Formulation and Optimization of Controlled Release Mucoadhesive Tablets of Atenolol Using Response Surface Methodology

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ABSTRACT

The aim of the current study was to design oral controlled release mucoadhesive compressed hydrophilic matrices of atenolol and to optimize the drug release profile and bioadhesion using response surface methodology. Tablets were prepared by direct compression and evaluated for bioadhesive strength and in vitro dissolution parameters. A central composite design for 2 factors at 3 levels each was employed to systematically optimize drug release profile and bioadhesive strength. Carbopol 934P and sodium carboxymethylcellulose were taken as the independent variables. Response surface plots and contour plots were drawn, and optimum formulations were selected by feasibility and grid searches. Compressed matrices exhibited non-Fickian drug release kinetics approaching zero-order, as the value of release rate exponent (n) varied between 0.6672 and 0.8646, resulting in regulated and complete release until 24 hours. Both the polymers had significant effect on the bioadhesive strength of the tablets, measured as force of detachment against porcine gastric mucosa ($P < .001$). Polynomial mathematical models, generated for various response variables using multiple linear regression analysis, were found to be statistically significant ($P < .01$). Validation of optimization study, performed using 8 confirmatory runs, indicated very high degree of prognostic ability of response surface methodology, with mean percentage error (± SD) as −0.0072 ± 1.087. Besides unraveling the effect of the 2 factors on the various response variables, the study helped in finding the optimum formulation with excellent bioadhesive strength and controlled release.

KEYWORDS: drug delivery, bioadhesion, mucoadhesive systems, central composite design, Carbopol, carboxymethylcellulose, controlled release.

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INTRODUCTION

Oral controlled release (CR) systems continue to be the most popular ones among all the drug delivery systems.[1] Mucoadhesive delivery systems offer several advantages over other oral CR systems by virtue of prolongation of residence time of drug in gastrointestinal (GI) tract, and targeting and localization of the dosage form at a specific site.[1-4] Also, these mucoadhesive systems are known to provide intimate contact between dosage form and the absorptive mucosa, resulting thereby in high drug flux through the absorbing tissue.[1,2,5]

Atenolol, a β-blocker, is prescribed widely in diverse cardiovascular diseases, eg, hypertension, angina pectoris, arrhythmias, and myocardial infarction.[6] The drug is also frequently indicated in the prophylactic treatment of migraine. Administration of conventional tablets of atenolol has been reported to exhibit fluctuations in the plasma drug levels, resulting either in manifestation of side effects or reduction in drug concentration at the receptor site.[7,8] Accordingly, studies have been reported on regulation of drug release by formulating its diverse CR systems such as hydrophilic matrices,[9-11] osmotic pumps,[7,8,12,13] and transdermal drug delivery systems.[14]

Response surface methodology (RSM) is a widely practiced approach in the development and optimization of drug delivery devices.[15-20] Based on the principal of design of experiments (DoE), the methodology encompasses the use of various types of experimental designs, generation of polynomial equations, and mapping of the response over the experimental domain to determine the optimum formulation(s).[17,21] The technique requires minimum experimentation and time, thus proving to be far more effective and cost-effective than the conventional methods of formulating dosage forms.

The current study aims at developing and optimizing an oral mucoadhesive drug delivery system of atenolol using RSM, as it may prove to be more productive than the conventional CR systems by virtue of prolongation of drug residence time in GI tract. Further, mucoadhesive tablets of the drug would involve relatively more economical and less complicated technology vis-à-vis many other drug delivery devices such as osmotic and transdermal delivery systems. Computer-aided optimization technique, using a

central composite design (CCD), was employed to investigate the effect of 2 independent variables (factors) (ie, the amounts of 2 swellable polymers) on drug release parameters and bioadhesive strength.

Materials and Methods

Materials

Atenolol was provided ex gratia by IPCA Laboratories Ltd (Mumbai, India) and Carbopol 934P (CP) was a gift from Noveon Pharmaceuticals (Cleveland, OH). High-viscosity grade sodium carboxymethylcellulose (Na CMC) was obtained from Loba-Chemie Indoaustranat Co (Mumbai, India). Porcine gastric mucosa, for determining bioadhesive strength, was obtained from a local slaughter house in Chandigarh, India. All other chemicals employed were of analytical grade.

Methods

Preparation of Mucoadhesive Compressed Matrices

Table 1 enlists the composition of different mucoadhesive formulations prepared using varying amounts of the polymers (ie, CP and Na CMC) and dicalcium phosphate as the diluent, along with the fixed quantity of magnesium stearate as the lubricant. Drug and the excipients were homogeneously blended and subsequently compressed into flat-faced tablets (410 mg, 12.9-mm diameter) using single-punch tablet compression machine (Cadmach, Ahmedabad, India).

Experimental Design

A CCD with $\alpha = 1$ was employed as per the standard protocol.[16,19] The amounts of CP (X_1) and Na CMC (X_2) were selected as the factors, studied at 3 levels each. The central point (0,0) was studied in quintuplicate. All other formulation and processing variables were kept invariant throughout the study. Table 2 summarizes an account of the 13 experimental runs studied, their factor combinations, and the translation of the coded levels to the experimental units employed during the study. Time taken to release 50% of the drug ($t_{50\%}$), release until 18 hours (rel_{18h}), diffusional release exponent (n), and bioadhesive strength (f) were taken as the response variables.

Table 1. Composition of Atenolol Tablets*

Ingredient	Amount (mg)
Atenolol	50
Carbopol 934 P	50-150
Sodium carboxymethylcellulose	100-200
Magnesium stearate	5
Dibasic calcium phosphate	qs to 410

* qs indicates quantity sufficient.

Table 2. Factor Combinations as per the Chosen Experimental Design

Trial No.	Coded Factor Levels	
	X_1	X_2
I	−1	−1
II	−1	0
III	−1	1
IV	0	−1
V	0	0
VI	0	1
VII	1	−1
VIII	1	0
IX	1	1
X	0	0
XI	0	0
XII	0	0
XIII	0	0
Translation of coded levels in actual units		
Coded level	−1	0	1
X_1: Carbopol 934 P (mg)	50	100	150
X_2: Sodium carboxymethylcellulose (mg)	100	150	200

Tablet Assay and Physical Evaluation

The tablets were assayed for drug content using methanol as the extracting solvent, and the samples were analyzed spectrophotometrically (Shimadzu 1601, Kyoto, Japan) at 275 nm. Tablets were also evaluated for hardness (n = 6), friability (n = 6), weight variation (n = 10), and thickness (n = 10).

In Vitro Drug Release Studies

Dissolution studies were performed for all the formulation combinations, in triplicate, employing *United States Pharmacopeia(USP)*-28 paddle method (Pharmatest PTW II, Pharmatest Apparatus, Hainburg, Germany) and phosphate buffer solution pH 6.8 (PBS) as the dissolution medium at 50 rpm and 37°C ± 0.5°C. A 5-mL aliquot of the sample was withdrawn periodically at suitable time intervals and the volume replaced with an equivalent amount of the plain dissolution medium. The samples were analyzed spectrophotometrically at 276 nm. Drug release data were analyzed using ZOREL software[22] after correcting the values for the drug loss occurred during sampling. Based primarily on the algorithms proposed by Peppas and Sahlin,[23,24] the software reports the values of the release exponent (n) indicating the kinetics of drug release, the kinetic constant (k), magnitudinal contributions of the Fickian diffusion (k_1)

and polymer relaxation (k_2), respectively. As the current study involved unequal time intervals in the entire 24-hour dissolution span, the weighted mean of drug release rate was computed with time intervals as the weights. Drug release profiles were drawn using MS-Excel software and the values of $t_{50\%}$ were interpolated by Stineman interpolation using GRAPH software (Version 2.0, MicroMath Inc, St Louis, MO).

Ex Vivo Bioadhesion Studies

Bioadhesion studies were conducted, using a modification of the assembly described earlier,[25] with porcine gastric mucosa as the model membrane. The mucosal membrane was excised by removing the underlying connective and adipose tissue, and equilibrated at 37°C ± 1°C for 30 minutes in PBS before the bioadhesion evaluation study. The tablet was lowered onto the mucosa under a constant weight of 5 g for a total contact period of 1 minute. Bioadhesive strength (f) was assessed in terms of the weight in grams required to detach the tablet from the membrane. To investigate the effect of the individual polymer on bioadhesive strength, a 2-way analysis of variance (ANOVA)-based factorial analysis was performed as per the standard algorithms.[26]

Optimization Data Analysis and Validation of Optimization Model

Various RSM computations for the current optimization study were performed employing Design Expert software (Version 6.0.10, Stat-Ease Inc, Minneapolis, MN). Polynomial models including interaction and quadratic terms were generated for all the response variables using multiple linear regression analysis (MLRA) approach. The general form of the MLRA model is represented as Equation 1.

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2 + \beta_4 X_1^2 + \beta_5 X_2^2 + \beta_6 X_1 X_2^2 + \beta_7 X_1^2 X_2 \quad (1)$$

where, β_0 is the intercept representing the arithmetic average of all quantitative outcomes of 13 runs; β_1 to β_7 are the coefficients computed from the observed experimental values of Y; and X_1 and X_2 are the coded levels of the independent variable(s). The terms X_1X_2 and X_i^2 (i = 1 to 2) represent the interaction and quadratic terms, respectively. Statistical validity of the polynomials was established on the basis of ANOVA provision in the Design Expert software. Subsequently, the feasibility and grid searches were performed to locate the composition of optimum formulations.[21,25] Also, the 3-D response surface graphs and 2-D contour plots were constructed in MS-Excel environment using the output files generated by the Design Expert software.

Eight optimum checkpoints were selected by intensive grid search, performed over the entire experimental domain, to validate the chosen experimental design and polynomial equations. The formulations corresponding to these checkpoints were prepared and evaluated for various response properties. Subsequently, the resultant experimental data of response properties were quantitatively compared with that of the predicted values. Also, linear regression plots between observed and predicted values of the response properties were drawn using MS-Excel, forcing the line through origin.

Results and Discussion

Drug Content and Physical Evaluation

The assayed content of drug in various formulations varied between 98.9% and 100.9% (mean 99.9%). Tablet weights varied between 409.2 and 413.7 mg (mean 411.4 mg), thickness between 2.20 and 2.32 mm (mean 2.25 mm), hardness between 5.6 and 7.5 kg cm^{-2} (mean 6.5 Kg cm^{-2}), and friability ranged between 0.29% and 0.53% (mean 0.34%). Thus, all the physical parameters of the compressed matrices were practically within control.

In Vitro Drug Release Studies

Table 3 lists various dissolution parameters computed for all the CR bioadhesive formulations. In the current study, the values of release rate exponent (n), calculated as per the algorithm proposed by Peppas and Sahlin,[23] ranged between 0.6672 and 0.8646. Using an aspect ratio of 5.4, the critical values of n for declaring Fickian diffusion and zero-order release were found to be 0.4500 and 0.9000, respectively. In general, the release pattern was found to be non-Fickian tending to approach zero-order, especially when intermediate levels of Na CMC were coupled with intermediate to high levels of CP. The values of kinetic constant (k), being a direct function of matrix solubility, were found to decline with increase in the amount of either polymer, in accordance with the characteristic nature of the parameter.[27,28] Much higher values of k_1 vis-à-vis k_2 clearly indicate that the drug release was governed predominantly by Fickian diffusion, with varying contribution of polymer relaxation (case 2 transport) mechanism as well. The contribution of case 2 relaxation (due to polymer swelling and erosion) tended to show an increasing trend with increase in the content of any of the polymers, except when high levels of Na CMC were used in conjunction with intermediate to high levels of CP.

Total amount of atenolol released from all the formulations until 24 hours ranged between 93.86% and 100.01% indicating almost complete drug release from all the formulations. As the mean values of overall rate of drug release

Table 3. Drug Release Parameters of Various Mucoadhesive Formulations Prepared as per the Experimental Design*

Trial No.	Factor Amount (mg)		Release Exponent	Kinetic Constant	Fickian Diffusion Constant	Polymer Relaxation Constant	Release Till 18 Hours	Release Till 24 Hours	$t_{50\%}$	Rate of Drug Release Till 18 Hours (mgh^{-1})
	X_1	X_2	(n)	(k)	(k_1)	(k_2)	(rel_{18h}, %)	(rel_{24h}, %)	Hours	(Mean ± SEM)
I	50	100	0.6672	0.181	1.196	0.032	98.24	99.41	3.71	2.75 ± 1.402
II	50	150	0.7238	0.116	1.084	0.044	93.20	99.68	7.32	2.58 ± 0.876
III	50	200	0.7789	0.096	1.053	0.050	91.98	99.03	8.05	2.55 ± 0.698
IV	100	100	0.6877	0.161	1.155	0.039	99.13	99.93	4.77	2.79 ± 1.399
V	100	150	0.8518	0.079	1.033	0.054	90.24	98.87	8.18	2.51 ± 0.472
VI	100	200	0.8060	0.084	1.036	0.052	90.63	99.30	8.79	2.51 ± 0.589
VII	150	100	0.7584	0.099	1.062	0.046	90.15	98.96	7.83	2.50 ± 0.634
VIII	150	150	0.8547	0.069	1.017	0.053	86.54	96.63	9.32	2.43 ± 0.398
IX	150	200	0.8273	0.072	1.027	0.049	71.74	93.86	9.91	1.99 ± 0.494
X	100	150	0.8646	0.061	1.097	0.057	92.96	99.41	8.14	2.53 ± 0.384
XI	100	150	0.8450	0.075	1.031	0.052	88.99	97.98	8.16	2.49 ± 0.545
XII	100	150	0.8424	0.076	1.030	0.051	91.26	100.01	8.22	2.51 ± 0.504
XIII	100	150	0.8552	0.068	1.019	0.055	89.28	99.25	8.20	2.50 ± 0.565

* X_1: Carbopol 934P; and X_2: sodium carboxymethylcellulose.

until 24 hours for all the formulations were not found to be discriminating, overall rate of drug release was computed until 18 hours. Rate of drug release (until 18 hours) tended to decrease with increase in the content of either CP or Na CMC. This is in agreement with literature findings[29,30] that the viscosity of the gel layer around the tablet increases with increase in the hydrogel concentration, thus limiting the release of active ingredient. As the carboxyl groups of CP dissociate highly at pH above their pK_a (ie, 6.0 ± 0.5), electrostatic repulsions between the negatively charged carboxyl groups cause uncoiling and expansion of molecules, resulting in polymer swelling and consequent gel formation.[30,31] The gel, thus formed, consists of closely packed swollen particles. With further increase in polymer amount, thicker gel forms inhibiting water penetration more strongly, resulting in significant reduction in the values of rel_{18h} indicating slower drug release. At high levels of both the polymers, a significant fraction of the drug (~28%) remained unreleased until 18 hours, which can eventually lead to significant reduction in the extent of bioavailability. Hence, in the subsequent RSM optimization studies, due consideration was taken to control the drug release profile without significant loss of unreleased drug in the formulation. Nevertheless, the loss in drug bioavailability is expected to be less in the light of the in vivo situation, where the bioadhesive dosage form is likely to be in intimate contact with the biological tissue for longer periods of time.

The values of $t_{50\%}$ enhanced markedly from 3.71 hours, observed at low levels of both the polymers, to as high as 9.91 hours, observed at high levels of both the polymers. This finding indicated considerable release-retarding potential of the polymers for atenolol. Figure 1 exhibits the dissolution profiles obtained for various formulations, prepared as per CCD. The formulations with lower levels of polymers exhibited higher initial burst in drug release (Figure 1 inset). This result could be attributed to the dissolution of drug present initially at the surface of the matrices and the availability of higher amount of unreleased drug present in the dosage form. This could also be because the dosage forms, in the early dissolution period, exhibit primarily first-order Fickian diffusion mechanism. The higher amount of drug released due to Fickian diffusion (ie, due to k_1) vis-à-vis that released due to polymer relaxation (ie, due to k_2) in early time periods also corroborates the same. Cumulative proportion of drug released due to case 2 relaxational transport constant (k_2) increased

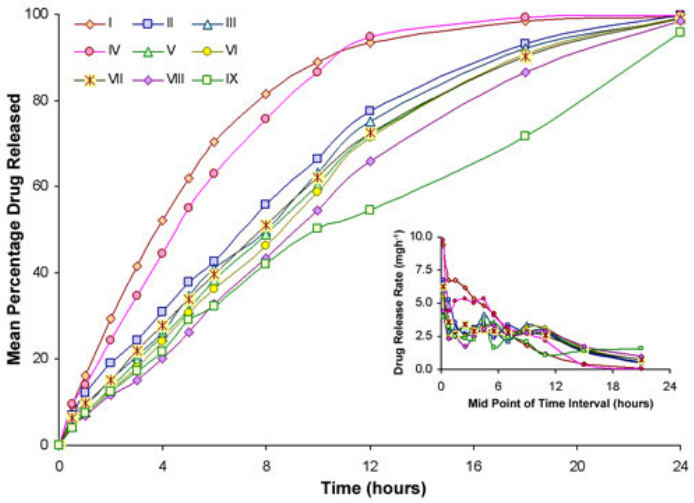

Figure 1. Percentage drug release profiles of bioadhesive formulations prepared as per the experimental design. The inset shows the corresponding drug release rate profiles. Graphs for formulation V represent mean of the 5 replicate studies.

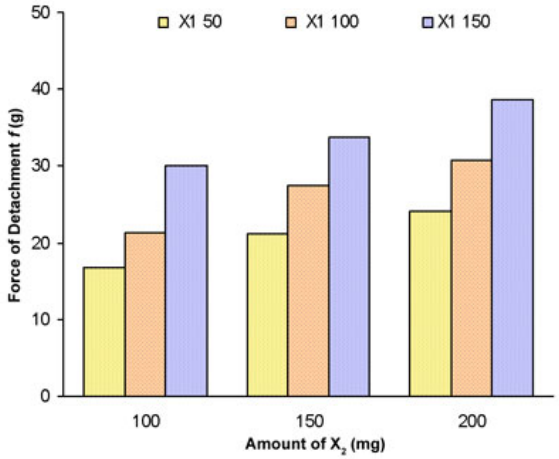

Figure 2. Bar chart showing the values of bioadhesive strength obtained at various levels of X_1 (Carbopol 934P) and X_2 (sodium carboxymethylcellulose).

for all the formulations with increasing dissolution time period, indicating that the release was significantly influenced by polymer relaxation in the later stages (data not shown). However, the formulations showed little burst effect at higher polymer levels, ratifying better sustenance of drug release. Overall, all the formulations showed quite regulated release from 4 hours onwards.

Ex Vivo Bioadhesive Strength Determination

Figure 2 shows the bar chart depicting significant variation in the values of bioadhesive strength, obtained using different ratios of polymers. The figure depicts an increasing trend in bioadhesive strength, as observed with porcine mucosa, with an increase in the amount of either polymer. Maximum bioadhesive strength, therefore, was seen at the

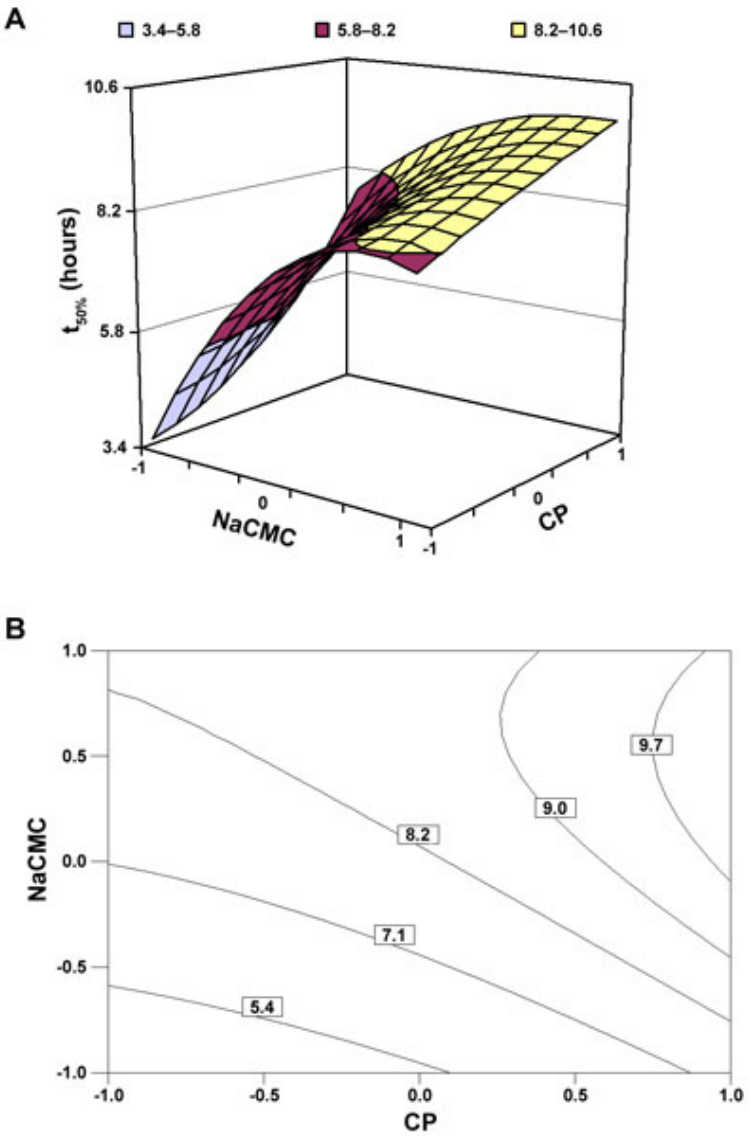

Figure 3. (A) Response surface plot showing the influence of Carbopol 934P (CP) and sodium carboxymethylcellulose (Na CMC) on $t_{50\%}$ and (B) Corresponding contour plot showing the relationship between various levels of 2 polymers.

highest levels of the 2 polymers. The hydrogels are known to swell readily, when they come in contact with hydrated mucous membrane.[2,31] Water sorption reduces the glass transition temperature below ambient conditions, and hydrogels become progressively rubbery due to uncoiling of polymer chains and subsequent increased mobility of the polymer chains. This glass-rubbery transition provides hydrogel plasticization resulting in a large adhesive surface for maximum contact with mucin and flexibility to the polymer chains for interpenetration with mucin.[31,32] Increasing the polymer amount may provide more adhesive sites and polymer chains for interpenetration with mucin, resulting consequently in the augmentation of bioadhesive strength.[33] Application of 2-way ANOVA-based factorial analysis indicated that both the polymers had very significant influence on the bioadhesive properties of the compressed matrices ($P < .001$ in each case).

RSM Optimization Results

Mathematical Modeling

Mathematical relationships generated using MLRA for the studied response variables are expressed as Equations 2 through 5.

$$t_{50\%} = 8.12 + 1.00X_1 + 2.01X_2 - 0.56X_1X_2 + 0.36X_1^2 - 1.18X_2^2 + 0.49X_1X_2^2 - 0.41X_1^2X_2 \quad (2)$$

$$rel_{18h} = 91.40 - 3.33X_1 - 4.25X_2 - 3.04X_1X_2 - 3.66X_1^2 + 1.35X_2^2 - 3.75X_1X_2^2 - 1.92X_1^2X_2 \quad (3)$$

$$n = 0.84 + 0.065X_1 + 0.059X_2 - 0.011X_1X_2 - 0.027X_1^2 - 0.069X_2^2 - 0.031X_1X_2^2 - 0.014X_1^2X_2 \quad (4)$$

$$f = 27.28 + 6.34X_1 + 4.68X_2 + 0.36X_1X_2 + 0.66X_1^2 - 0.79X_2^2 + 0.60X_1X_2^2 - 0.72X_1^2X_2 \quad (5)$$

All the polynomial equations were found to be statistically significant ($P < .01$), as determined using ANOVA, as per the provision of Design Expert software.

The polynomial equations comprise the coefficients for intercept, first-order main effects, interaction terms, and higher-order effects. The sign and magnitude of the main effects signify the relative influence of each factor on the response. The values obtained for main effects of each factor in Equations 2 and 3 reveal that Na CMC, individually, has rather more pronounced effect on the values of $t_{50\%}$ and rel_{18h}, respectively. On the other hand, the main effect coefficients in Equations 4 and 5 show that CP has a more influential role on the response variables, *n* and *f*. At a given set of factor levels, however, these higher-order polynomials yield results as the net effect of all the coefficient terms contained in the polynomial.

Response Surface Analysis

Figures 3A to 6A portray the 3-dimensional response surface plots, while Figures 3B to 6B are the corresponding contour plots for the studied response properties viz $t_{50\%}$, rel_{18h}, *n,* and *f*. Figures 3A and B depict a nonlinear trend of $t_{50\%}$ in an ascending order, with an augmentation of CP levels. However with Na CMC, this inclining trend is observed until intermediate level, followed by an asymptotic

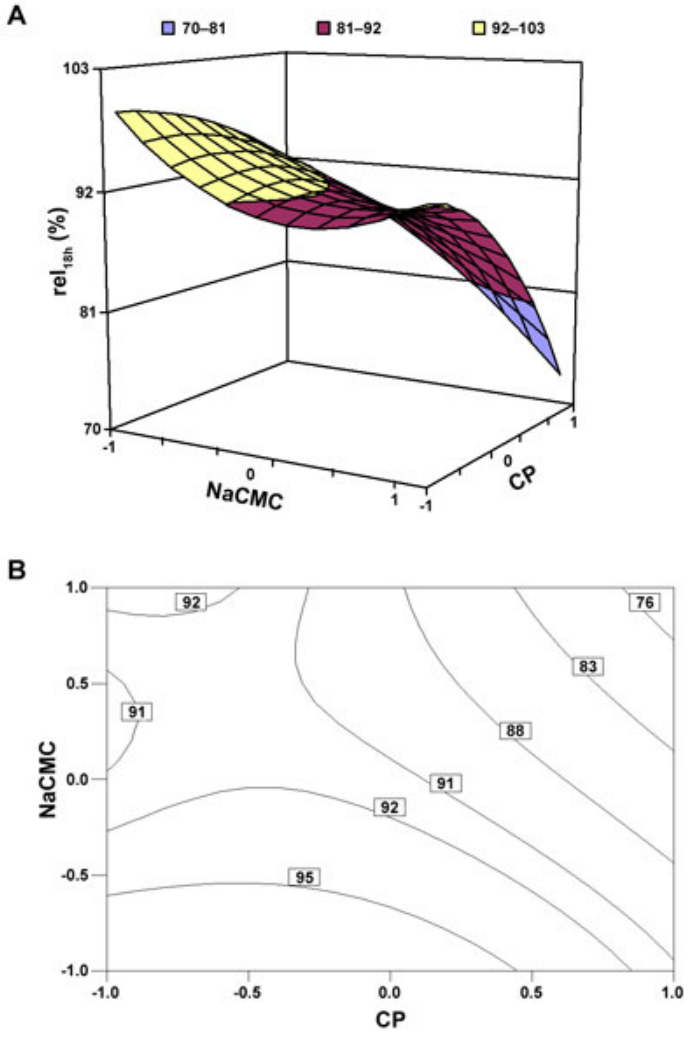

Figure 4. (A) Response surface plot showing the influence of Carbopol 934P (CP) and sodium carboxymethylcellulose (Na CMC) on rel_{18h} and (B) Corresponding contour plot showing the relationship between various levels of 2 polymers.

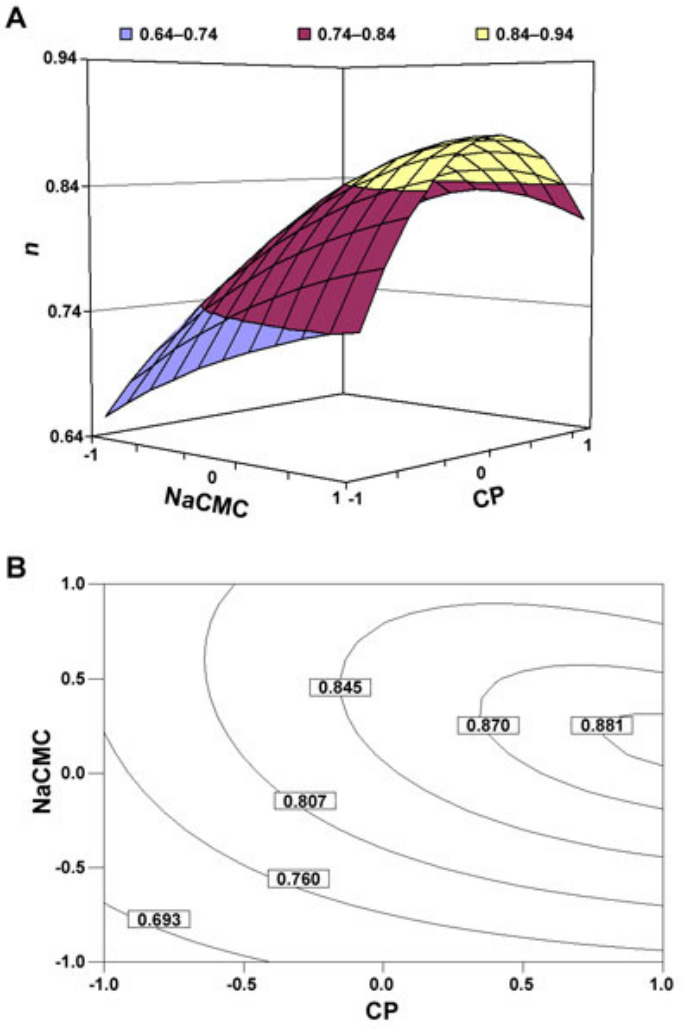

Figure 5. (A) Response surface plot showing the influence of Carbopol 934P (CP) and sodium carboxymethylcellulose (Na CMC) on *n* and (B) Corresponding contour plot showing the relationship between various levels of 2 polymers.

plateau at higher levels. This may be explained on the basis of mathematical models generated for the response variable, $t_{50\%}$ (Equation 2). It can be deduced from the model that at higher levels of Na CMC, the negative influence of higher-order terms (eg, X_2^2, X_1X_2, $X_1^2X_2$) tend to outweigh the positive linear contribution of the polymer (X_2) alone.

Figures 4A and B also exhibit that rel_{18h} vary in a nonlinear manner, but in a descending pattern with an increase in the amount of each polymer. Except at high level of CP, this declining trend was observed until intermediate levels of Na CMC, after which a near plateau was discernible (ie, the drug release values did not decrease appreciably). The contour plot (Figure 4B) shows that Na CMC has a comparatively greater influence on the response variable than CP.

Figures 5A and B show a "region of maximum" for *n*, lying between the intermediate to high levels of both the polymers. Herein, the values of *n* tend to indicate nearly zero-order release kinetics within the experimental domain.

In contrast to the results of drug release parameters, response surface and contour plot for *f* (Figures 6A and B) reveal that *f* varies in somewhat linear fashion with increase in the amount of each polymer. However, the effect of CP seems to be more pronounced as compared with that of Na CMC.

The optimum formulation was selected based on the criteria of attaining complete and controlled drug release with highest possible bioadhesive strength. Upon "trading off" various response variables, the following maximizing criteria were adopted: $t_{50\%} > 8.0$ hours; $rel_{18h} > 85\%$; $n > 0.80$; $f > 25$ g. Upon comprehensive evaluation of feasibility search and subsequently exhaustive grid searches, the formulation composition with polymer levels of CP, 78.5 mg, and Na CMC, 195 mg, fulfilled maximum requisites of an

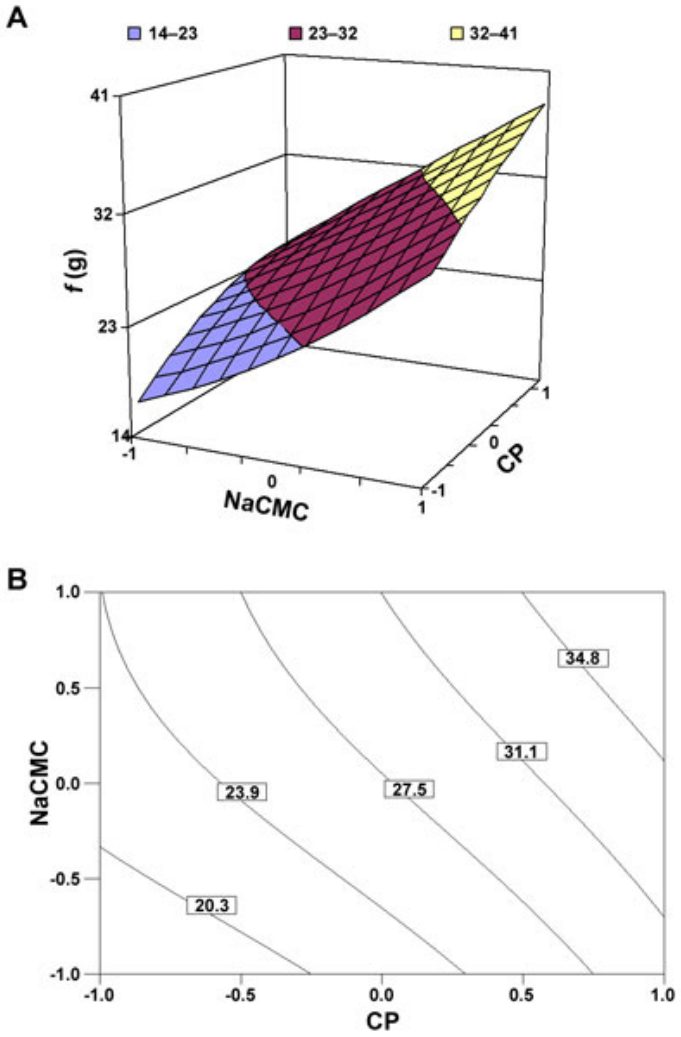

Figure 6. (A) Response surface plot showing the influence of Carbopol 934P (CP) and sodium carboxymethylcellulose (Na CMC) on *f* and (B) Corresponding contour plot showing the relationship between various levels of 2 polymers.

Table 4. Composition of the Checkpoint Formulations, the Predicted and Experimental Values of Response Variables, and Percentage Prediction Error*

Composition CP: Na CMC (mg)	Response Variable	Experimental Value	Predicted Value	Percentage Error
78.5:195.0	$t_{50\%}$	8.56	8.58	−0.234
	rel_{18h}	91.69	91.59	+0.109
	n	0.8170	0.8178	−0.098
	f	27.56	27.79	−0.849
80.0:164.5	$t_{50\%}$	8.31	8.28	+0.361
	rel_{18h}	90.52	91.4	−0.972
	n	0.8294	0.8221	+0.880
	f	26.57	26.04	+1.995
104.0:162.0	$t_{50\%}$	8.86	8.61	+2.822
	rel_{18h}	90.92	90.09	+0.913
	n	0.8566	0.8548	+0.210
	f	28.49	28.88	−1.369
110.0:174.0	$t_{50\%}$	8.92	8.99	−0.785
	rel_{18h}	89.08	88.36	+0.808
	n	0.8626	0.8616	+0.116
	f	30.22	30.69	−1.555
130.0:150.0	$t_{50\%}$	8.84	8.85	−0.113
	rel_{18h}	86.52	88.08	−1.803
	n	0.8600	0.8693	−1.082
	f	31.87	31.32	+1.726
135.0:100.0	$t_{50\%}$	6.72	6.74	−0.297
	rel_{18h}	93.57	93.31	+0.278
	n	0.7378	0.7386	−0.108
	f	27.39	27.09	+1.095
140.0:138.0	$t_{50\%}$	8.82	8.79	+0.340
	rel_{18h}	88.95	88.20	+0.843
	n	0.8539	0.8594	−0.644
	f	31.11	31.67	−1.800
142.0:190.0	$t_{50\%}$	9.66	9.72	−0.621
	rel_{18h}	79.04	78.26	+0.987
	n	0.8439	0.8488	−0.581
	f	36.21	36.5	−0.801

* Percentage Error (mean ± SD) −0.0072 ± 1.087

optimum formulation because of better regulation of release rate and higher bioadhesive strength. The formulation showed $t_{50\%}$ as 8.58 hours, rel_{18h} as 91.59%, *n* as 0.8178 and *f* as 27.79 g. The said formulation, however, released the drug completely (ie, 99.78% drug in 24 hours).

Validation of RSM Results

For all of the 8 checkpoint formulations, the results of the physical evaluation and tablet assay were found to be within limits. Table 4 lists the compositions of the checkpoints, their predicted and experimental values of all the response variables, and the percentage error in prognosis. Figure 7 shows linear correlation plots between the observed and predicted response variables, and the residual plots showing the scatter of the residuals versus observed values.

Upon comparison of the observed responses with that of the anticipated responses, the prediction error varied between −1.803% and 2.82% (mean ± SD as −0.0072 ± 1.087). The linear correlation plots drawn between the predicted and observed responses demonstrated high values of r^2 (ranging between 0.9617 and 0.9983), indicating excellent goodness of fit ($P < .001$). Relatively less magnitudes of r^2 observed with *f* (0.9617) and $t_{50\%}$ (0.9676) could be attributed to the biological variation of the model membrane (porcine gastric mucosa) and indirect estimation of $t_{50\%}$ values through interpolation techniques, respectively. Upon validation, the optimum formulation exhibited percentage error for various response variables, varying between −0.849% and 0.109%. Thus, the low magnitudes of error as well as the significant values of r^2 in the current study indicate a high prognostic ability of RSM.

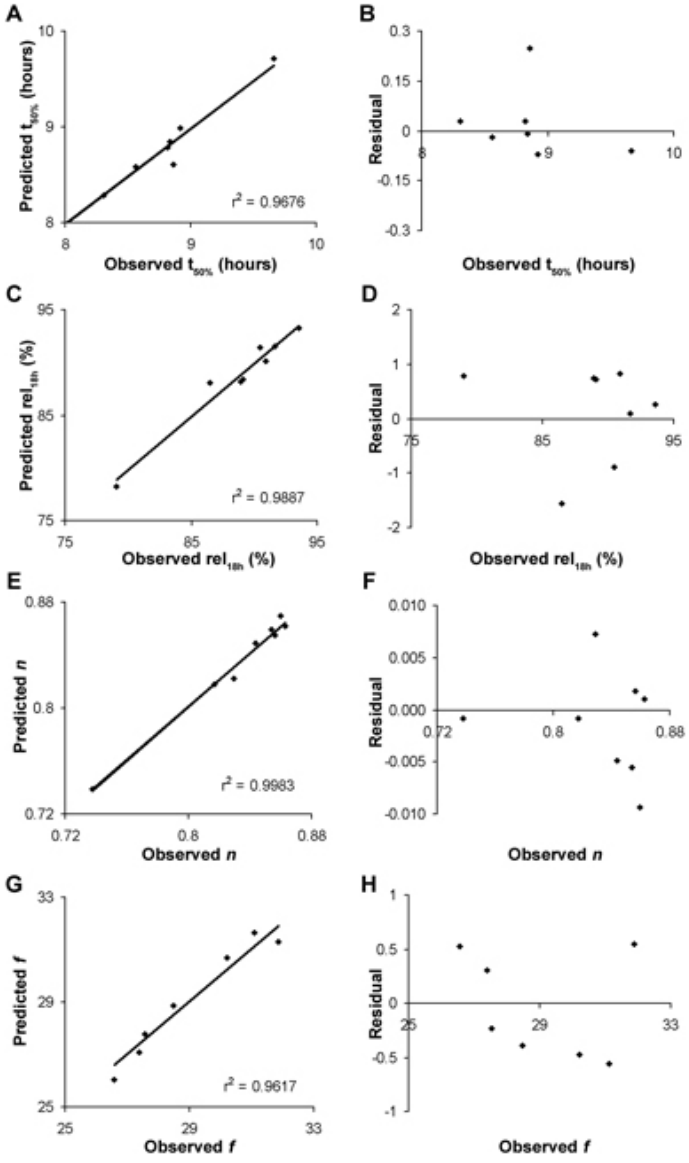

Figure 7. Linear correlation plots (A, C, E, G) between observed and predicted values and the corresponding residual plots (B, D, F, H) for various variables.

CONCLUSIONS

Regulated drug release in zero-order manner attained in the current study indicates that the hydrophilic matrix tablets of atenolol, prepared using CP 934P and Na CMC, can successfully be employed as a once-a-day oral controlled release drug delivery system. High bioadhesive strength of the formulation is likely to increase its GI residence time, and eventually, improve the extent of bioavailability. However, appropriate balancing between various levels of the 2 polymers is imperative to acquire proper controlled release and bioadhesion. High degree of prognosis obtained using RSM corroborates that a 2-factor CCD is quite efficient in optimizing drug delivery systems that exhibit nonlinearity in response(s).

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REFERENCES

1. Ponchel G, Irache J. Specific and non-specific bioadhesive particulate systems for oral delivery to the gastrointestinal tract. *Adv Drug Deliv Rev.* 1998;34:191–219.

2. Peppas NA, Sahlin JJ. Hydrogels as mucoadhesive and bioadhesive materials: a review. *Biomaterials.* 1996;17:1553–1561.

3. Hou SY, Cowles VE, Berner B. Gastric retentive dosage forms: a review. *Crit Rev Ther Drug Carrier Syst.* 2003;20:459–497.

4. Lavelle EC. Targeted delivery of drugs to the gastrointestinal tract. *Crit Rev Ther Drug Carrier Syst.* 2001;18:341–386.

5. Woodley J. Bioadhesion: new possibilities for drug administration? *Clin Pharmacokinet.* 2001;40:77–84.

6. Hoffman BB. Catecholamines, sympathomimetics drugs, and adrenergic receptor antagonists. In: Hardman JG, Limbird LE, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics.* 10th ed. New York, NY: McGraw Hill; 2001.

7. Vaithiyalingam SR, Sastry SV, Dehon RH, Reddy IK, Khan MA. Long-term stability characterization of a controlled release gastrointestinal therapeutic system coated with a cellulose acetate pseudolatex. *Pharmazie.* 2001;56:66–69.

8. Sastry SV, Reddy IK, Khan MA. Atenolol gastrointestinal therapeutic system: optimization of formulation variables using response surface methodology. *J Control Release.* 1997;45:121–130.

9. Perez-Marcos B, Iglesias R, Gomez-Amoza JL. Mechanical and drug release properties of atenolol-carbopol hydrophilic matrix tablets. *J Control Release.* 1991;17:267–276.

10. Rouge N, Allemann E, Gex-Fabry M, et al. Comparative pharmacokinetic study of a floating multiple-unit capsule, a high-density multiple-unit capsule and an immediate-release tablet containing 25 mg atenolol. *Pharm Acta Helv.* 1998;73:81–87.

11. Vázques M-J, Casalderrey M, Duro R, et al. Atenolol release from hydrophilic matrix tablets with hydroxypropyl methylcellulose (HPMC) mixtures as gelling agent: effects of the viscosity of the HPMC mixture. *Eur J Pharm Sci.* 1996;4:39–48.

12. Sastry SV, Khan MA. Aqueous based polymeric dispersion: Plackett-Burman design for screening of formulation variables of atenolol gastrointestinal therapeutic system. *Pharm Acta Helv.* 1998;73:105–112.

13. Sastry SV, Khan MA. Aqueous-based polymeric dispersion: face-centered cubic design for the development of atenolol gastrointestinal therapeutic system. *Pharm Dev Technol.* 1998; 3:423–432.

14. Kim J, Shin SC. Controlled release of atenolol from the ethylene-vinyl acetate matrix. *Int J Pharm.* 2004;273:23–27.

15. Dave BS, Amin AF, Patel MM. Gastroretentive drug delivery system of ranitidine hydrochloride: formulation and in vitro evaluation. *AAPS PharmSciTech.* 2004;5:E34.

16. Singh B, Kumar R, Ahuja N. Optimizing drug delivery systems using systematic "design of experiments". Part I: Fundamental aspects. *Crit Rev Ther Drug Carrier Syst.* 2005;22:27–105.

17. Lewis GA, Mathieu D, Phan-Tan-Luu R. *Pharmaceutical Experimental Design*. New York, NY: Marcel Dekker; 1999. (Singh B, Ahuja N. Book review on *Pharmaceutical Experimental Design*). *Int J Pharm.* 2000;195:247–248.

18. Singh B, Dahiya M, Saharan V, Ahuja N. Optimizing drug delivery systems using systematic "design of experiments". Part II: Retrospect and prospects. *Crit Rev Ther Drug Carrier Syst.* 2005;22:215–293.

19. Singh B, Mehta G, Kumar R, Bhatia A, Ahuja N, Katare OP. Design, development and optimization of nimesulide-loaded liposomal systems for topical application. *Curr Drug Deliv.* 2005;2:143–153.

20. Aberturas MR, Molpeceres J, Guzmán M, García F. Development of a new cyclosporine formulation based on poly(caprolactone) microspheres. *J Microencapsul.* 2002;19:61–72.

21. Singh B, Ahuja N. Response surface optimization of drug delivery system. In: Jain NK, ed. *Progress in Controlled and Novel Drug Delivery Systems.* New Delhi, India: CBS Publishers and Distributors; 2004.

22. Singh B, Singh S. A comprehensive computer program for the study of drug release kinetics from compressed matrices. *Indian J Pharm Sci.* 1998;60:358–362.

23. Peppas NA, Sahlin JJ. A simple equation for the description of solute release. III. Coupling of diffusion and relaxation. *Int J Pharm.* 1989;57:169–172.

24. Peppas NA. Analysis of Fickian and non-Fickian drug release from polymers. *Pharm Acta Helv.* 1985;60:110–111.

25. Singh B, Ahuja N. Development of controlled-release buccoadhesive hydrophilic matrices of diltiazem hydrochloride: optimization of bioadhesion, dissolution, and diffusion parameters. *Drug Dev Ind Pharm.* 2002;28:431–442.

26. Daniel WW, ed. Analysis of variance. *Biostatistics: A Foundation for Analysis in the Health Sciences.* 7th ed. New York: John Wiley and Sons; 2000.

27. Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. *Int J Pharm.* 1983;15:25–35.

28. Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA. Mechanisms of potassium chloride release from compressed, hydrophilic polymeric matrices: effect of entrapped air. *J Pharm Sci.* 1983;72:1189–1191.

29. Ford JL, Rubinstein MH, Hogan JE. Formulation of sustained release promethazine hydrochloride tablets using hydroxypropyl methyl cellulose matrices. *Int J Pharm.* 1985;24:327–338.

30. Vazques MJ, Perez-Marcos B, Gomez-Amoza JL, Martinez-Pacheco R, Souto C, Concheiro A. Influence of technological variables on release of drugs from hydrophilic matrices. *Drug Dev Ind Pharm.* 1992;18:1355–1375.

31. Technical Literature on 'Bioadhesion'. *Bulletin 16*. Cleveland, OH: Noveon Pharmaceuticals Ltd; 1994.

32. Duchene D, Touchard F, Peppas NA. Pharmaceutical and medicinal aspects of bioadhesive systems for drug administration. *Drug Dev Ind Pharm.* 1988;14:283–318.

33. Ponchel G, Touchard F, Duchene D, Peppas NA. Bioadhesive analysis of controlled release systems. I. Fracture and interpenetration analysis in poly(acrylic acid) containing systems. *J Control Release.* 1987;5:129–141.