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Development of three layered buccal compact containing metoprolol tartrate by statistical optimization technique

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Abstract

The objective of this work to evaluate the effect of formulation variables on release properties and bioadhesive strength in development of three layered buccal compact containing highly water-soluble drug metoprolol tartrate (MT) by statistical optimization technique. Formulations were prepared based on rotatable central composite design with peripheral polymer ratio (carbopol 934P: HPMC 4KM) and core polymer ratio (HPMC 4KM: sodium alginate) as two independent formulation variables. The three layered buccal compact comprises a peripheral layer, core layer and backing layer. Four dependent (response) variables were considered: bioadhesion force, percentage MT release at 8 h, $T_{50\%}$ (time taken to release 50% of drug) and release exponent (n). The release profile data was subjected to curve fitting analysis for describing the release mechanism of MT from three layered buccal compact. The main effects and interaction terms was quantitatively evaluated by quadratic model. The decrease in MT release was observed with an increase in both the formulation variables and as the carbopol: HPMC ratio increases the bioadhesive strength also increases. The desirability function was used to optimize the response variables, each having a different target and the observed responses were highly agreed with experimental values. The results demonstrate the feasibility of the model in the development of three layered buccal compact containing highly water-soluble drug MT.

Keywords: Metoprolol tartrate; Three layered buccal compact; Bioadhesion; Central composite design

1. Introduction

The oral cavity is being increasingly used for the administration of drugs, which are mainly designed for the contained medicaments through the oral mucosa into the systemic circulation. Buccal mucosa consist of stratified squamous epithelium supported by a connective tissue lamina propia (Squier and Wertz, 1996) was investigated as a site for drug delivery several decades ago and the interest in this area for the trasmucosal drug administration is still growing. Buccal mucosa makes a more appropriate choice of site if prolonged

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drug delivery is desired because buccal site is less permeable than the sublingual site. Buccal compacts or buccal bioadhesive drug devices designed to remain in contact with buccal mucosa and release the drug over a long period of time in a controlled fashion. Such a delivery of drug through buccal mucosa overcomes premature drug degradation with in the GI tract, as well as active drug loss due to first pass metabolism, and another is inconvenience of parenteral administration. In addition, there is excellent acceptability and the drug can be applied, localized and may be removed easily at any time during the treatment period.

Metoprolol tartrate (MT) chemically, 1-(isopropylamino)-3-*p*-(2-methoxyethyl)phenoxy-2-propanol (2:1) dextro-tartrate (Rao et al., 1985) is a β_1 selective adrenergic blocking agent and widely used as a drug of choice in the management of hypertension, angina pectoris and arrhythmias (Hoffman, 2001). The drug is freely soluble in water and administered at a dose of 100 mg daily, the half-life of MT is about 3–4 h and its oral bioavailability has been reported to be about 50% (Kendall et al., 1991). Drugs which are highly water soluble are considered difficult to deliver in the form of sustained or controlled release formulation due to their susceptibility to dose dumping. Hence, an attempt is made to formulate a three layered buccal compact, to regulate the release process of MT by using mocoadhesive polymers, with extended clinical effect, reduced dosing frequency and avoid dose dumping.

The strategy for designing buccoadhesive is based principally on the utilization of polymers with suitable physicochemical properties. Combined usage of HPMC and carbopol in delivering the clotrimazole for oral canididiasis has been reported (Khanna et al., 1997). Similar polymer combination was studied by Perez Marcos et al. (1994) and concluded that the amount of water penetrated in HPMC K4M was higher than that of carbopol 974P. Jadhav et al. (2004) developed a control release mucoadhesive tablet of eugenol for gingival application by using carbopol 934P and HPMC as polymers. Based on the release studies it was concluded that increase in carbopol concentration increases the release rate of eugenol and where as HPMC retards. Different ratio of carbopol 934P and HPMC K100LV was studied to develop and optimize the controlled release mucoadhesive hydrophilic compressed matrices of diltiazem for buccal delivery (Singh and Ahuja, 2002). In this study, a 3^2 factorial design was employed with amount of carbopol and HPMC as independent variables and based on the results it was concluded that suitable combination of the two polymers provided adequate bioadhesive strength and can fairly regulate the release of drug upto 10 h. Liabot et al. (2002) studied a double-layered mucoadhesive tablet of nystatin containing different ratios of carbomer and HPMC. The release of nystatin was modulated by swelling and diffusion. However, there has been no study to date designed to evaluate the release rate and mucoadhesive property of three layered buccal compacts by using combination of these polymers (carbopol 934P, sodium alginate and HPMC K4M). The aim of this research work was to systemically study the effect of several formulation variables on the release rate and mucoadhesive property of buccal compact using MT as model drug. Design of experiments has been widely used in pharmaceutical field to study the effect of formulation variables and their interaction on dependent (response) variables (Lewis et al., 1999). In the present study, a rotatable (orthogonal) central composite Box–Wilson design was used. The different independent variables include: peripheral polymer ratio (X_1); and core polymer ratio (X_2). The formulation variables and their ranges were chosen from the knowledge obtained from the preliminary studies and in the experiments previously reported. The typical three layered buccal compacts was prepared containing peripheral layer, core layer and backing layer as given in Fig. 1. The peripheral layer contains lactose, different ratio of carbopol and HPMC K4M which acts has as a rate controlling layer. The core layer consists of drug MT, HPMC K4M and sodium alginate at different ratio. In order to provide the unidirectional drug release towards the mucosa and avoid backward diffusion, ethyl cellulose (EC) and magnesium stearate were included as backing layer. The in vitro release data was subjected to curve fitting analysis to obtain the release parameters $T_{50\%}$ (time taken to release 50% of drug) and release exponent (n). All the response variables

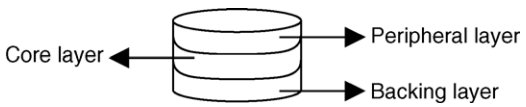

Fig. 1. A typical three layered buccal compact.

were fitted to quadratic model and regression analysis was carried out to get a quantitative relationship between the dependent and the analyzed independent variables.

2. Materials and methods

2.1. Materials

Metoprolol tartrate was received as gift sample from M/s Astra Zeneca India Pvt. Ltd., Bangalore, India. Hydroxylpropylmethylcellulose (Methosil®) K4M, sodium alginate (alginic acid sodium salt) and ethyl cellulose were obtained by the courtesy of M/s Bangalore Pharmaceutical Research Labs, Bangalore, India. Other materials were purchased from commercial source; Mg stearate (Loba Chemicals, Mumbai, India), and directly compressible lactose (Strides Arco Labs, Bangalore, India). All other chemicals used in the study were of analytical grade.

2.2. Experimental design

A randomized rotatable central composite design was implanted for the optimization of buccal compacts. According to the model it contains four full factorial design points, four axial points and three centre points. Higher and lower levels of each factor were coded as +1 and −1, respectively, and the mean value as 0. The selected factor levels are summarized in Table 1. The center points were repeated three times to estimate the pure experimental uncertainty at the factor levels (Lieberman et al., 1988). The two independent formulation variables evaluated include:

X_1: peripheral polymer ratio (Carbopol: HPMC K4M); X_2: core polymer ratio (HPMC K4M: sodium alginate).

Table 1
Factors and their corresponding levels implemented for the construction of CCD

Factor	Factor level				
	−1.41	−1	0	1	1.41
X_1: peripheral polymer ratio (Carbopol: HPMC)	0.96:1	2:1	4.5:1	7:1	8.04:1
X_2: core polymer ratio (HPMC: sodium alginate)	0.96:1	2:1	4.5:1	7:1	8.04:1

The response variables tested include:

Y_1: bioadhesion force; Y_2: percentage MT release at 8 h; Y_3: diffusion exponent (n); Y_4: time taken for 50% of MT release ($T_{50\%}$).

2.3. Preparation of three layered buccal compacts

The formulations were prepared at random following a CCD; Table 2 shows the experimental design. Before direct compression all the ingredients were screened through 120 μm sieve and then thoroughly blended in glass mortar with pestle. Blending was carried out separately for peripheral, core and backing layer. The blended powder of backing layer was compressed on 13 mm flat faced punch and die set, in an IR hydraulic press at a force of 50 kg cm^{-2}. Above this, blended powder of core layer was added and compressed at a force of 50 kg cm^{-2}. Finally, the blended powder of peripheral layer was added to get three layered buccal compact by compressing at a force of 240 kg cm^{-2}.

2.4. Evaluation of buccal compacts

2.4.1. Thickness

The thickness of buccal compact was determined using digital micrometer (Mitituo, New Delhi, India). Ten individual compacts from each batch were used and the results averaged.

2.4.2. Weight variation test

Weight variation was performed for 20 compacts from each batch using an electronic balance (Denver APX-100, Arvada, Colorado) and average values were calculated.

2.4.3. Assay

The content of MT in five randomly selected buccal compacts of each formulation was analyzed spectrophotometrically at 275 nm using an Elico UV SL-159 spectrophotometer. Each measurement was carried out in triplicate and the average drug content was calculated.

2.4.4. Measurement of bioadhesion

Bioadhesion studies were carried out ex-vivo using freshly obtained mucosa without any further treatment. The peak force of detachment was determined by mea-

Table 2
Composition of three layered buccal compacts in mg as per CCD

Formulation code	Peripheral layer			Core layer			Backing layer	
	Carbopol	HPMC	Lactose	MT	HPMC	Sodium alginate	Mg stearate	Ethyl cellulose
1	53.34	26.66	20	50	33.33	16.67	25	25
2	70	10	20	50	33.33	16.67	25	25
3	53.34	26.66	20	50	43.75	6.25	25	25
4	70	10	20	50	43.75	6.25	25	25
5	39.18	40.82	20	50	40.91	9.09	25	25
6	71.15	8.85	20	50	40.91	9.09	25	25
7	65.45	14.55	20	50	24.49	25.51	25	25
8	65.45	14.55	20	50	44.47	5.53	25	25
9	65.45	14.55	20	50	40.91	9.09	25	25
10	65.45	14.55	20	50	40.91	9.09	25	25
11	65.45	14.55	20	50	40.91	9.09	25	25

suring the tensile strength required for complete breakdown of bioadhesive bond between the dosage form and the surface of mucosa. The apparatus and procedure adapted was previously described (Gupta et al., 1993). The backing layer was glued to the Teflon® cylinder while the peripheral layer was exposed to the mucosal surface. Each measurement was carried out in triplicate and the results averaged.

2.4.5. *In vitro release studies*

The in vitro drug release studies of buccal compacts were carried out using the USP dissolution apparatus I (Disso 2000-Lab, India). In order to mimic the in vivo adhesion of the devises, the buccal compact was attached through cyanoacryl adhesive to the bottom end of the stirring rod instead of basket fixtures. By this only peripheral layer of the buccal compact was exposed to the dissolution medium. The paddle rotation rate was 100 rpm and 500 ml of phosphate buffer pH 6.6 was used as dissolution medium maintained at $37 \pm 1\,^{\circ}C$. Aliquots were withdrawn at different time intervals and analyzed spectrophotometrically at 275 nm. The dissolution studies were conducted in triplicates and the mean values plotted verses time with standard error of mean, indicating the reproducibility of the results.

2.5. *Curve fitting*

Release data were fitted to various mathematical models for describing the release mechanism from buccal compact; Korsmeyer–Peppas (Eq. (1)) (Korsmeyer et al., 1983), zero-order (Eq. (2)) (Lee, 1984) and Higuchi release models (Eq. (3)) (Higuchi, 1963).

$$\frac{M_t}{M_\infty} = k_{KP} t^n \tag{1}$$

M_t/M_∞ is fraction of drug released at time 't'; k_{KP} the release rate constant; and n the release exponent.

$$M_t = M_0 + k_0 t \tag{2}$$

M_t is the amount of drug released at time 't'; M_0 the concentration of drug in the solution at $t = 0$; k_0 the zero-order release constant.

$$M_t = k_H t^{1/2} \tag{3}$$

M_t is the amount of drug release at time '$\sqrt{t}$'; and k_H the Higuchi release constant.

All curve fitting, simulation and plotting was carried out by using commercially available SigmaPlot® version 9 (Systat Software Inc.) and GraphPad PRISM® version 3.02 (GraphPad Software Inc.) software's.

2.6. *Regression analysis*

The effect of formulation variables on the response variables were statistically evaluated by applying one-way ANOVA at 0.05 level using a commercially available software package Design-Expert® version 6.05 (Stat-Ease Inc.). To describe the response surface curvature, the design was evaluated by quadratic model, which bears the form of equation (Eq. (4)):

$$Y = b_0 + b_1 X_1 + b_2 X_2 + b_3 X_1^2 + b_4 X_2^2 + b_5 X_1 X_2 \tag{4}$$

where y is the response variable, b_0 the constant and b_1, $b_2, \ldots, b_5$ the regression coefficient. X_1 and X_2 stand for the main effect; X_1X_2 are the interaction terms, show how response changes when two factors are simultaneously changed. X_1^2 and X_2^2 are quadratic terms of the independent variables to evaluate the nonlinearity.

3. Results and discussion

3.1. Formulation of three layered buccal compact

Buccoadhesive drug delivery offer distinct advantages over peroral administration (Khanna et al., 1998) and the selection of appropriate muccoadhesive polymer plays a crucial step for the development of controlled release buccal compact containing highly water-soluble drug. As reported previously (Maggi et al., 2000; Conte and Maggi, 1996), multilayered matrix tablet are proving to be more potential among the various formulations in the development of oral controlled release dosage form containing highly water-soluble drug to prevent the faster release and dose dumping. Hence, an attempt is made in this research work to formulate a three layered buccal compact containing a highly water-soluble drug MT. The amount of MT in the formulation was established according to its clinical use (Regardh et al., 1974). Three layered buccal compact was prepared following CCD, the materials used and composition are presented in Table 2. The backing layer contains EC and Mg stearate. EC was selected because of its hydrophobic nature and has low water permeability, moderate flexibility (Jian-Hwa and Cooklock, 1996), thus preventing drug loss by backward diffusion. Mg stearate was included as anti-adherent (Collins and Deasy, 1990). MT, sodium alginate and HPMC K4M comprises the core layer. HPMC K4M is a water swellable polymer (Heng et al., 2001; Takka et al., 2001) which controls the release of drug from the core layer by forming a matrix or gel layer. To increase the release of drug, sodium alginate was included as a water soluble polymer results in formation of porous channel (Ikinici et al., 2004). In order to study the effect of concentration of HPMC K4M, ratio of HPMC K4M: sodium alginate was increased from 2:1 to 7:1 by keeping the total polymer content at 1:1 ratio with respect to drug. Peripheral layer which adhere to the mucosa should possess good bioadhesive strength and also control the release. Hence, carbopol 934P a potential mucoadhesive polymer (Smart, 1993; Smart, 1991) along with HPMC K4M was included in peripheral layer. To achieve a good bioadhesive strength and optimum release, the ratio of carbopol 934P to HPMC K4M was varied from 2:1 to 7:1. Directly compressible lactose was included as diluent for its high aqueous solubility and increases the rate and amount of water imbibition to peripheral layer (Nandita and Sudip, 2004) their by increasing the rate of swelling of polymers in peripheral layer which in turn forms a gelled matrix to control the release. As reported previously (Rekhi et al., 1999), in formulating a water-soluble drug MT for sustained release, hydration of polymer is necessary in a short time, hence HPMC K4M and lactose were included.

In the present work, an attempt was made to study the effect of polymer loading on mucoadhesion and release of highly water-soluble drug MT from buccal compact. The independent variables include: X_1, peripheral polymer ratio (carbopol 934P: HPMC K4M) and X_2, core polymer ratio (HPMC K4M: sodium alginate). The dependent variables studied include; bioadhesion force, percentage MT release at 8 h, time taken to release 50% of the drug ($T_{50\%}$) and release exponent (n). For the generation of polynomial models, only coefficients found to be significant ($p < 0.05$) were used.

3.2. Thickness, weight variation and assay

The average thickness of all prepared buccal compacts ranged from 1.38 ± 0.0623 to 1.48 ± 0.0370 mm. The average percentage deviation of 20 buccal compacts of each formula was less than $\pm 5\%$, which provided a good weight uniformity. In all the formulations, the assay for drug content was found to be uniform among different batches of the buccal compacts and ranged from 97.62 to 105.19% of the theoretical value.

3.3. Release profile

Figs. 2–4 illustrates the release profiles of the four factorial, four axial and three central points of the CCD. It is clear from the Fig. 2 except formulation 4, the other formulations showed a linear pattern of MT release, indicating the appropriate choice of the range of formulation variables. In case of formulation

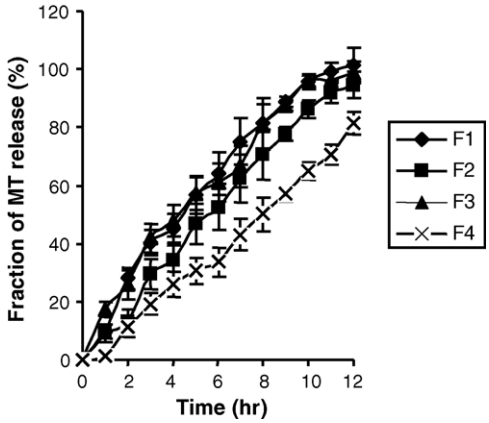

Fig. 2. MT release profiles for formulations prepared from four factorial points of CCD.

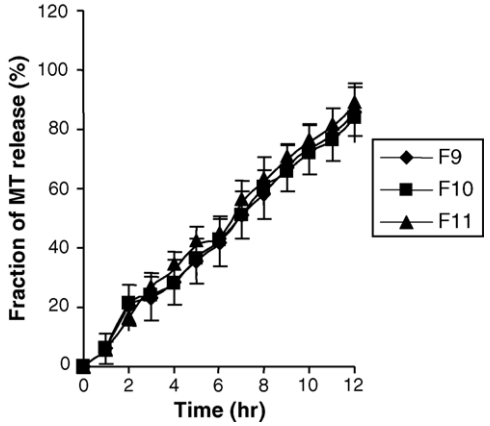

Fig. 4. MT release profiles for formulations prepared from three centre points of CCD.

1, which had lowest peripheral and core polymer ratio showed $101.53 \pm 4.28\%$ of MT release as compared to that of formulation 4 had a highest peripheral and core polymer ratio showed $81.42 \pm 3.65\%$ at the end of 12 h dissolution studies, indicating as the formulation variables are increased the release rate decreases. Such a decrease in drug release may be due to increased thickness of the gel layer, which is formed upon contact with dissolution medium and thus retarding the drug diffusion from the core layer. Fig. 3 represents the percentage MT release at 12 h for axial points. As per CCD, formulation 6 contains highest polymer load ($\alpha = 1.14$) in peripheral layer and formulation 8 contains highest polymer load in core layer, exhibited a

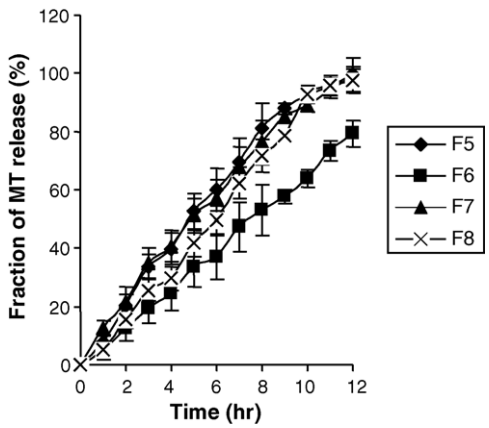

Fig. 3. MT release profiles for formulations prepared from four axial points of CCD.

$79.35 \pm 4.87\%$ and $97.46 \pm 4.26\%$, respectively. The results from the axial points indicated the significant effect of peripheral polymer layer than core polymer layer in controlling the release of MT from buccal compacts. To calculate the lack of fit for the suggested regression model, centre points were included in the design to calculate the pure error due to experimental procedure. From Fig. 4, we can conclude that the release of all three centre points overlaps each other, indicates that the error due to experimental procedure were found to be less in generating a meaning full fitting for the dependent variables.

The data of $T_{50\%}$ values are summarized in Table 3. Formulation 1 and formulation 4 showed a low $T_{50\%}$ values, due to rapid release of MT from the buccal compacts. This type of behavior is attributed due to low polymer concentration in the peripheral layer and these formulations relatively have high percentage MT release at 12 h. Due to low polymer concentration, the viscosity of gel matrix formed is low, which in turn increases the drug diffusion and water uptake through the matrix. As the polymer concentration in the compacts increased, increases the viscosity and strength of the gel layer, which results in the reduction of drug diffusion and water uptake through the gel layer and thereby increases the $T_{50\%}$ values.

3.4. Release mechanism

In order to understand the complex mechanism of drug release from the buccal compact, the in vitro MT

Table 3
Results of bioadhesion force and release parameters obtained for formulations by CCD

Formulation code	Bioadhesion force ($\times 10^3$ dyne cm^{-2})	MT release at 8 h (%)	Releae exponent (n)	$T_{50\%}$ (h)
1	6.88	81.25	0.79	4.92
2	10.24	70.52	0.93	5.78
3	5.49	80.51	0.75	4.57
4	11.48	50.11	1.12	7.84
5	5.31	81.07	0.72	5.12
6	11.68	53.05	1.03	7.65
7	8.01	76.30	0.81	5.89
8	8.02	71.69	1.03	5.14
9	8.05	58.13	0.96	6.86
10	7.98	60.23	0.92	6.89
11	8.09	62.43	0.93	6.52

release data were fitted to Korsmeyer–Peppas release model (Korsmeyer et al., 1983) and interpretation of release exponent values (n) enlightens in understanding the release mechanism from the dosage form. The release exponent values thus obtained were ranged from 0.72 to 1.12. Formulations 1, 3, 5, and 7 exhibited anomalous (non-fickian transport) diffusion mechanism with a value ranging between 0.72 to 0.81 (Table 3). These formulations also yielded a quality adjustment with Highuchi release model. For formulations 2, 4, 6, and 8, the release exponent values observed between 0.93 to 1.12 (Table 3), indicating the release mechanism of MT from these buccal compacts follows super case II transport, where drug release is due to polymer dissolution and chain disentanglement. In case of center points, the release exponent values were found to be 0.92 to 0.96. These formulations also showed as highest R^2 values for zero-order kinetics indicating the MT release from these buccal compacts were by both diffusion and erosion (Table 4) (Bravej et al., 1987).

3.5. Effect of formulation variables on bioadhesion force

The phenomenon of bioadhesion is related to the ability of some synthetic or biologic macromolecules and hydrocolloids adhere to biological tissues. During the process of bioadhesion between materials, the surface energy of the system is decreased and a new interface is formed by destroying the two free surfaces (Junginger, 1990). The possible mechanism of bioadhesion may include electronic interaction, hydrogen bonding and diffusion and interpenetration of macromolecules (Li et al., 1998). Many hydrophilic polymers capable of forming hydrogen bonds have shown good adhesion properties. The property of polymer is closely associated with bioadhesion because polymer swelling

Table 4
Results of curve fitting analysis

Formulation code	Korsmeyer–Peppas K_{KP} (h^{-n})	R^2	Zero-order K_0 (% h^{-1})	R^2	Higuchi K_H (%, $h^{-1/2}$)	R^2
F1	16.88 ± 1.21	0.9915	9.65 ± 0.30	0.9508	27.83 ± 0.95	0.9385
F2	10.01 ± 0.85	0.9926	8.54 ± 0.13	0.9902	24.26 ± 1.30	0.8764
F3	17.92 ± 1.24	0.9909	9.45 ± 0.32	0.9546	27.34 ± 0.80	0.9508
F4	4.917 ± 0.44	0.9948	6.40 ± 0.10	0.9901	17.97 ± 1.30	0.8175
F5	13.46 ± 1.26	0.9887	9.26 ± 0.22	0.9731	26.53 ± 1.19	0.9061
F6	6.09 ± 0.32	0.9978	6.53 ± 0.05	0.9974	18.45 ± 1.15	0.8474
F7	13.87 ± 0.75	0.9958	9.05 ± 0.20	0.9748	25.98 ± 1.02	0.9226
F8	8.02 ± 0.86	0.9910	8.61 ± 0.13	0.9906	24.31 ± 1.57	0.8389
F9	7.84 ± 0.57	0.9949	7.24 ± 0.08	0.9944	20.55 ± 1.13	0.8692
F10	8.52 ± 0.64	0.9941	7.18 ± 0.15	0.9913	20.42 ± 1.05	0.8822
F11	8.93 ± 0.52	0.9965	7.59 ± 0.91	0.9941	21.58 ± 1.12	0.8817

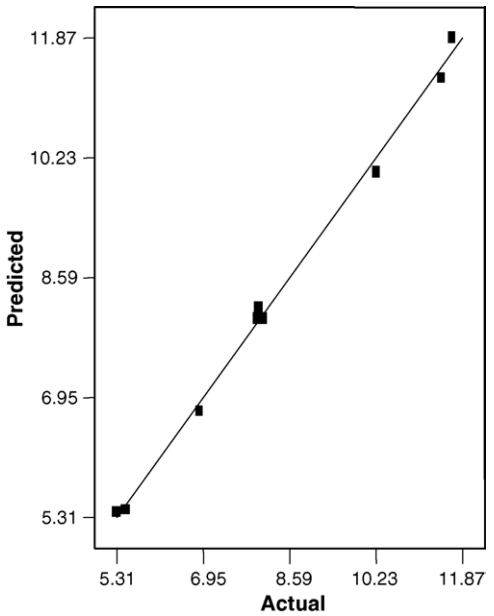

Fig. 5. Correlation between actual and predicted values for bioadhesion force (Y_1).

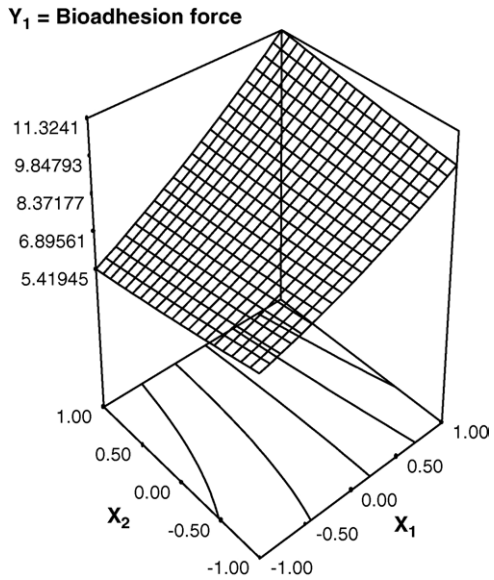

Fig. 6. Response surface plot showing the effect of peripheral polymer ratio (X_1) and core polymer ratio (X_2) on bioadhesion force (Y_1).

depended upon the water imbibition which in turn increases the diffusion and interpenetration of macromolecules (Machida and Nagai, 1999). The constant and regression coefficient for Y_1 (bioadhesion force) are as follows:

$$Y_1 = 8.04 + 2.29X_1 + 0.29X_1^2 + 0.66X_1X_2$$

The quadratic model was found to be significant with an F value of 265.17 ($p < 0.0001$). Fig. 5 represents the observed response values compared to that of predicted values. Bioadhesion of the buccal compact increases significantly with increase in carpobol concentration in the peripheral layer. The combined effect of factor X_1 and X_2 can be further elucidated with the help of response surface plot (Fig. 6). High level of factor X_1 gave high value of bioadhesion force at all the level of factor X_2 which indicates that the factor X_1 has significant positive effect on bioadhesion force. The possible explanation for such a behavior is due to high concentration of carbopol upon exposure to the moist surfaces, the pH of the microenvironment became acidic which caused an increase in bioadhesion. The results obtained were in accordance with the earlier report (Ikinici et al., 2004).

3.6. Effect of formulation variables on percentage MT release at 8 h

The model terms for Y_2 (MT release at 8 h) were found to be significant with an F value of 35.46 (0.0007), high R^2 value of 0.9726 indicate the adequate fitting of quadratic model. In this case, all the factors were found to be significant and the model describing the percentage MT release at 8 h can be written as:

$$Y_2 = 60.26 - 10.09X_1 - 3.46X_2 + 3.42X_1^2 + 6.88X_2^2 - 4.92X_1X_2$$

As the polymer-to-polymer ratio (carbopol 934P: HPMC K4M) in peripheral layer and core layer (HPMC K4M: sodium alginate) increased, causes an increase in viscosity of the swollen gel matrix, which contribute more hindrance for drug diffusion and consequently decreases the release rate. The combined effect of X_1 and X_2 can be further elucidated with the help of response surface plot (Fig. 7). Highest value of percentage MT release at 8 h was observed in formulation 1 having low value of either of the independent variables, which may be due to low polymer concentration

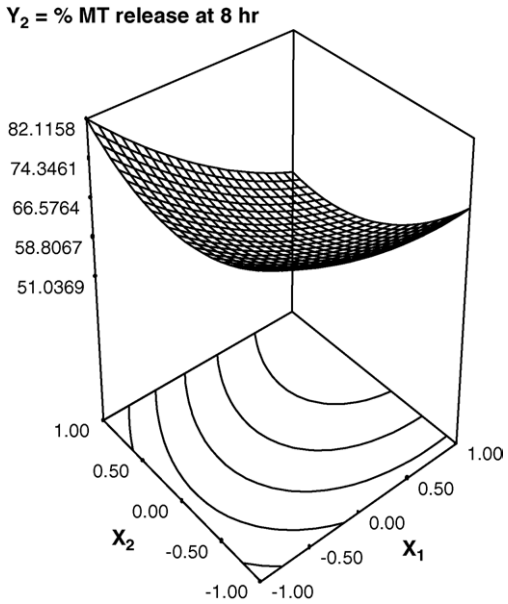

Fig. 7. Response surface plot showing the effect of peripheral polymer ratio (X_1) and core polymer ratio (X_2) on %MT release at 8 h (Y_2).

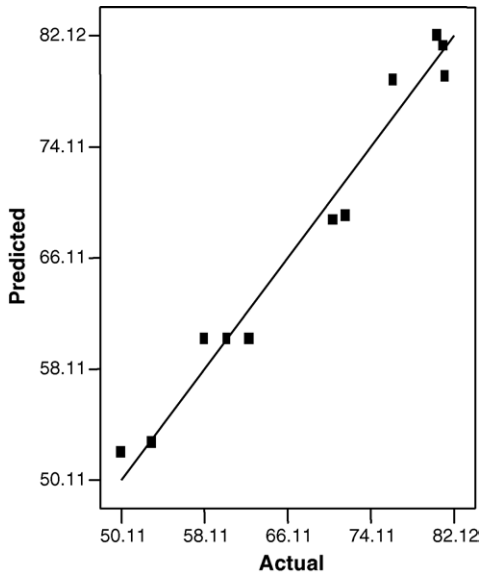

Fig. 8. Correlation between actual and predicted values for %MT release at 8 h (Y_2).

in both peripheral and core layer thus weakening the gel strength of the matrix. High level of X_2 gave low value of percentage MT release at 8 h at all the level of X_1. From the results, it can be concluded that both the independent variables have negative effect and factor X_1 has more significant effect than that of factor X_2 on percentage MT release at 8 h. Such a behavior of decreases in MT release may be attributed due to increased viscosity and strength of gel matrix formed due to carbopol 934P and HPMC K4M. The swelling behavior of carbopol may be due to uncharged –COOH group which forms hydrogen bonds with imbibing water and also holds water inside the gel matrix. Increasing the amount of HPMC K4M in core layer also forms a gel network and there the drug diffusion is controlled by penetration of liquid through the gelled network. Sodium alginate a water soluble polymer is included which probably results in formation of porous channels causing a faster release of MT from the compacts, as observed incase of formulation 1, containing 2:1 ratio of HPMC K4M and sodium alginate. Fig. 8 represents the observed response values compared to that of predicted values.

3.7. Effect of formulation variables on release exponent (n)

The quadratic model for Y_3 (n) was found to be significant with an F value of 33.16 (0.0008). In this case, factor X_1, X_2 and along with interaction factor X_1X_2 were found to be significant. Thus, model then becomes:

$$Y_3 = 0.94 + 0.12X_1 + 0.058X_2 + 0.057X_1X_2$$

As the concentration of polymer in peripheral layer and core layer is increased, the release exponent value also increases. Fig. 9 represents the predicted versus measured data. The response surface plot in Fig. 10 clearly illustrates the effect of interaction between X_1 and X_2 on release exponent. If X_1 was kept at low level and X_2 was increased from low to higher level, then the effect was found to be marginal. But the same release exponent value increases drastically from 0.90 to 1.13 when X_2 was increased from -1 to +1 level. The probable explanation for this may be due to increased polymer concentration in the delivery system and the system take a complete control over the release of MT (Li et al., 2001). At the same time, the release mechanism from the device shifts to zero-order release due to the equivalence

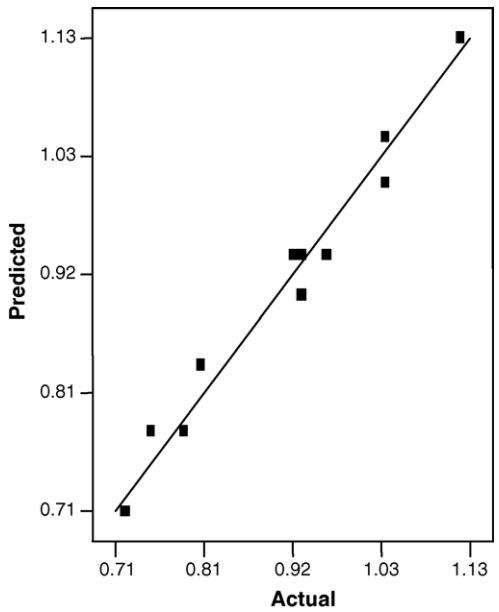

Fig. 9. Correlation between actual and predicted values for release exponent (Y_3).

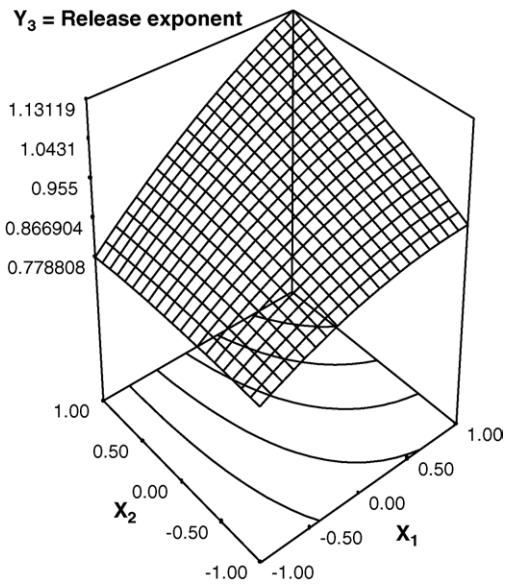

Fig. 10. Response surface plot showing the effect of peripheral polymer ratio (X_1) and core polymer ratio (X_2) on release exponent (n) (Y_3).

of the rates of swelling and erosion (Rao et al., 1990).

3.8. Effect of formulation variables on $T_{50\%}$

Along with the model terms, factor X_1, X_2^2 and interaction factor X_1X_2 were found to be significant with an F value of 18.24. The polynomial equation relating to response Y_4 can be written as:

$$Y_4 = 6.76 + 0.96X_1 - 0.75X_2^2 + 0.60X_1X_2$$

As the amount of polymer in peripheral layer increases, the corresponding $T_{50\%}$ also increases. As discussed earlier, increasing amount of carbopol forms a high viscous gel along with HPMC K4M which decrease the water diffusion into the core layer and thereby decreases the release rate and in turn increases the $T_{50\%}$.

3.9. ANOVA, pure error, lack of fit

The results of ANOVA in Table 6 for the dependent variables demonstrate that the model was significant for all response variables. Regression analysis was carried out to obtain the regression coefficients (Table 5) and the effects as follows; all the factors were found to be significant for Y_2. Similarly, only peripheral polymer ratio and its interaction term with core polymer ratio were found to be significant for Y_1, Y_3 and Y_4. The quadratic terms X_1^2 and X_2^2 were found to be significant for Y_1 and Y_4, respectively. The above results conveyed us that both peripheral polymer ratio and core polymer ratio plays an important role in the formulation of three layered buccal compact containing highly water-soluble drug MT. Hence, an appropriate range of formulation variables yields an optimized buccal compact with good bioadhesive strength and drug release. The data of pure error and lack of fit are summarized in Table 6, which can provide a mean response and an estimate of pure experimental uncertainty (Lieberman et al., 1988). The residuals are the difference in the observed and predicted value. Since, the computed F values were, respectively, less than the critical F value, which denotes non-significance of lack of fit.

3.10. Optimization

A numerical optimization technique by the desirability approach was used to generate the optimum

Table 5
Summary of ANOVA table for dependent variables from CCD

Source	d.f.	Sum square	Mean square	F value	Probability
Bioadhesion force ($\times 10^3$ dyne cm^{-2})					$R^2 = 0.9962$
X_1	1	42.13	42.13	1259.44	<0.0001
X_1^2	1	0.49	0.49	14.63	0.0123
X_1X_2	1	1.73	1.73	51.69	0.0008
MT release at 8 h (%)					$R^2 = 0.9726$
X_1	1	815.19	815.19	112.30	0.0001
X_2	1	95.70	95.70	13.18	0.0150
X_1^2	1	65.88	65.88	9.07	0.0297
X_2^2	1	267.55	267.55	36.85	0.0018
X_1X_2	1	96.72	96.72	13.32	0.0147
Release exponent (n)					$R^2 = 0.9707$
X_1	1	0.11	0.11	118.29	0.0001
X_2	1	0.027	0.027	27.96	0.0032
X_1X_2	1	0.013	0.013	13.91	0.0136
$T_{50\%}$ (h)					$R^2 = 0.9480$
X_1	1	7.43	7.43	55.01	0.0007
X_2^2	1	3.21	3.21	23.78	0.0046
X_1X_2	1	1.45	1.45	10.75	0.0220

Table 6
Summary of ANOVA results in analysing lack of fit (LOF) and pure error

Source	Sum square	d.f.	Mean square	F value	Probability > F
Bioadhesion force ($\times 10^3$ dyne cm^{-2})					
Model	44.36	5	8.87	265.17	<0.0001*
Residual	0.17	5	0.0328	–	–
Total	44.53	10	–	–	–
Lack of fit	0.16	3	0.054	17.32	0.0551^{ns}
Pure error	0.0062	2	0.0031	–	–
MT release at 8 h (%)					
Model	1287.15	5	257.43	35.46	0.0007*
Residual	36.30	5	7.26	–	–
Total	1323.45	10	–	–	–
Lack of fit	27.05	3	9.02	1.95	0.3567^{ns}
Pure error	9.25	2	4.62	–	–
Releae exponent (n)					
Model	0.16	5	0.032	33.16	0.0008*
Residual	0.0047	5	0.0095	–	–
Total	0.16	10	–	–	–
Lack of fit	0.0038	3	0.0012	2.99	0.2607^{ns}
Pure error	0.0086	2	0.0043	–	–
$T_{50\%}$ (h)					
Model	12.31	5	2.46	18.24	0.0032*
Residual	0.68	5	0.14	–	–
Total	12.99	10	–	–	–
Lack of fit	0.59	3	0.20	4.66	0.1817^{ns}
Pure error	0.084	2	0.042	–	–

Note: (*) Significant ($p < 0.05$), ns: non-significant.

Table 7
Composition of optimized formulation

Ingredients	Quantities (mg)
Peripheral layer	
Carbopol 934P	70
HPMC K4M	10
Lactose	20
Core layer	
MT	50
HPMC K4M	33.33
Sodium alginate	16.67
Backing layer	
Mg stearate	25
Ethyl cellulose	25

Table 8
Comparison between the experimented (*E*) and predicted (*P*) values for the most probable optimal formulation

Dependent variables	Optimized formulation	
	E	*P*
Bioadhesion force ($\times 10^3$ dyne cm^{-2})	10.72 ± 1.13	10.04
MT release at 8 h (%)	70.85 ± 3.21	68.84
Releae exponent (n)	0.92 ± 0.08	0.90
$T_{50\%}$ (h)	5.68 ± 0.65	5.99

settings for the formulation. The process was optimized for the dependent (response) variables Y_1–Y_4 and the optimized formula was arrived by maximizing the bioadhesion force. The MT release at 8 h was targeted to 75% with release exponent and time required for 50% of drug release was kept at range. Optimized results therefore obtained were included in the Table 7, to gainsay the reliability of the response surface model, new optimized formulation were prepared according to the predicted model and evaluated for the responses. The results in Table 8 showed a good relationship between the experimented and predicted values, which confirms the practicability and validity of the model.

4. Conclusions

A CCD was performed to study the effect of formulation variables on the release properties and bioadhesion force by applying the computer optimization technique. The peripheral polymer ratio is a major factor affecting the release and bioadhesive strength of the three layered buccal compact. At higher polymer concentration in peripheral layer, the MT release from the system can be controlled with good bioadhesion. Observed responses were in close agreement with the predicted values of the optimized formulation, there by demonstrating the feasibility of the optimization procedure in developing three layered buccal compact containing highly water-soluble drug MT. Finally, it is concluded that with limited number of experiments an optimal formulation with target release and good bioadhesion can be designed with appropriate statistical experimental design and optimization technique.

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