RESEARCH ARTICLE

Formulation development of Domperidone buccal bioadhesive hydrophilic matrix tablets

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Buccoadhesives have long been employed to improve the bioavailability of drugs undergoing significant hepatic first pass metabolism. Domperidone is also reported to have low oral bioavailability due to an extensive hepatic first-pass effect. Buccoadhesive hydrophilic matrices containing Domperidone were prepared using a 3^2 factorial design. The amounts of Carbopol 934P (CP) and Methocel K100LV (HPMC) were taken as the formulation variables (factors) for optimizing bioadhesion and kinetics of dissolution. A mathematical model was generated for each response parameter. Bioadhesive strength tended to vary quite linearly in an increasing order with an increasing amount of each polymer. The drug release pattern for all the formulation combinations was found to be non Fickian, approaching zero-order kinetics. A suitable combination of two polymers provided adequate bioadhesive strength and fairly regulated the release profile up to 4 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 were found to be in close agreement with the experimental findings.

Key words: *Bioadhesion, buccal delivery, Domperidone, factorial design, optimization, response surface methodology*

INTRODUCTION

The 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 the saliva, facile removal of the formulation, better patient acceptance and compliance are some other prominent meritorious visages of the buccoadhesive systems.[1-4]

Domperidone is a dopamine receptor (D2) antagonist. It is used as an antiemetic agent for short-term treatment of nausea and vomiting of various etiologies. It is also used for its prokinetic actions. It is rational to formulate the buccoadhesive dosage form of Domperidone as it is known to have a low oral bioavailability due to extensive first-pass effect. Sudden death may occur when Domperidone is administered intravenously in high doses. The plasma half-life of Domperidone is 7.5 hr. It has a low molecular weight (425.92) and no objectionable taste. These make it an appropriate candidate for being incorporated into the buccoadhesive formulation.[5-8]

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Systematic optimization techniques have frequently been employed for the design and development of pharmaceutical dosage forms.[9,10] 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.[11,12] Factorial designs (FDs), 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.[13,14]

The aim of the current study was to develop and optimize the mucoadhesive hydrophilic compressed matrices of Domperidone for buccal delivery. A computer-aided optimization process using a 3^2 FD was employed to investigate the effect of two independent

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variables (factors), i.e. amount of two swellable polymers: Methocel K100LV (HPMC) and Carbopol 934P (CP). Release till 4 h (rel4h), time taken to release of 50% of the drug (t50%) and bioadhesive strength (f) were taken as the response variables.

MATERIALS AND METHODS

Materials

Domperidone was a gift sample from BURGEON Pharmaceuticals Pvt. Ltd. (Chennai, India), Methocel K100LV by Colorcon Asia Pvt. Ltd. (Goa, India), Carbopol 934P from M/s Loba Chemie Ltd. (Mumbai, India) and lactose, magnesium stearate and citric acid (M/s Loba Chemie Ltd.) were procured from commercial sources. 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 lactose along with a fixed quantity of magnesium stearate and citric acid. The drug and excipients were homogeneously blended and subsequently compressed into flat-faced tablets (100 mg, 8mm diameter) using a Rimek MINI PRESS-II MT tablet machine (Karnawati Eng. Ltd., Mehsana, India) to achieve a tablet thickness of 1.5±0.1mm.

FD

A 3^2 full FD was constructed, where the amounts of CP (X1) and HPMC (X2) 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 and their factor combinations and Table 3 summarizes 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 Domperidone was accurately weighed and extracted with a suitable volume of phosphate buffer (PB) solution, pH 6.8. Each extract was suitably diluted and analyzed spectrophotometrically (Jasco V-530 UV/VIS spectrophotometer, Jasco Corporation, Easton, USA) at 283 nm. Spectrophotometric analysis of the formulation excipients, i.e. CP, HPMC, lactose, citric acid and magnesium stearate, using the highest concentration employed in the formulation, indicated no interference at 283 nm in the PB (pH 6.8).

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 for 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*.,[15] as in Figure 1. Porcine buccal mucosa was used as the model membrane. The mucosa was kept frozen in PB,

Table 1: Composition of Domperidone buccoadhesive hydrophilic compressed matrices (100.0mg)

Ingredients	Quantity (mg)
Domperidone	10
Carbopol 934P	10-30
HPMC K 100LV	10-30
Citric Acid	15
Magnesium stearate	2
Lactose	q.s.

Table 2: A 3^2 full factorial experimental design layout

	Coded factor levels	
Trial no.	XI	X2
F1	-1	-1
F2	-1	0
F3	-1	1
F4	0	-1
F5	0	0
F6	0	1
F7	1	-1
F8	1	0
F9	1	1

Table 3: Translation of coded levels in actual units

Coded level	-1	0	1
X1: CP (mg)	10	20	30
X2: HPMC (mg)	10	20	30

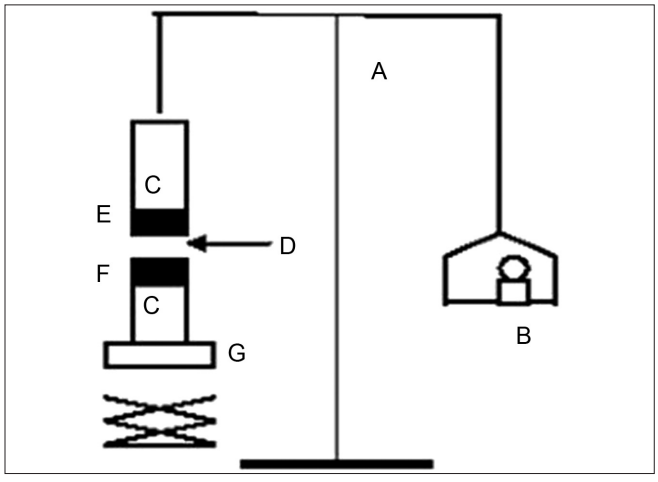

Figure 1: Bioadhesion test assembly; (a) modified balance; (b) weights; (c) glass vial; (d) bioadhesive buccal tablet; (e) membrane; (f) supportive adhesive tape; (g) height adjustable pan

pH 6.8, and thawed to room temperature before use. The mucosal membrane was excised by removing the underlying connective and adipose tissues and was equilibrated at 37±1°C for 30min buffer (PB pH 6.8) 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 1min. 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 a dissolution test apparatus (DA-6D USP Standard). PB, pH 6.8 (500 ml), was taken as the release medium at 75 rpm and 37±1°C employing the USP II paddle method (Apparatus 2). Aliquots of small samples were periodically withdrawn and the sample volume was replaced with an equal volume of fresh dissolution medium. The samples were analyzed spectrophotometrically at 283 nm. The formulation excipients did not interfere with the spectrophotometric analysis of the drug at 283 nm in PBs.

Data analysis

The data obtained from the dissolution kinetics studies were analyzed using ZOREL software.[16] The software has in-built provisions for correcting the amount release for the drug loss during sampling.[17] 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.*,[18] as in Eq. (1):

$$\text{Log } (Mt/M\infty) = \log k + n \log t \quad (1)$$

where $Mt/M\infty$ is the fraction of drug released at time t. The values of t50% were calculated by Stineman interpolation using GRAPH software (Version 2, Micromath Inc.,Saint Louis, Missouri USA). 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 the f values using MS-Excel (2000).

Various computations for the current optimization study using RSM were carried out employing the Design Expert Version 7 software. Statistical second-order models, including interaction and polynomial terms, were generated for all the response variables.

The general form of the model is represented in Eq. (2):

$$Y = \beta 0 + \beta 1X1 + \beta 2X2 + \beta 3X1X2 + \beta 4X^21 + \beta 5\, X^22 + \beta 6\, X1\, X^22 + \beta 7\, X^21\, X2 + \beta 8\, X^21\, X^22 \quad (2)$$

Where $\beta 0$, the intercept, is the arithmetic average of all quantitative outcomes of nine runs, $\beta 1$ to $\beta 8$ are the coefficient computed from the observed experimental values of Y and X1 and X2 are the coded levels of the independent variable(s). The terms X1X2 and X^2i (I = 1, 2) are the interaction and polynomial terms, respectively. The statistical validity of the polynomials was established on the basis of Yates' ANOVA. Subsequently, feasibility as well as grid search was performed to locate the composition of the optimum formulations. Also, three-dimensional response surface graphs and contour plots were drawn in MS-Excel using the output files generated by the DESIGN EXPERT VER-7 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. rel4hr, t50% and f. 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 the predicted values. Also, linear correlation graphs between experimentally observed and predicted properties of optimum Domperidone buccoadhesive tablets attempted using MS-Excel.

RESULT AND DISCUSSION

The literature documents that a significant reduction in dose can be achieved via buccal drug delivery of drugs with a high first-pass metabolism.[19-21] The bioavailability of Domperidone can be enhanced via buccal delivery, owing to the avoidance of a hepatic first-pass effect. However, as a buccoadhesive tablet, film or patch is unlikely to remain on the buccal mucosa for a long period of time, drug release in the present study was investigated only up to 4 h. Preliminary studies carried out prior to the experimental design revealed that the tablet formed with a low polymer content exhibited 100% drug release, but was vulnerable to fragmentation. On the other hand, the tablet formed with very high polymer content possessed good structural integrity but showed undesirably slow release. Accordingly, a suitable range for each of the polymer amounts was selected, as depicted in Table 1.

Physical evaluation

Tablet weights varied between 98.5 and 102.5 mg, thickness between 1.4 and 1.6mm and hardness between 4.5 and 6.5 kg/cm^2. The assay content of Domperidone 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

An increasing trend in the bioadhesive strength (with porcine mucosa) was seen with an increase in the amount of polymer(s). Maximum bioadhesive strength (f) was seen with the highest level 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 ($P < 0.001$).Subsequent application of one-way ANOVA, keeping the levels of one of the polymers fixed, also showed a statically significant difference among the observed data of bioadhesive strength ($P < 0.001$), ratifying the significant positive influence of each polymer on bioadhesion.

In vitro release studies

Table 5 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, using an aspect ratio of 8.6, were found to be 0.472 and 0.944 for declaring the Fickian diffusion and zero order, respectively. In all the nine cases studied, the exponent varied between 0.500 and 0.650, delineating a distinctly non-Fickian release approaching zero order. Further, the magnitudes of the Fickian diffusion constant (k1) ranging between 1.2387 and 1.4373, and in case II relaxation constant (k2) ranging between 0.0297 and 0.1844, reveal that the mechanism of drug release is predominantly diffusion, with a relativelyminor contribution of polymer relaxation as well. Although, in the present study, the magnitude of k2 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 depend on the amount of two polymers and their characteristic nature, which are the direct functions of matrix solubility. The overall rate of drug release tended to decrease with an increase in the 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 the active ingredient. Consequently, the values of t50% vary in between 1.1341 and 2.2097 h according to the content of the polymers.

Table 4: The bioadhesive strength for all the buccoadhesive formulations (n=5) prepared as per 3^2 full factorial experimental design

Trial no.	CP mg	HPMC	Bioadhesive strength (gm)
1	10	10	3.788±0.1517
2	10	20	4.892±0.0622
3	10	30	9.180±0.0803
4	20	10	6.524±0.1504
5	20	20	8.79±0.1790
6	20	30	10.798±0.1057
7	30	10	7.638±0.1878
8	30	20	12.392±0.1006
9	30	30	15.526±0.1955

Optimization results

The mathematical relationships constructed for the studied response variables are expressed as Eqs. (3)–(5). All the polynomial equations were found to be highly statistically significant ($P < 0.001$), as determined by ANOVA:

$$\text{rel 4hr} = 91.69 - 4.60\,X1 - 0.56X^2 1 - 7.57\,X2 - 0.62\,X^2 2 - 1.63\,X1X2 - 0.27\,X^2 1X2 + 0.0033\,X1X^2 2 - 0.17\,X^2 1X^2 2 \quad (3)$$

$$t50\% = 1.54 + 0.14\,X1 + 0.012X^2 1 + 0.28\,X2 + 0.13\,X^2 2 + 0.15\,X1X2 - 0.049\,X^2 1X2 + 0.04\,X1X^2 2 - 0.033\,X^2 1X^2 2 \quad (4)$$

$$f = 8.84 + 2.95\,X1 + 0.066\,X^2 1 + 2.93\,X2 + 0.073\,X^2 2 + 0.62\,X1X2 + 0.39 - 0.40\,X1X^2 2 + 0.058\,X^2 1X^2 2 \quad (5)$$

Figures 4a–6a portray the response surface plots. Figures 4b–6b are the corresponding contour plots for the studied response properties. Figure 4 shows that rel4hr. varies in a nearly line and is a descending pattern, with a change in the amount of polymers. Figure 2 also exhibits a near line trend of t50%, but in an ascending order. Figure 3 exhibits *in-vitro* dissolution profile of optimized formulations obtained from 3^2 FD. As there is no confounding of the contour lines in Figures 4 or 5, both the polymers seem to contribute independently toward drug release.

The response surface and contour plot for f-values [Figure 6] reveal that it varies in a somewhat linear fashion with the amount of two polymer (s).

For all the six optimum formulations, the value of n ranged between 0.685 and 0.839, visibly indicating a non-Fickian release behavior approaching zero-ordered kinetics. The values of k1 and k2 ranged narrowly between 1.0413 and

Table 5: Dissolution parameters for all buccoadhesive hydrophilic matrix formulations (n=3) prepared as per 3^2 factorial design

Trial no.	CP mg	HPMC mg	N	kl	k2	k	t50%	rel4hr	R^2
1	10	10	0.647	1.2387	0.1844	0.4069	1.3773	101.13	0.9329
2	10	20	0.563	1.3826	0.0887	0.4162	1.3067	97.92	0.9614
3	10	30	0.601	1.2961	0.1125	0.3761	1.5506	88.73	0.9467
4	20	10	0.57	1.4042	0.1203	0.4652	1.3243	99.53	0.9758
5	20	20	0.567	1.3890	0.0963	0.4273	1.1341	93.38	0.9623
6	20	30	0.504	1.3996	0.0297	0.3694	2.0906	85.49	0.9608
7	30	10	0.524	1.4373	0.0593	0.4277	1.4412	95.21	0.9269
8	30	20	0.558	1.3718	0.0719	0.3918	1.4303	88.11	0.9326
9	30	30	0.564	1.2799	0.0802	0.3337	2.2097	76.27	0.9478

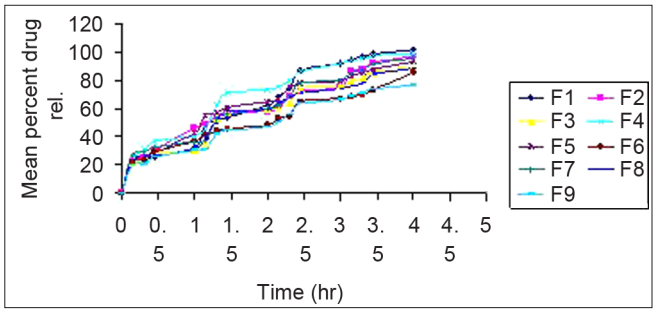

Figure 2: *In vitro* dissolution profile of buccoadhesive formulation of domperidone. The plot shows release profile of nine formulations as per 3² factorial design

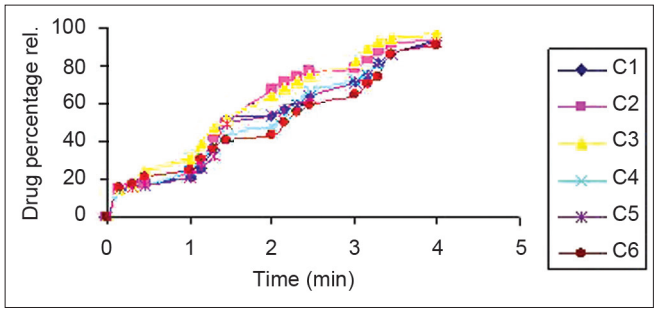

Figure 3: *In vitro* dissolution profile of buccoadhesive formulation of Domperidone. The plot shows release profile of an optimum formulation

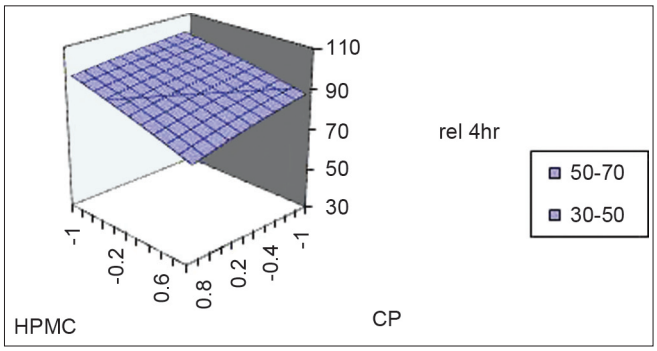

Figure 4a: Response surface plot showing the influence of CP and HPMC on the rel 4hr. values for buccoadhesive tablet of domperidone

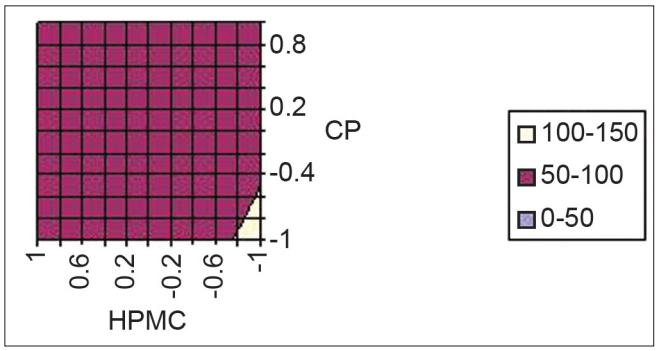

Figure 4b: Contour plot showing relationship between various levels of two polymers to attain fixed values of rel 4hr

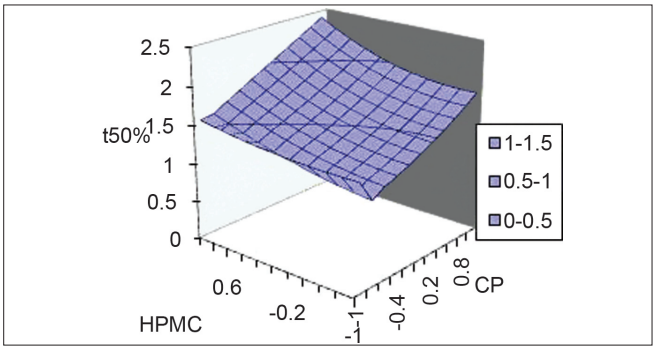

Figure 5a: Response surface plot showing the influence of CP and HPMC on the t50% values for buccoadhesive tablet of Domperidone

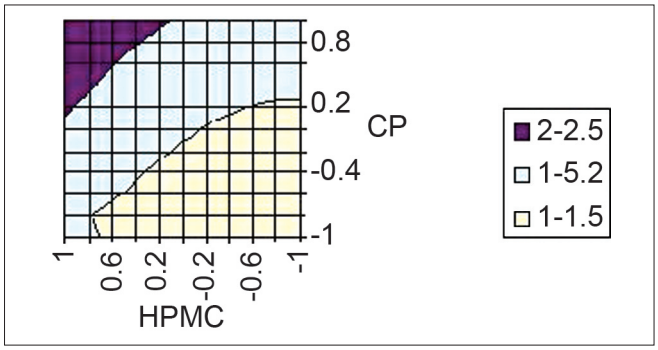

Figure 5b: Contour plot showing relationship between various levels of two polymers to attain fixed values of t50%

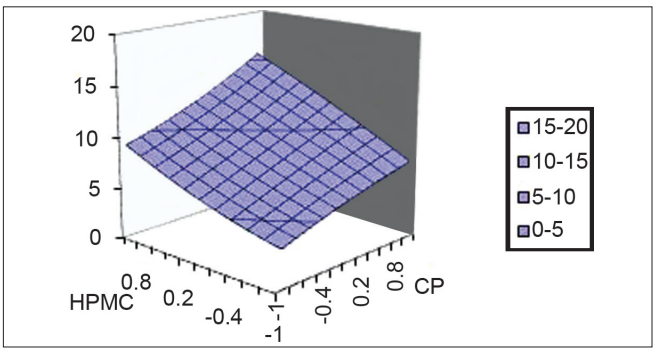

Figure 6a: Response surface plot showing the influence of CP and HPMC on the bioadhesive strength (f) values for buccoadhesive tablet of Domperidone

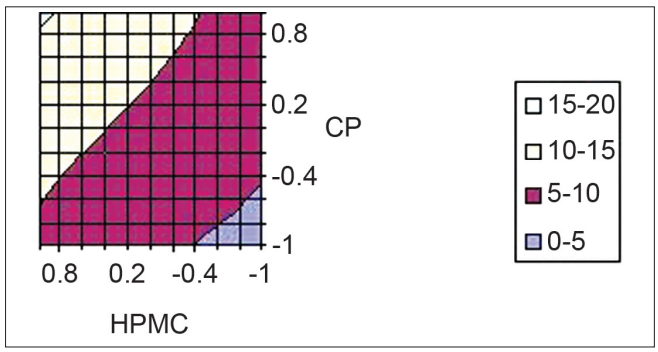

Figure 6b: Contour plot showing relationship between various levels of two polymers to attain fixed values of f

Table 6: Experimentally observed response parameteters of six optimum formulation and comparison with predicted values for validation of RSM

Formulation code	Formulation composition CP/HPMC (mg)	Response property	Experimental value	Predicated value	Percentage error
C1	10/24	rel4hr	93.69	93.11	0.62
		t50%	1.428	1.453	-1.72
		f	7.10	7.12	-0.28
C2	20/18	rel4hr	93.21	93.17	0.042
		t50%	1.496	1.489	0.47
		f	8.27	8.25	0.24
C3	26/10	rel4hr	96.99	96.69	0.31
		50%	1.612	1.647	-2.12
		f	7.02	7.04	-0.28
C4	27/15.25	rel4hr	92.29	92.24	0.005
		50%	1.512	1.504	0.053
		f	9.15	9.20	-0.54
C5	24.25/15.75	rel4hr	92.96	93.05	-0.009
		50%	1.495	1.484	0.74
		f	8.72	8.69	0.34
C6	28/16.75	rel4hr	90.32	90.51	-0.20
		50%	1.559	1.554	0.32
		f	10.05	10.01	-0.39
Mean (±SD) of % error					-0.1±0.7397

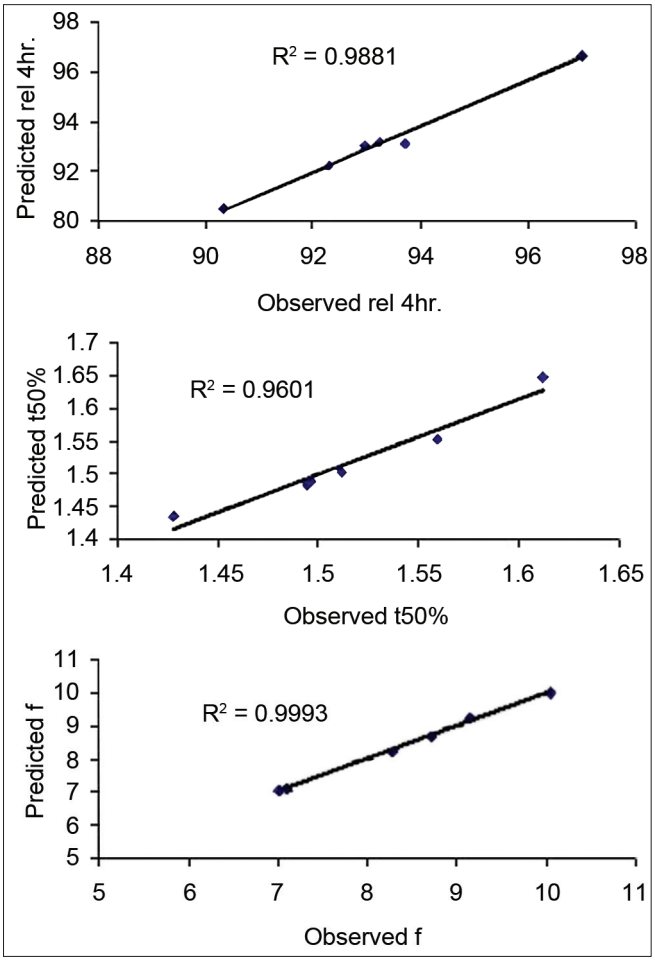

Figure 7: Linear correlation graphs of the experimentally observed properties of optimum domperidone buccoadhesive tablet with the values predicted using RSM

1.1183 and 0.1743 and 0.2580, respectively. For all these formulations, the bioadhesive strength ranged between 7.10 and 10.05 g. Evidently, the values of dissolution parameters had a propensity to range optimally between relatively controlled limits rather than those of the original formulations [Table 4] designed as per 3^2 FD.

Table 6 records the values of the observed and predicted responses using FD along with the percentage predicted errors for these six optimum formulations. The predicted error for the response variables ranged between -2.12 and 0.62%, with the mean±SD of the percentage error being -0.13±0.7397%. Also, the linear plots [Figure 7] drawn between the predicted and observed responses demonstrated high r^2 (ranging between 0.9601 and 0.9993), indicating excellent goodness of fit. Thus, the low magnitude of error as well as the significant values of r^2 designate a high prognostic ability of RSM.

CONCLUSIONS

The computer-based factorial optimization yields results with a high degree of prediction and fruition. The study can, therefore, enable the formulator to rich and quantify the optimum decrease in experimentation during formulation.

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