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RESEARCH PAPER

Development of Controlled-Release Buccoadhesive Hydrophilic Matrices of Diltiazem Hydrochloride: Optimization of Bioadhesion, Dissolution, and Diffusion Parameters

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ABSTRACT

Buccoadhesives have long been employed to improve the bioavailability of drugs undergoing significant hepatic first-pass metabolism. Diltiazem hydrochloride (DLZ) is also reported to have low oral bioavailability due to an extensive hepatic first-pass effect. Controlled-release buccoadhesive hydrophilic matrices containing DLZ were prepared using a 3^2 factorial design. Amounts of Carbopol® 934P (CP) and Methocel® K100LV (HPMC) were taken as the formulation variables (factors) for optimizing bioadhesion, and kinetics of dissolution and diffusion. A mathematical model was generated for each response parameter. Bioadhesive strength tended to vary quite linearly in increasing order with increasing amount of each polymer. The drug release pattern for all the formulation combinations was found to be non-fickian, approaching zero-order kinetics. The values of permeation coefficient tended to vary non-linearly with polymer amount, depicting the plausibility of interaction between the two polymers. Suitable combinations of the two polymers provided adequate bioadhesive strength and a fairly regulated release profile up to 10 hr. The response surfaces and contour plots for each response parameter are presented for further interpretation of the results. The optimum formulations were chosen and their predicted results found to be in close agreement with experimental findings.

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Key Words: *Bioadhesion; Buccal delivery; Controlled release; Diltiazem; Factorial design; Optimization; Response surface methodology*

INTRODUCTION

Buccal mucosa offers a convenient route for local and systemic drug delivery (1). In recent years, buccoadhesive drug delivery systems have gained considerable interest with regard to systemic delivery of drugs undergoing hepatic first-pass metabolism and premature drug degradation within the gastrointestinal tract (2). Lower enzymatic activity of saliva, facile removal of formulation, better patient acceptance, and compliance are some other prominent meritorious visages of buccoadhesive systems (1–4).

Diltiazem hydrochloride (DLZ) is widely used in the treatment of angina pectoris and hypertension. It is rational to formulate the buccoadhesive dosage forms of DLZ, as it is known to have low oral bioavailability due to an extensive first-pass effect (5). Further, its short half-life (3–5 hr), optimum oil–buffer partition coefficient (158 at pH 7.4), and low molecular weight (450.98) make it an appropriate candidate for being incorporated into buccoadhesive controlled-release formulations (5,6).

Systematic optimization techniques have frequently been employed for the design and development of controlled-release pharmaceutical dosage forms (7,8). Such studies are usually carried out through response surface methodology (RSM), embodying the use of appropriate experimental designs, generation of polynomial relationships, and optimum search methods, generally using pertinent software (9,10). Factorial designs (FD), where all the factors are studied in all possible combinations, are considered to be the most efficient in estimating the influence of individual variables (main effects) and their interactions using minimum experimentation. An FD for two factors at three levels each (3^2) is considered identical to a two-factor composite design, and has the added advantage of determining a quadratic response surface (11,12).

The aim of the current study was to develop and optimize the controlled-release mucoadhesive hydrophilic compressed matrices of DLZ for buccal delivery. A computer-aided optimization process using a 3^2 FD was employed to investigate the effect of two independent variables (factors), i.e., amounts of two swellable polymers: Methocel® K100LV (HPMC) and Carbopol® 934P (CP). Release till 10 hr (rel_{10h}), time taken to release 50% of the drug ($t_{50\%}$), bioadhesive strength (f), and permeation coefficient (P_{cof}) were taken as the response variables.

EXPERIMENTAL

Materials

Diltiazem hydrochloride was provided ex gratis by M/s Cipla Ltd. (Mumbai, India), Carbopol 934P by B.F. Goodrich (Cleveland, Ohio, USA), and Methocel K100LV by M/s Panacea Biotec Ltd. (New Delhi, India). Seamless cellulose dialysis tubing (D-0405; Lot 16H0385) was procured from M/s Sigma Chemicals (St. Louis, MO, USA), mannitol from M/s S.D. Fine Chemicals Ltd. (Boisar, India), and magnesium stearate from M/s Loba Chemie Ltd. (Mumbai, India). All other chemicals used in the study were of analytical grade.

Methods

Preparation of Buccoadhesive Compressed Matrices

Table 1 lists the composition of different buccoadhesive formulations prepared using varying amounts of CP, HPMC, and mannitol along with a fixed quantity of magnesium stearate. Drug and the excipients were homogeneously blended and subsequently compressed into flat-faced tablets (250 mg,

Table 1

Composition of Diltiazem Hydrochloride Buccoadhesive Hydrophilic Compressed Matrices (250.0 mg)

Ingredients	Quantity (mg)
Diltiazem hydrochloride	30.0
Methocel K100LV	40.0–80.0
Carbopol 934P	50.0–100.0
Magnesium stearate	2.5
Mannitol	q.s.

12.9 mm diameter) using a single-punch tablet machine (Cadmach, Ahmedabad, India) to achieve a tablet thickness of 1.5±0.1 mm.

Factorial Design

A 3^2 full FD was constructed where the amounts of CP (X_1) and HPMC (X_2) were selected as the factors. The levels of the two factors were selected on the basis of the preliminary studies carried out before implementing the experimental design. All other formulation and processing variables were kept invariant throughout the study. Table 2 summarizes the experimental runs, their factor combinations, and the translation of the coded levels to the experimental units used in the study.

Tablet Evaluation

Tablet Assay

Five tablets from each batch were powdered individually and a quantity equivalent to 10 mg of DLZ was accurately weighed and extracted with a suitable volume of methanol. Each extract was suitably diluted and analyzed spectrophotometrically (Spectronic 1201, Milton Roy, NY) at 239 nm. Spectrophotometric analysis of the formulation excipients, i.e., HPMC, CP, mannitol, and magnesium stearate, using the highest concentration employed in the formulation, indicated no interference at 239 nm in methanol.

Table 2

A 3^2 Full Factorial Experimental Design Layout

	Coded Factor Levels	
Trial No.	X_1	X_2
1	−1	−1
2	−1	0
3	−1	1
4	0	−1
5	0	0
6	0	1
7	1	−1
8	1	0
9	1	1

Translation of coded levels in actual units:

Coded level	−1	0	1
X_1: HPMC (mg)	40	60	80
X_2: CP (mg)	50	75	100

Physical Evaluation

Ten tablets from each batch were evaluated for uniformity in tablet weight and thickness. Six tablets from each batch were examined for friability using a Roche-type friabilator (Tropical Equipment Pvt. Ltd., Mumbai, India) and hardness using a Monsanto-type hardness tester (Campbell, Mumbai, India).

In Vitro Bioadhesion Studies

The in vitro bioadhesion studies were conducted using a modification of a bioadhesion test assembly described by Gupta et al. (13) as in Fig. 1. Porcine buccal mucosa was used as the model membrane. The mucosa was kept frozen in phosphate buffer (PB) pH 7.4 and thawed to room temperature before use. The mucosal membrane was excised by removing the underlying connective and adipose tissue and was equilibrated at 37±1°C for 30 min in buffer (PB pH 6.6) 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 min. Bioadhesive strength was assessed in terms of weight (g) required to detach the tablet from the membrane.

In Vitro Release Study

Drug release studies (n = 3) were conducted for all the formulation combinations using dissolution rate test apparatus (Pharmatest, Piscataway, NJ, USA). Phosphate buffer pH 6.6 (900 mL) was taken as the release medium at 75 rpm and 37±1°C employing USP XXIII paddle method (Apparatus

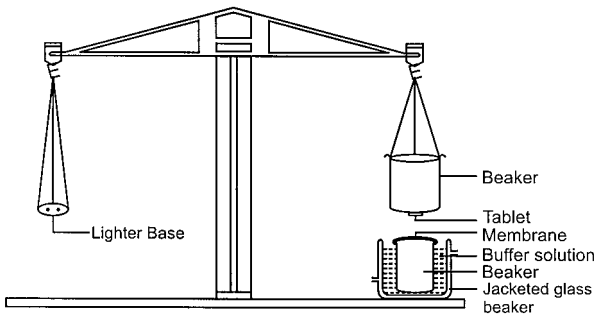

Figure 1. Bioadhesion test assembly.

2). Aliquots of small samples were periodically withdrawn and the sample volume replaced with an equal volume of fresh dissolution medium. The samples were suitably diluted and analyzed spectrophotometrically at 236 nm. The formulation excipients did not interfere with the spectrophotometric analysis of the drug at 236 nm in phosphate buffers.

In Situ Diffusion Studies

Dialysis tubing was treated before diffusion studies as per the procedure recommended by the supplier. The tubing was first washed with distilled water and subsequently cut open to expose the maximum surface area just before use. In situ diffusion studies (n = 3) were performed for all the formulation combinations using a modified Franz diffusion cell. The membrane was glued onto the upper surface of the receptor compartment using acrylate adhesive. The donor compartment was filled with 10 mL of PB pH 6.6 (representing buccal pH), while the receptor compartment was filled with PB pH 7.4 (representing physiological pH). The assembly was stirred magnetically and maintained at 37±1°C. Samples were withdrawn at fixed intervals, replaced with an equal volume of PB pH 7.4, diluted, and analyzed spectrophotometrically at 236 nm.

Data Analysis

The data obtained from dissolution kinetics studies were analyzed using ZOREL software (14). The software has in-built provisions for correcting the amount of drug release for the drug loss during sampling (15). The software also computes the values of kinetic constant (k) and diffusional release exponent (n) using logarithmic transformation of the relationship proposed by Korsmeyer et al. (16) as in Eq. (1):

$$\log(M_t/M_\infty) = \log k + n \log t \tag{1}$$

where M_t/M_∞ is the fraction of drug released at time t. The values of $t_{50\%}$ were calculated by Stineman interpolation using GRAPH software (Version 2, Micromath Inc., USA). Permeability coefficients (P_{cof}) were calculated for all the formulation combinations using Eq. (2):

$$\frac{A}{S} = \frac{P_{cof} A_{tot}}{V}\left[t - \frac{h^2}{6D}\right] \tag{2}$$

where A_{tot}, V, h, and D represent the total drug amount in the donor compartment, the volume in the donor compartment, the thickness of the dialysis membrane, and the diffusion coefficient, respectively (17). The term $P_{cof}\, A_{tot}/V$ represents the slope [flux (J)] and the term $h^2/6D$ represents the x-axis intercept yielding the lag time value when the amount per unit surface area (A/S) is plotted vs. time (t). To investigate the influence of polymers on bioadhesive strength, a two-way analysis of variance (ANOVA)-based factorial analysis followed by several one-way ANOVAs at fixed levels of other polymers was performed on f values using MS-Excel (2000).

Various computations for the current optimization study using RSM were carried out, employing another in-house built software, FACTOP (18). Statistical second-order models including interaction and polynomial terms were generated for all the response variables using an approach suggested by Box et al. (19). The general form of the model is represented as in Eq. (3):

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2 + \beta_4 X_1^2 + \beta_5 X_2^2 + \beta_6 X_1 X_2^2 + \beta_7 X_1^2 X_2 + \beta_8 X_1^2 X_2^2 \tag{3}$$

where β_0, the intercept, is the arithmetic average of all quantitative outcomes of nine runs, β_1 to β_8 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 ($i = 1, 2$) are the interaction and polynomial terms, respectively. The statistical validity of the polynomials was established on the basis of Yates' ANOVA (20). Subsequently, feasibility as well as grid search was performed to locate the composition of optimum formulations. Also, three-dimensional response surface graphs and contour plots were drawn in MS-Excel using the output files generated by the FACTOP software.

Validation of Optimization Model

Six optimum checkpoints (formulation compositions) were selected by intensive grid search, performed over the entire experimental domain, to validate the chosen experimental design and polynomial equations. The criterion for selection of checkpoints was primarily based on the highest possible values of the response parameters, i.e., rel_{10h}, $t_{50\%}$, f, and P_{cof}. The formulations corresponding to

these checkpoints were prepared and evaluated for various response properties. The resultant experimental data of response properties were subsequently quantitatively compared with predicted values. Also, linear regression plots between observed and predicted values of the response properties were attempted using MS-Excel, forcing the line through the origin.

RESULTS AND DISCUSSION

The literature documents that the dose of DLZ can be reduced up to 80% via buccal delivery, owing to the avoidance of a hepatic first-pass effect (21). Therefore, buccoadhesive matrices containing the lowest dose of DLZ, i.e., 30 mg, were worked upon in the current study. Another work carried out on buccal patches of DLZ corroborates the use of this dose level (22). There are reports indicating that the buccoadhesives have been studied for drug release up to 2 days (23,24). However, as a buccoadhesive tablet, film, or patch is unlikely to remain on the buccal mucosa for such long times, drug release in the present study was investigated only up to 12 hr. Preliminary studies carried out prior to the experimental design revealed that the tablets formed with very low polymer content exhibited 100% drug release, but were vulnerable to fragmentation. On the other hand, the tablets formed with very high polymer content possessed good structural integrity, but showed undesirably slow release (100% drug release above 18 hr). Accordingly, a suitable range for each of the polymer amounts was selected as depicted in Table 1.

Physical Evaluation

Tablet weights varied between 248.5 and 252.7 mg, thickness between 1.4 and 1.6 mm, and hardness between 5.5 and 7.5 kg/cm^2. The assay content of DLZ varied between 98.2 and 99.8%, and the friability ranged between 0.3 and 0.6%. Thus, all the physical parameters of the compressed matrices were practically within control.

In Vitro Bioadhesion Strength Determination

Figure 2 depicts an increasing trend in the bioadhesive strength (with porcine mucosa) with increase in the amount of polymer(s). Maximum bioadhesive strength (f) was seen with the highest levels of the two polymers. Application of two-way ANOVA-based factorial analysis indicated that the polymers had a significant influence on the bioadhesive properties of the compressed matrices ($p < .001$). Subsequent application of one-way ANOVA, keeping the levels of one of the polymers fixed, also showed a statistically significant difference amongst the observed data of bioadhesive strength ($p < .001$), ratifying the significant positive influence of each polymer on bioadhesion.

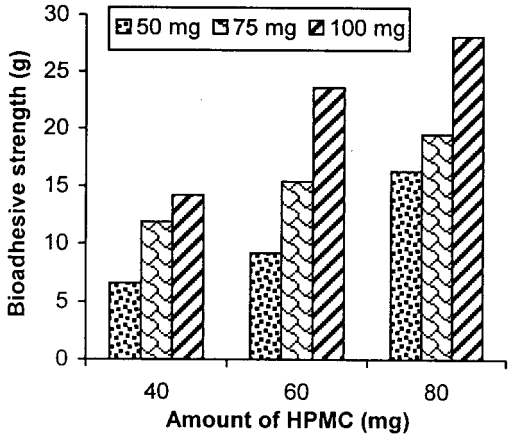

Figure 2. Bar diagram showing the influence of levels of CP 934P at three fixed levels of HPMC K100LV on bioadhesive strength ($n = 10$).

In Vitro Release Studies

Table 3 lists various dissolution kinetic parameters computed for all nine batches. In the current study, the critical values of n as per the algorithm proposed by Peppas and Sahlin (25), using an aspect ratio of 8.6, were found to be 0.472 and 0.944 for declaring fickian diffusion and zero order, respectively. In all the nine cases studied, the exponent varied between 0.784 and 0.906, delineating a distinctly non-fickian release behavior approaching zero order. Further, the magnitudes of fickian diffusion constant (k_1) ranging between 0.995 and 1.032, and case II relaxation constant (k_2) ranging between 0.037 and 0.086, reveal that the mechanism of drug release is predominantly diffusion, with a relatively minor contribution of polymer relaxation as well. Although, in the present study, the magnitude of k_2 is quite small, yet it

seems to have a marked influence on the overall drug release behavior as the values of n are much higher than their threshold limit for declaring fickian diffusion, i.e., 0.472. The kinetic constant k was found to decline with an increase in the amount of two polymer(s), in accordance with its characteristic nature, being a direct function of matrix solubility (16). The overall rate of drug release and rel_{10h} tended to decrease with increase in polymer amount. This may be attributed to the fact that with an increase in hydrogel concentration, the viscosity of the gel layer around the tablet tends to limit further the release of active ingredient. Consequently, the values of $t_{50\%}$ significantly enhanced from 4.92 to 11.99 hr with a rise in the content of polymers.

In Situ Diffusion Studies

The mean cumulative amount permeated across the dialysis membrane varied between 0.65 and 1.19 mg per square centimeter of membrane (Table 4). The parameter was observed to have a declining trend with increase in polymer amount. However, the values of J and P_{cof} tended to vary nonlinearly with polymer content. High values of the coefficient of determination (r^2) and statistical significance ($p < .005$) confirm the reliability of the

Table 3

Dissolution Parameters for All the Buccoadhesive Hydrophilic Matrix Formulations (n = 3) Prepared as per 3^2 Factorial Design

Trial No.	Formulation Composition (mg)		n	k_1	k_2	k	$t_{50\%}$ (hr)	rel_{10h} (%)	Mean Rate of Drug Release (mg/hr)
	HPMC	CP							
1	40	50	0.875	1.032	0.086	0.113	4.92	80.58	2.38
2	40	75	0.878	1.008	0.070	0.082	7.56	72.66	1.91
3	40	100	0.906	0.995	0.070	0.071	8.22	66.90	1.82
4	60	50	0.838	1.016	0.069	0.087	7.51	68.36	1.95
5	60	75	0.836	1.016	0.059	0.079	8.62	59.06	1.73
6	60	100	0.850	1.015	0.052	0.069	9.84	50.74	1.58
7	80	50	0.875	1.011	0.066	0.079	8.29	57.02	2.01
8	80	75	0.784	1.031	0.045	0.078	10.36	48.14	1.65
9	80	100	0.801	1.021	0.037	0.060	11.99	35.86	1.39

Table 4

Diffusion Parameters for All the Buccoadhesive Hydrophilic Matrix Formulations (n = 3) Prepared as per 3^2 Factorial Design

Trial No.	Formulation Composition (mg)		Mean Cumulative Amount of Drug Released per Unit Surface Area ($\mu g/cm^2$)	J ($\mu g/cm^2/hr$)	P_{cof} ($mL/cm^2/hr$)	r^{2a}
	HPMC	CP				
1	40	50	1190.9	89.1	0.0297	0.9871
2	40	75	710.6	60.4	0.0201	0.9988
3	40	100	651.3	55.9	0.0186	0.9983
4	60	50	1174.1	81.2	0.0271	0.9899
5	60	75	990.4	79.5	0.0271	0.9986
6	60	100	753.7	63.6	0.0212	0.9799
7	80	50	896.4	75.5	0.0252	0.9997
8	80	75	862.3	68.9	0.0229	0.9823
9	80	100	917.7	65.5	0.0218	0.9964

[a] $p < .001$ in all cases.

computation of P_{cof} from all the linear permeability curves.

Optimization Results

The mathematical relationships constructed for the studied response variables are expressed as Eqs. (4)–(7). All the polynomial equations were found to be highly statistically significant ($p < .001$), as determined by Yates' ANOVA:

$$\begin{aligned} rel_{10h} &= 59.93 - 13.19X_1 - 8.74X_2 - 1.88X_1X_2 \\ &\quad + 0.81X_1^2 - 0.04X_2^2 - 10.4X_1X_2^2 \\ &\quad + 0.11X_1^2X_2 - 0.09X_1^2X_2^2 \end{aligned} \quad (4)$$

$$\begin{aligned} t_{50\%} &= 8.59 + 1.66X_1 + 1.56X_2 + 0.10X_1X_2 \\ &\quad - 0.10X_1^2 - 0.38X_2^2 + 0.39X_1X_2^2 \\ &\quad + 0.59X_1^2X_2 - 0.07X_1^2X_2^2 \end{aligned} \quad (5)$$

$$\begin{aligned} f &= 16.07 + 5.22X_1 + 5.62X_2 + 1.10X_1X_2 \\ &\quad + 0.04X_1^2 + 0.72X_2^2 + 2.11X_1X_2^2 \\ &\quad - 2.38X_1^2X_2 - 0.04X_1^2X_2^2 \end{aligned} \quad (6)$$

$$\begin{aligned} P_{cof} &= 0.024 - 0.003X_1 - 0.003X_2 + 0.002X_1X_2 \\ &\quad - 0.002X_1^2 + 0.001X_2^2 - 0.002X_1X_2^2 \\ &\quad - 0.001X_1^2X_2 - 0.001X_1^2X_2^2 \end{aligned} \quad (7)$$

Figures 3A–6A portray the response surface plots. Figures 3B–6B are the corresponding contour plots for the studied response properties. Figure 3 shows that rel_{10h} varies in a nearly linear descending pattern with a change in the amount of polymers. Figure 4 also exhibits a near linear trend of $t_{50\%}$, but in ascending order. As there is no confounding of the contour lines in Figs. 3 or 4, both the polymers seem to contribute independently towards drug release.

The response surface and contour plot for f values (Fig. 5) reveal that it varies in a somewhat linear fashion with the amount of two polymer(s). However, the steeper ascent in the response surface with CP than with HPMC (Fig. 5A) is clearly discernible, indicating that the effect of CP is comparatively more pronounced than that of HPMC. Figure 6 shows a non-linear twisted relationship for P_{cof} at intermediate and high levels of the polymers. This can be attributed to the potential occurrence of interaction between the two polymers at the corresponding factor levels, construing that each polymer is tending to modify the effect of another towards permeation.

For all the six optimum formulations, the value of n ranged between 0.839 and 0.863, visibly indicating a non-fickian release behavior approaching zero-order kinetics. The values of k_1 and k_2 ranged narrowly between 1.0110 and 1.0177, and 0.0654 and 0.0694, respectively, and the mean release rate between 1.93 and 1.98 mg/hr. For all these formulations, the bioadhesive strength ranged between 10.2 and 12.2 g. The values of mean cumulative amount of drug diffused per unit surface area varied between 0.85 and 0.96 mg/cm^2, J between 70.3 and 81.8 μg/cm^2/hr, and P_{cof} between 0.023 and 0.027 mL/cm^2/hr. Evidently, the values of

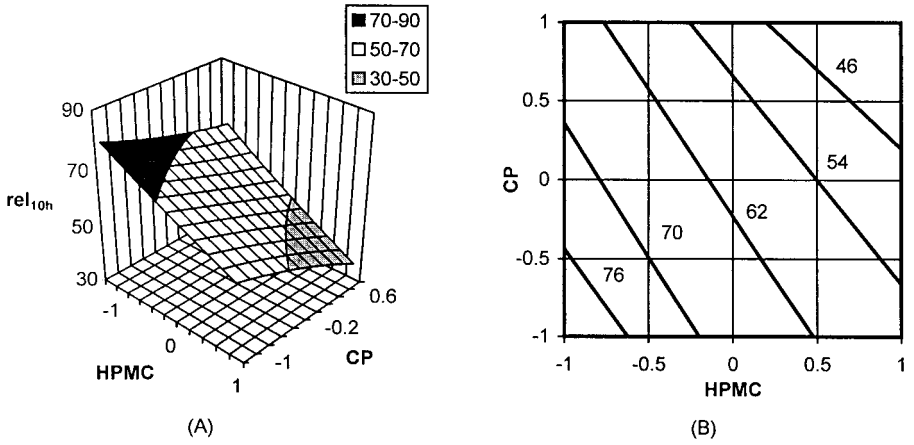

Figure 3. (A) Response surface plot showing the influence of HPMC and CP on rel_{10h} values for buccoadhesive hydrophilic matrix formulations of DLZ. (B) Contour plot showing relationship between various levels of two polymers to attain fixed values of rel_{10h}.

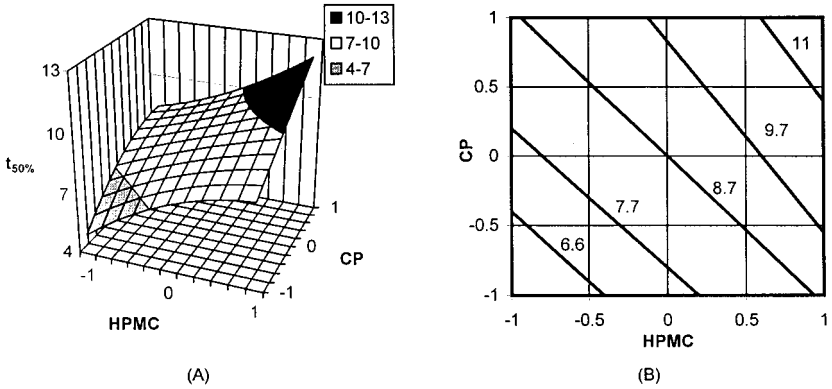

Figure 4. (A) Response surface plot showing the influence of HPMC and CP on $t_{50\%}$ values for buccoadhesive hydrophilic matrix formulations of DLZ. (B) Contour plot showing relationship between various levels of two polymers to attain fixed values of $t_{50\%}$.

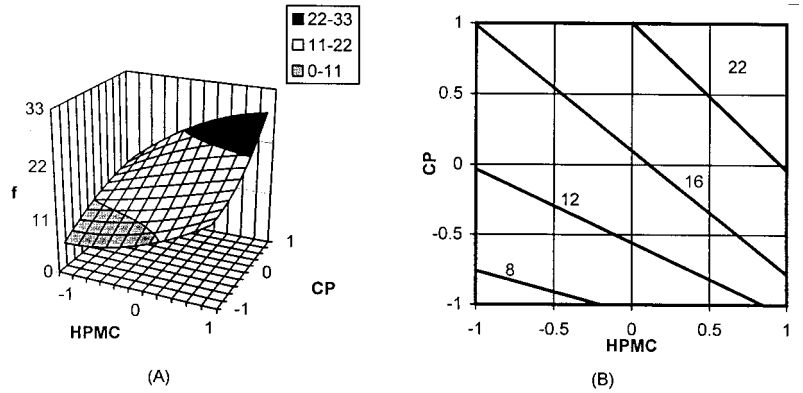

Figure 5. (A) Response surface plot showing the influence of HPMC and CP on biadhesive strength (f) values for buccoadhesive hydrophilic matrix formulations of DLZ. (B) Contour plot showing relationship between various levels of two polymers to attain fixed values of f.

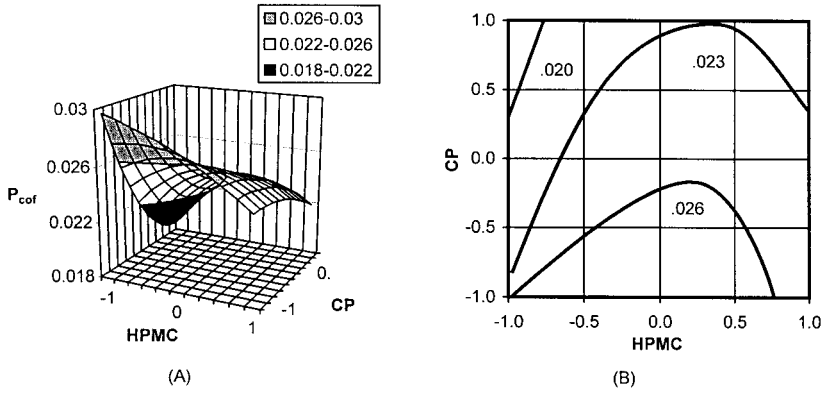

Figure 6. (A) Response surface plot showing the influence of HPMC and CP on P_{cof} values for buccoadhesive hydrophilic matrix formulations of DLZ. (B) Contour plot showing relationship between various levels of two polymers to attain fixed values of P_{cof}.

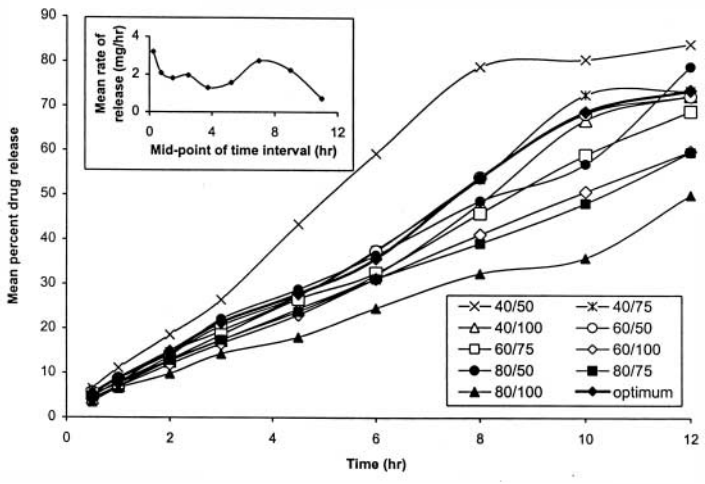

Figure 7. In vitro dissolution profiles of buccoadhesive matrix formulations of DLZ. The plot shows release profiles of nine formulations prepared as per 3^2 FD and that of an optimum formulation. The inset portrays the mean drug release rate of the optimum formulation at the corresponding midpoints of time intervals.

Table 5

Experimentally Observed Response Parameters of Six Optimum Formulations and Comparison with Predicted Values for Validation of RSM

Formulation Composition HPMC/CP (mg)	Response Property	Experimental Value	Predicted Value	Percentage Error
44.8/70.0	$t_{50\%}$	7.46	7.47	−0.14
	rel_{10h}	70.6	70.7	−0.14
	f	11.6	11.6	0.00
	P_{cof}	0.0233	0.0235	−0.73
45.6/70.0	$t_{50\%}$	7.54	7.54	0.00
	rel_{10h}	70.0	70.1	−0.14
	f	11.6	11.7	−0.86
	P_{cof}	0.0239	0.0237	0.84
47.2/72.5	$t_{50\%}$	7.76	7.82	−0.77
	rel_{10h}	68.1	68.3	−0.29
	f	12.2	12.5	−2.46
	P_{cof}	0.0236	0.0236	0.00
48.0/65.0	$t_{50\%}$	7.40	7.40	0.00
	rel_{10h}	70.2	70.2	0.00
	f	10.5	10.9	−3.81
	P_{cof}	0.0251	0.0252	−0.40
52.0/62.5	$t_{50\%}$	7.55	7.57	−0.27
	rel_{10h}	68.7	68.6	0.15
	f	10.4	10.8	−3.85
	P_{cof}	0.0259	0.0261	−0.77
54.4/60.0	$t_{50\%}$	7.60	7.61	−0.13
	rel_{10h}	67.9	68.0	−0.15
	f	10.2	10.5	−2.94
	P_{cof}	0.0269	0.0267	0.74
Mean(±SD) of percentage error				−0.66±1.25

dissolution and diffusion parameters had a propensity to range optimally between relatively controlled limits rather than those of the original formulations (Tables 3 and 4) designed as per 3^2 FD.

The release profiles of all six optimum formulations were found to be more or less superimposable, presumably because of the lower invariance amongst their chosen polymer compositions. The drug release profile of one of the optimum formulations (HPMC:CP 52:62.5) vis-à-vis nine original formulations, prepared as per the experimental design, is shown in Fig. 7. The graph vividly exhibits the superiority of the optimum formulation in regulating the drug release amongst the dissolution profiles characterized by diverse release behavior. The formulations, which were slower at releasing, showed markedly low extents of drug release, while the others released the drug relatively rapidly. The inset graph plotted between the mean rate of release and the midpoints of the time intervals for the optimum formulation unambiguously reveals that the optimum formulation exhibited a small initial burst effect followed by a quite regulated release up to 10 hr, whereafter the rate of release tended to decline.

Table 5 records the values of observed and predicted responses using factorial design along with the percentage prediction errors for these six optimum formulations. The prediction error for the response variables ranged between −3.9 and 0.8%, with the mean±SD of the percentage error being −0.66±1.25%. Also, the linear plots (Fig. 8) drawn between the predicted and observed responses demonstrate high values of r^2 (ranging between 0.944 and 0.992), indicating excellent goodness of fit. Thus the low magnitudes of error as well as the

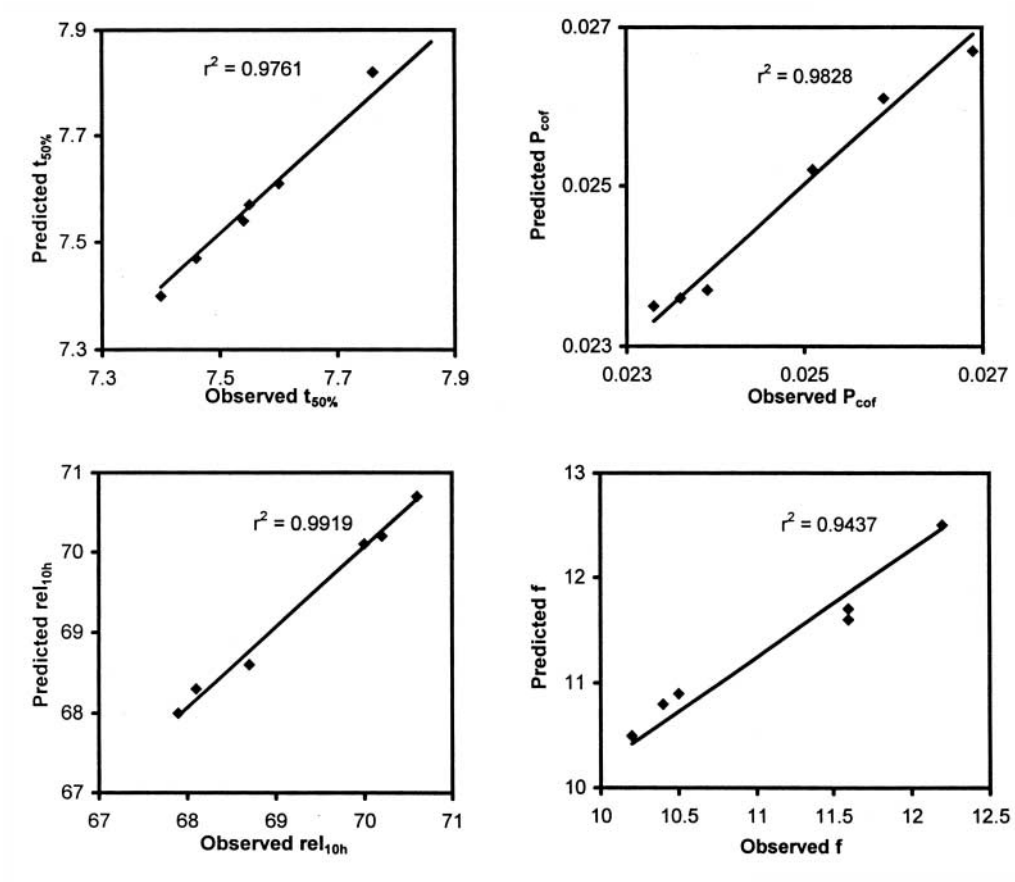

Figure 8. Linear correlation graphs of the experimentally observed properties of optimum DLZ buccoadhesive matrix formulations with the values predicted using RSM.

significant values of r^2 designate a high prognostic ability of RSM.

CONCLUSIONS

The study suggests that the hydrophilic compressed matrices of DLZ prepared using HPMC and CP provide regulated release till 10 hr. The matrices demonstrated ample bioadhesive strength with porcine buccal mucosa. However, an appropriate balance between the levels of the two polymers, CP and HPMC, is imperative to acquire minimum dose dumping with extended release and adequate bioadhesion. The computer-based factorial optimization technique yields results with a high degree of prediction and fruition. The study can, therefore, enable the formulator to reach and quantify the optimum decreasing experimentation during formulation.

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