3_{EP}$	$R1_{AB}$	$R2_{AB}$	$R3_{AB}$	$R4_{AB}$
EP1/AB1	−1	−1	5.7±0.2	1.6±0.2	5.1±0.1	30.7±1.2	52.8±3.2	100±4.0	46±3
EP2/AB2	−1	0	6.0±0.1	2.2±0.1	5.9±0.1	29.3±0.8	50.0±2.2	99.7±3.2	59±2
EP3/AB3	−1	+1	7.5±0.3	3.9±0.1	7.0±0.3	27.1±1.1	47.4±2.0	98.4±2.7	67±3
EP4/AB4	0	−1	7.0±0.3	3.5±0.2	6.8±0.4	27.0±0.9	48.2±1.8	98.3±2.0	62±3
EP5/AB5	0	0	7.7±0.3	5.4±0.2	7.5±0.3	25.4±1.4	45.1±1.7	96.7±3.1	75±4
EP6/AB6	0	+1	8.2±0.2	7.2±0.3	7.9±0.2	23.1±0.7	42.8±1.9	94.9±3.3	81±1
EP7/AB7	+1	−1	8.7±0.2	6.7±0.4	8.5±0.1	22.5±0.6	43.5±1.5	95.3±2.1	67±0
EP8/AB8	+1	0	9.0±0.1	8.5±0.3	9.2±0.4	20.4±0.8	40.1±0.9	92.1±2.5	77±3
EP9/AB9	+1	+1	9.5±0.4	9.2±0.4	9.7±0.2	18.2±1.1	37.3±1.0	89.4±1.7	85±2
$CHK1_{EP}/CHK1_{AB}$	+0.77/-0.11	−0.21/−0.26	8.5±0.1	7.2±0.04	8.3±0.12	25.8±1.0	49.1±1.4	95.4±2.2	67.0±1.5
$CHK2_{EP}/CHK2_{AB}$	−0.35/+0.95	−0.10/+0.55	7.7±0.1	4.5±0.03	7.5±0.05	20.0±0.9	38.2±0.4	94.0±1.7	84.0±2.5
Translation of coded level in actual units									
Coded level				−1		0		+1	
$X1_{EP}$-HPMC K100LV (mg)				40		50		60	
$X2_{EP}$-Polyox® 303WSR (mg)				30		40		50	
$X1_{AB}$-HPMC K4M (mg)				80		100		120	
$X2_{AB}$-Noveon® AA-1 (mg)				30		50		70	

EP: Erodible capsule plug, AB: Alginate beads

Table 4: Composition of drug coating layer

Ingredient	Amount (mg)/1 g solid
CNR	500
Fumaric acid	120
HPMC K4M	80-120
Noveon® AA-1	30-70
Talc	50
MCC	q.s. 1000

CNR: Cinnarizine, MCC: Microcrystalline cellulose

was optimized by applying a 3 × 2 full factorial design selecting two ingredients $X1_{AB}$ (HPMC K4M) and $X2_{AB}$ (Noveon® AA-1) as independent factors. Factorial batches AB1-AB9 and checkpoint batches $CHK1_{AB}$ and $CHK1_{AB}$ composition are presented in Table 3. Inlet air temperature was set at 60°C. Spheronizer was loaded with core AB and rotated at 200 rpm. Hot air was supplied from the bottom to partially fluidize the bed. A cycle of solvent (ethanol: water:PG - 65:30:05) spray and powder blend layering was repeated at an appropriate interval avoiding aggregation or adhesion of beads by adjusting speed between 100 and 300 rpm throughout the process. The process was run up to weight gain of 200% of the uncoated core weight. These coated beads were further coated with coating solution (Opadry® enteric (94 series) polymer: HPMC E50 (5:0.5) solution in ethanol: water (80:20) up to weight gain of 10% of the uncoated core weight in a fluid bed processor (Cronimach Machinery, Ahmedabad, India).

Preparation of multiunit capsules

Multiunit capsule batches were prepared by filling components of corresponding factorial batch, i.e., multiunit capsule batch FF1 = EP1 + AB1. Enteric coated (Opadry® enteric 94 series; 5% w/v in 90%v/v ethanol: water solvent; coated up to 7% weight gain) hard gelatin capsule (size 00) body was filled with one part of AB (equivalent to 40% of total drug), followed by EP. The second part of AB (equivalent to 40% of total drug) and fast-dissolving granules (equivalent to 20% of total drug) were filled to the body and closed with uncoated cap. It was stored for further characterization.

Characterization of multiunit capsules

Physical characterization

Prepared multiunit capsules were evaluated for uniformity of weight (n = 10) and assay (n = 10). Capsule components AB and fast dissolving granules were characterized by flow properties (angle of repose) measured using fixed funnel method.[13]

Erosion time, floating lag time, and total floating time

These tests were performed simultaneously with *in vitro* drug release study of corresponding batch of multiunit capsules. Time required to start floating was considered as floating lag time. Period up to which the capsule remained buoyant was taken as total floating time. Time taken to

expose second part to the dissolution media was considered as erosion time.

Mucoadhesion potential test

It was performed for uncoated AB. Previously reported modified test apparatus was used for the test.[14] Mucoadhesion potential was measured as adhering percentage at 8 h.

Surface pH of multilayer AB

Acidic pH of microenvironment was measured by surface pH microelectrode (Phoenix Technologies Ltd., U.K.) at specified interval during dissolution test. pH <4 was set as required criteria to ensure pH-independent release of the drug.

In vitro drug release study

To produce more bio-relevant dissolution environment, the study was conducted using modified multicompartment dissolution apparatus [Figure 2]. Minor modifications were done in originally developed apparatus for floating dosage form of CNR.[15] Dissolution test parameters were set as follows:

- Test parameters:
  - Dissolution media
    - Stomach compartment reservoir (A): 0.1 N HCl solution
    - Intestine compartment reservoir (B): pH 6.8 phosphate buffer
    - Stomach compartment (C): 90 ml 0.1 N HCl solution
    - Intestine compartment (D): 450 ml pH 6.8 phosphate buffer.
  - Rotating speed = 100 rpm (both compartments)
  - Temperature: 37 ± 0.5°C
  - Flow rate
    - A to C, B to C, C to D - 2 ml/min
    - D to E - 4 ml/min.
  - Beads transfer rate (C to D): Half of the beads released in first part after 1 h and remaining half after 2 h of release; repeated after second part released
  - Sampling interval: 10 min, 20 min, 30 min, 1 h, 2 h, every 2 h up to 12 h, every 4 h up to 24 h (sampling from all the three compartments - C, D and E)

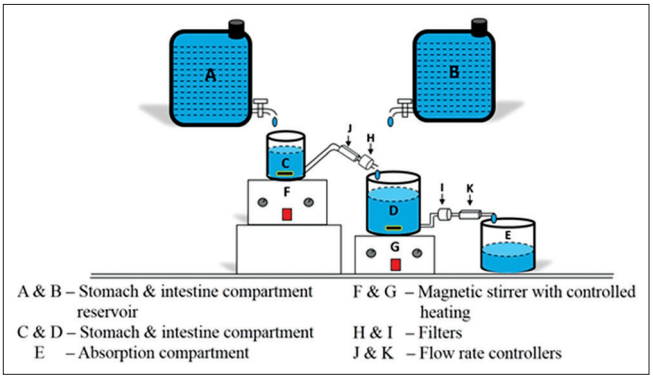

Figure 2: Modified multicompartment dissolution apparatus

- Sample analysis: UV spectroscopy analysis (UV-1800 UV-VIS spectrophotometer, Shimadzu, Japan) at λ = 254 nm.

In vitro drug release kinetics

In vitro drug release data of OP were analyzed using different kinetic equations: Zero-order, first-order kinetics, Higuchi, Hixon-Crowell, Korsmeyer-Peppas, and Weibull kinetic models.[16,17]

Effect of pH on drug release

In vitro drug release test of OP was carried out at two different pH (pH 1.2 and pH 3.0) of stomach compartment fluid. The similarity between drug release profiles was compared using similarity factor f2.[18]

RESULTS

Preparation and optimization of EP

Responses of factorial batches [Table 3] were analyzed using response surface methodology. ANOVA was applied to derive statistical models of each responses using Design expert® software (Version 7, Stat-Ease Inc.: Minneapolis, USA). Full and reduced (significance level 5%) statistical models derived for responses $R1_{EP}$, $R2_{EP}$, and $R3_{EP}$ are shown in Equation 1A-1C and Equation 2A-2C, respectively. Corresponding response surface plots and overlay plot are shown in Figure 3. Derived equations were validated using checkpoint batches [Table 5].

$$R1_{EP}=7.5+1.5X1+0.6X2-0.25X1X2+0.1X1^2+0.2X2^2+0.05X1^2X2-0.25X1X2^2 \quad (1A)$$

$$R2_{EP}=5.38+3.15X1+1.85X2+0.05X1X2-0.017X1^2-0.017X2^2-0.65X1^2X2-0.55X1X2^2 \quad (1B)$$

$$R3_{EP}=7.42+1.65X1+0.65X2-0.18X1X2+0.17X1^2-0.033X2^2+0.22X1^2X2-0.12X1X2^2 \quad (1C)$$

$$R1_{EP}=7.7+1.33X1+0.63X2 \quad (2A)$$

$$R2_{EP}=5.36+3.15X1+1.85X2+0.05X1X2-0.65X1^2X^2-0.55X1X2^2 \quad (2B)$$

$$R3_{EP}=7.51+1.57X1+0.7X2 \quad (2C)$$

Preparation and optimization of AB

Optimization of AB was performed in a similar manner to optimization of EP. Full and reduced models derived for responses $R1_{AB}$, $R2_{AB}$, $R3_{AB}$ and $R4_{AB}$ [Table 3] are shown

in Equation 3A-3D and Equation 4A-4D, respectively. Corresponding response surface plots are represented in Figure 4. A validation of derived models was performed using checkpoint batches [Table 5]. Derived equations were validated using checkpoint batches [Table 5].

$$R1_{AB}=25.34-4.45X1-1.95X2-0.18X1X2-0.47X1^2-0.27X2^2-0.025X1^2X2+0.18X1X2^2 \quad (3A)$$

$$R2_{AB}=45.19-4.95X1-2.7X2-0.2X1X2-0.18X1^2+0.27X2^2-0.2X1^2X2+0.1X1X2^2 \quad (3B)$$

$$R3_{AB}=96.71-3.8X1-1.7X2-1.08X1X2-0.82X1^2-0.12X2^2-0.17X1^2X2+0.38X1X2^2 \quad (3C)$$

$$R4_{AB}=74.22+9.0X1+9.5X2-0.75X1X2-5.83X1^2-2.33X2^2+0.25X1^2X2+0.75X1X2^2 \quad (3D)$$

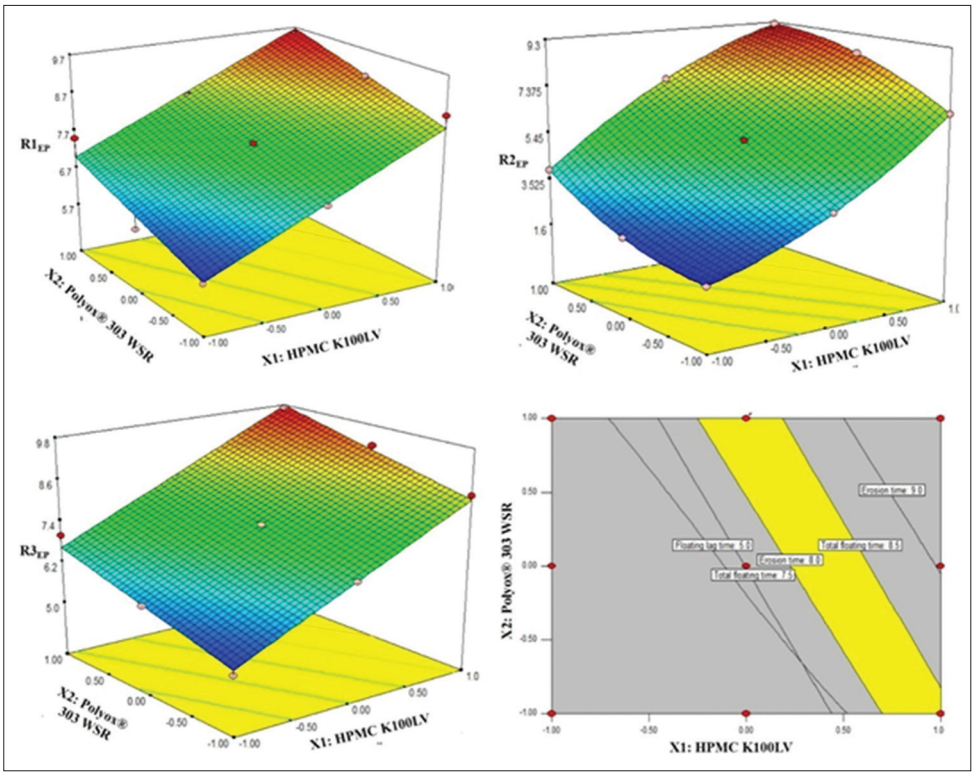

Figure 3: Response surface plots and overlay plot for optimization of erodible capsule plug

Table 5: Validation of statistical models using checkpoint batches

Capsule component	Response	Checkpoint batch	Experimental value±SD (n=3)	Predicted value	Relative error %
EP	$R1_{EP}$	$CHK1_{EP}$	8.5±0.1	8.6	1.2
		$CHK2_{EP}$	7.7±0.08	7.4	4.1
	$R2_{EP}$	$CHK1_{EP}$	7.2±0.04	7.4	2.7
		$CHK2_{EP}$	4.5±0.03	4.5	0.0
	$R3_{EP}$	$CHK1_{EP}$	8.3±0.12	8.6	3.5
		$CHK2_{EP}$	7.5±0.05	7.2	4.2
AB	$R1_{AB}$	$CHK1_{AB}$	25.8±1.0	26.8	3.7
		$CHK2_{AB}$	20.0±0.9	19.6	2.0
	$R2_{AB}$	$CHK1_{AB}$	49.1±1.4	47.2	4.0
		$CHK2_{AB}$	38.2±0.4	39.1	2.3
	$R3_{AB}$	$CHK1_{AB}$	95.4±2.2	97.5	2.2
		$CHK2_{AB}$	94.0±1.7	91.2	3.1
	$R4_{AB}$	$CHK1_{AB}$	67.0±1.5	69.2	3.2
		$CHK2_{AB}$	84.0±2.5	82.6	1.7

EP: Erodible capsule plug, AB: Alginate beads

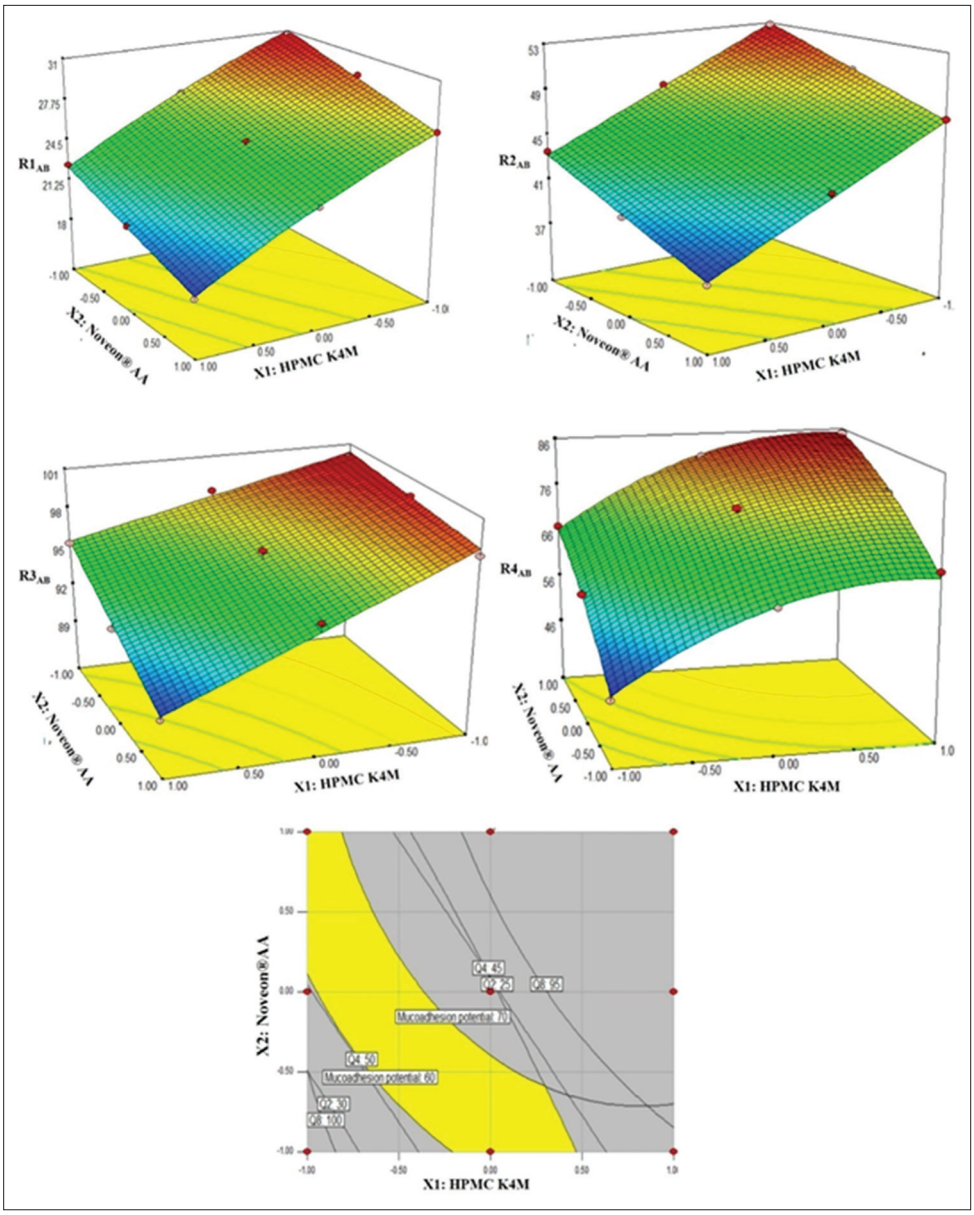

Figure 4: Response surface plots and overlay plot for optimization of AB

$$R1_{AB}=25.17-4.33X1-1.97X2-0.47X1^2 \quad (4A)$$

$$R2_{AB}=45.24-4.88X1-2.83X2 \quad (4B)$$

$$R3_{AB}=96.09-3.55X1-1.82X2-1.08X1X2 \quad (4C)$$

$$R4_{AB}=74.22+9.5X1+9.67X2-5.83X1^2-2.33X2^2 \quad (4D)$$

Characterization of multiunit capsules

Physical characterization results of multiunit capsule batches are shown in Table 6. The content of active ingredient and uniformity of weight of all the batches followed pharmacopoeia requirements. Fast dissolving granules revealed good flow properties, while flow properties of component AB of all the batches were excellent.

Erosion time, floating lag time, and total floating time of EP were measured simultaneously with *in vitro* drug release study of multiunit capsule. Results of corresponding factorial batches are represented in Table 3. *In vitro* drug release profiles of factorial batches of multiunit capsule and optimized batch OP are presented in Figure 5a-d.

Mucoadhesion potential of the factorial batches of AB is presented in Table 3. It was affected by the combined effect of HPMC K4M and Noveon® AA-1, the latter being major effector. Surface pH of multilayer AB was maintained below pH 4, ensuring acidic pH_M throughout the drug release.

Parameters derived by the model fitting of *in vitro* drug release profile of OP in different release kinetic models are listed in Table 7. Release exponent n derived from Korsmeyer-Peppas kinetic equation was 0.494.

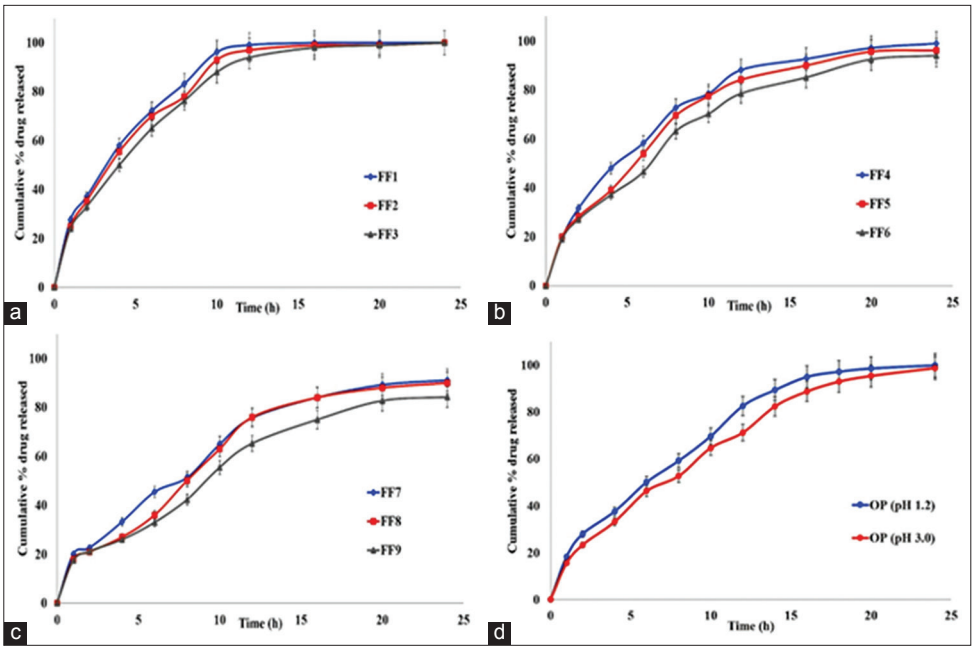

Figure 5: *In vitro* drug release profiles of factorial batches (a) F1-F3, (b) F4-F6 and (c) F7-F9 of multiunit capsule and of (d) OP at two different pH

Table 6: Physical characterization of multiunit capsule

Batch code	Assay (%)	Uniformity of weight (mg)	Angle of repose (θ) (*n*=3)	
			Granules	AB
FF1	98.2	777.1±20.3	33.1±2.5	26.4±3.2
FF2	99.7	783.5±15.5	33.1±2.5	27.2±2.1
FF3	98.3	781.1±21.2	33.1±2.5	25.0±3.7
FF4	100.2	775.3±27.7	33.1±2.5	26.1±1.9
FF5	97.4	785.4±31.5	33.1±2.5	24.8±2.0
FF6	99.8	772.6±17.7	33.1±2.5	26.0±1.1
FF7	101.6	778.0±20.2	33.1±2.5	25.5±1.7
FF8	102.3	783.9±29.4	33.1±2.5	25.4±2.5
FF9	97.7	782.5±25.8	33.1±2.5	24.7±2.0

AB: Alginate beads

Table 7: Model fitting for *in vitro* drug release of OP

In vitro drug release kinetic model	R^2	SSR	*F* value
Zero order	0.7629	3978.5	306.0
First order	0.9850	250.9	19.3
Higuchi	0.9777	374.9	28.8
Korsmeyer-Peppas	0.9777	374.9	31.2
Hixson-Crowell	0.9888	188.1	14.5
Weibull	0.9922	130.5	11.9

SSR: Sum of square of residuals

Effect of pH on drug release

Similarity factor f2 between *in vitro* drug release profiles of OP measured at two different gastric pH values (i.e., pH 1.2 and pH 3.0) was above 70 [Figure 5d].

DISCUSSION

Systematic optimization of formulation components EP and AB was performed by applying the experimental design on selected variables. Statistical models derived for individual responses by performing ANOVA revealed that some of the terms were insignificant for particular response at 5% significance level ($P > 0.05$). Accordingly derived reduced models were further considered for optimization of the respective components.

Coefficients of reduced statistical models for EP revealed that both X1 and X2 exhibit positive effect on all three responses. X1 showed comparatively more prominent effect than X2.

It was concluded from the reduced statistical models of AB that both X1 and X2 exhibited a negative effect on the responses $R1_{AB}$, $R2_{AB}$, and $R3_{AB}$, while opposite effect was exhibited to the response $R4_{AB}$. Thus, the optimum level of the variables needs to be selected for desired responses.

Differences between predicted values and experimental values of responses were statistically insignificant (at 5% significance level). Thus derived statistical models proven valid for the selected levels of variables under the study.

In vitro drug release profiles revealed cumulative % drug release with time. It can be illustrated from the chart [Figure 5] that effective control over drug release could not be attained at low levels of matrix former. On the contrary, a higher amount of matrix former retarded drug release. Thus, the optimum amount of matrix former is required to be selected to get desired release profile. Dotted line OP represents the *in vitro* drug release profile of the optimized batch OP derived using response surface methodology. Higher R^2 value and *F* value revealed that *in vitro* drug release of OP followed Weibull kinetic equation. Diffusional release mechanism predicted from the release exponent n was anomalous transport (non-Fickian diffusion). pH_M modulated AB showed pH-independent release in higher pH (intestinal compartment) dissolution media. Moreover, overall release profile was not significantly ($f2 > 70$) affected by change in the pH of dissolution media of stomach compartment. It can be concluded from these finding that the drug release was pH-independent throughout the drug release study.

CONCLUSION

In this study, MR drug delivery system for pH-independent extended release of cinnarizine was developed and characterized. Systematic optimization by response surface methodology assisted to select best levels of variables. The patient compliance can be improved by reducing dosing frequency by such extended release formulation. pH_M modulation technique can be used to formulate pH-independent delivery system of poorly soluble pH-dependent drugs like cinnarizine. In the nutshell, further studies of the developed formulation can be carried out to evaluate *in vivo* performance and possible applicability to develop a drug delivery platform for similar drugs.

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