Asian Journal of Chemistry Vol. 20, No. 2 (2008), 1328-1336

Optimized Buccoadhesive Miconazole Tablet Using Simplex Centroid Experimental Design

A.R. MADGULKAR*, SHIVAJIRAO KADAM and VARSHA POKHARKAR
Department of Pharmaceutical Chemistry, Bharati Vidyapeeths
Poona College of Pharmacy, Pune-411 038, India
Tel: (91)9823350059; E-mail: ashwini.madgulkar@indiatimes.com

The purpose of present work was to prepare miconazole nitrate buccal adhesive preparations using simplex centroid experimental design to optimize polymer ratio, which will provide desired drug release and mucoadhesion to prepared tablets. Various polymers such as carbopol 934P, hydroxy propyl methylcellulose K4M and sodium carboxy methyl cellulose to prepare buccal adhesive tablet of miconazole nitrate. Tablet properties such as swelling index, mucoadhesive strength and *in vitro* drug release were evaluated. The drug release and bioadhesion was dependent on type and composition of the polymer used. The combination, which gave good result, was further optimized using a simplex centroid experiment design. The dissolution of miconazole from tablets was sustained for 6 h. Based on the results obtained, it can be said that prepared slow release buccoadhesive tablets of miconazole would markedly prolong the duration of the antifungal activity with more patient compliance.

Key Words: Simplex, Miconazole, Bioadhesion, Antifungal.

INTRODUCTION

The term bioadhesion is used to describe attachment of synthetic or natural polymers to biological surface. If the adhesion surface is mucous membrane coated with a thin layer of mucus, the term mucoadhesion is employed[1]. Adhesion to specific sites such as oral and nasal cavities increase bioavailability by virtue of optimum contact with adhesion surface increases absorption of drug and prolongs gastric residence. In recent years, an increasing interest in the development of novel mucoadhesive buccal dosage form used both for systemic delivery of drug as well as for local targeting of drugs to buccal cavity. To determine the bioadhesive potential of different polymers, several techniques were reported. Most systems are based on tensile testing systems for evaluation of strength of mucoadhesive interactions as well as specific contact time[2]. Studies involved measurement of adhesive strength using *ex vivo* test. Miconazole nitrate is an established drug for the treatment of topical and systemic

fungal infections. Buccal gels containing miconazole are currently used, because the drug does not persist in the oral cavity, thus gels have to be applied several times a day. Maximal salivary concentrations of miconazole nitrate are seen in applications but the drug is rapidly cleared from the oral cavity. Earlier studies involving miconazole buccoadhesive preparations involved, combinations of modified starches with poly acrylic acid[3], comparison of anionic, cationic and nonionic polymers[4], use of hydroxy propyl methyl cellulose (HPMC), carbopol 934P (C 934P) combination to prepare novel buccoadhesive tablet are reported[5]. Several polymers including PEG, cellulose derivatives and polyacrylic acid have been used in formulation of bioadhesive system. Some of these adhere well although some are mildly irritating to oral mucosa; polyacrylates has been shown to induce severe irritation[6]. Present work is an attempt to formulate buccoadhesive tablet of miconazole using carbopol, HPMC K4 M, sodium carboxy methyl cellulose (NaCMC) and combinations thereof. Buccoadhesive preparations using polymers and their combinations were prepared and evaluated for hardness, friability, diameter, drug content, swelling index, *in vitro* drug release and bioadhesive strength. The polymer combination, which gives best response, was optimized using a simplex centroid experimental design[7]. The model was adequate to design the buccoadhesive system with desired features (r = 0.9458).

Mixture designs[8] are specialized designs, particularly useful for formulation development in which the measured response is a function of only the proportions of the components in the product. Various types of mixture designs are simplex lattice, simplex centroid, extreme vertices and mixture-process variable design.

EXPERIMENTAL

Miconazole nitrate was provided by Sankalp Health Care, Karad, Maharashtra. The polymers HPMC K4 M, Carbopol 934P and poly vinyl pyrollidone (PVP K30) were obtained as gift samples from Ranbaxy Research Centre, Jejury.

Preparation of buccoadhesive miconazole tablets: Formulations were prepared by direct compression using a flat face 8 mm punch. Each tablet contained 10 mg of Miconazole nitrate, mannitol, talc and bioadhesive polymers carbopol, HPMC K4 M, sodium CMC and combinations thereof. All materials were passed through a 125 µ sieve and retained on 90 µ sieve. Miconazole was first mixed with the buccal bioadhesive polymer mixture. Mannitol and talc were then added and mixing was continued. The tablet weight was adjusted for *ca.* 100 mg.

Mucoadhesive strength was measured using the apparatus developed in the laboratory.

The swelling index was determined by weighing 5 tablets and recording individual tablet (W1) and placing in petridish containing 25 mL phosphate buffer pH 6.8. At regular intervals the tablets were removed and the excess surface water was removed carefully using filter paper and swollen tablets were reweighed (W2). The swelling index was calculated using formula

$$\text{Swelling index} = [(W_2 - W_1)/W_1] \times 100$$

Evaluation of the prepared tablets:

Weight uniformity: Test was done according to USP procedure[9]

Diameter and thickness: 10 randomly selected tablets of each formulation were evaluated and average diameter and thickness reported.

Hardness and friability: 10 randomly selected tablets of each formulation was determined using Monsanto hardness tester and Roche friabilator[10].

Drug content uniformity: 10 tablets were weighed accurately and powdered. Powder equivalent to 10 mg miconazole nitrate was transferred to 100 mL volumetric flask containing 50 mL of phosphate buffer pH 6.8, sonicated for 0.5 h and stirred continuously for 8 h on a magnetic stirrer. The volume was made up to 100 mL with phosphate buffer (pH 6.8) and the absorbance was measured in a UV spectophotometer at 220 nm.

***In vitro* drug release study:** Miconazole nitrate released from the prepared buccoadhesive tablets was determined in standard USP type II dissolution test apparatus containing 900 mL of phosphate buffer pH 6.8 maintained at 37 °C. Samples of 5 mL were withdrawn at predetermined time intervals over 6 h and replaced with equal volumes of the dissolution medium equilibrated at the same temperature; drug concentration of withdrawn samples was analyzed after filtration (0.45 μ millipore) by UV spectroscopy at 220 nm.

Statistical analysis: The results were expressed as mean ± SEM. All statistical comparisons were made by Anova followed by Tukey Kramer multiple comparison test using graph pad instat version 3.01 for Windows 95, graph pad software Inc, 5755, Oberlin drive # 110, San Diego, California 92121, USA. P values < 0.05 were considered significant.

RESULTS AND DISCUSSION

Five tablet formulations F1, F2, F3, F4 and F5 were prepared with different combinations of HPMC K4M, carbopol 934, sodium CMC (Table-1). PVP was included to improve drug release. The tablet properties are summarized in Table-3. Tablets fulfill criteria for drug content, weight variation, hardness and friability values.

The data obtained from dissolution kinetics studies were analyzed using ZOREL software[11].

TABLE-1
COMPOSITION OF DIFFERENT BUCCOADHESIVE TABLET FORMULATIONS

Ingredients	F1	F2	F3	F4	F5
Miconazole nitrate	10 mg	10 mg	10 mg	10 mg	10 mg
Carbopol 934	90 mg	-	-	20 mg	15 mg
HPMC K4 M	-	90 mg	-	-	15 mg
PVP	-	-	-	10 mg	10 mg
Na CMC	-	-	90 mg	20 mg	-
Mannitol	-	-	-	37 mg	47 mg
Talc	-	-	-	03 mg	03 mg

TABLE-2
DOE PARAMETER SETTINGS INCLUDING INGREDIENTS AND PROPORTION (%) IN THE MIXTURE OF EXCIPIENTS

Contents	A	B	C	AB	BC	AC	ABC
Drug	10	10	10	10	10	10	10.0
Carbopol	50	-	-	25	25	-	16.6
HPMC	-	50	-	25	-	25	16.6
PVP	-	-	50	-	25	25	16.6
Mannitol	37	37	37	37	37	37	37.0
Talc	3	3	3	3	3	3	3.0

Coded level of Variables (1 = 50 mg of total polymer concentration in formulation)

Variables in total excipient	Level	
	Low	High
A = Fraction of Carbopol	0	1
B = Fraction of HPMC	0	1
C = Fraction of PVP	0	1

TABLE-3
EVALUATION OF MUCOADHESIVE TABLETS

Physical parameter	F1	F2	F3	F4	F5
Weight (mg)	100.00 ± 2.125	100.00 ± 1.954	100.00 ± 2.125	100.00 ± 1.984	100.00 ± 2.154
Hardness (kg/cm^2)	7.00 ± 0.954	7.80 ± 0.856	7.80 ± 0.995	7.40 ± 0.945	7.20 ± 0.975
Friability (%)	0.23 ± 0.002	0.32 ± 0.003	0.21 ± 0.001	0.12 ± 0.001	0.26 ± 0.002
Diameter (mm)	8.10 ± 1.001	8.00 ± 0.994	8.10 ± 1.032	8.00 ± 1.012	8.00 ± 1.002
Thickness (mm)	1.50 ± 0.032	1.50 ± 0.056	1.50 ± 0.045	1.50 ± 0.064	1.50 ± 0.054
Drug content (%)	98.06 ± 1.452	99.30 ± 1.265	98.60 ± 1.542	99.20 ± 0.956	99.80 ± 1.025
Swelling index (6 h)	10.09 ± 0.040	3.71 ± 0.050	3.71 ± 0.040	2.36 ± 0.010	1.75 ± 0.030

The drug release profiles from the prepared buccal buccoadhesive miconazole tablets are shown in Fig. 2. Miconazole was gradually released from all formulations over a period of 6 h. Therefore release from all the prepared tablets could be adequately sustained. Formulations containing carbopol F1 and HPMC F2 showed incomplete drug release in 6 h period. Formulation containing only sodium CMC F3 dissolved completely and the release was slower and less than both carbopol and HPMC formulations. The values of swelling index support release profiles. One-way Anova showed the drug release profiles from all formulations to be different ($p < 0.5$). The values of diffusional exponent, kinetic constant using power law and correlation coefficient are summarized in Table-4. The value of 'n' which is between 0.5 and 1 for F1 and F2 which means the release is Non Fickian while for formulation F3, F4 and F5 the $n < 0.5$ which means release is Fickian.

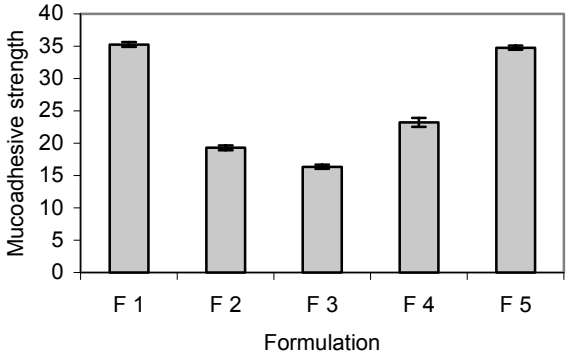

Fig. 1. Bioadhesive strength of formulations

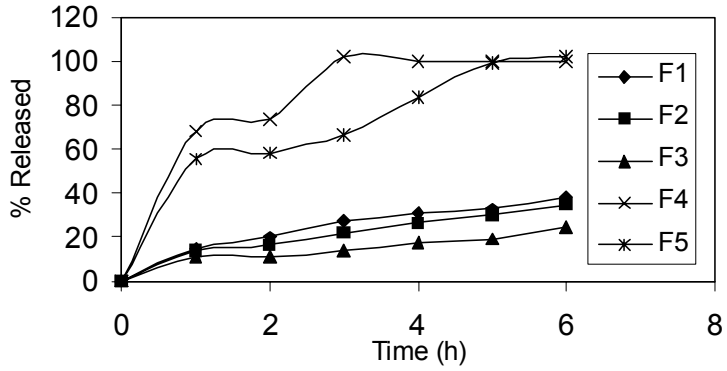

Fig. 2. Drug release profiles of formulations

TABLE-4
ESTIMATED VALUES OF 'n' (DIFFUSIONAL EXPONENT), K (KINETIC CONSTANT) AND R^2 (CORRELATION COEFFICIENT)

Formulation	n	K	R^2
F1	0.5597	0.1434	0.9879
F2	0.5489	0.1269	0.9749
F3	0.4593	0.0938	0.8587
F4	0.2777	0.6716	0.8796
F5	0.3898	0.4982	0.8809

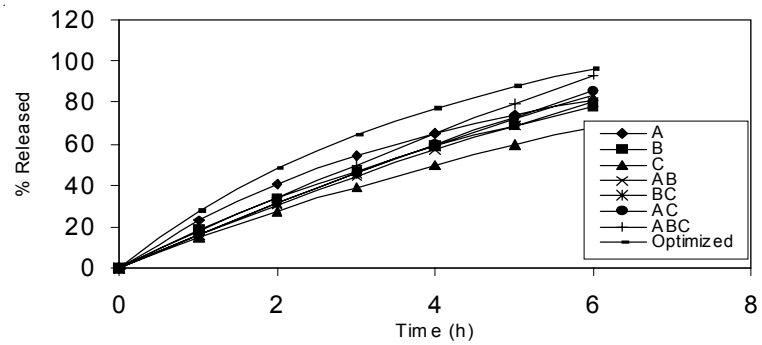

Fig. 3. Drug release profiles of formulations prepared as per simplex centroid design and optimized formulation

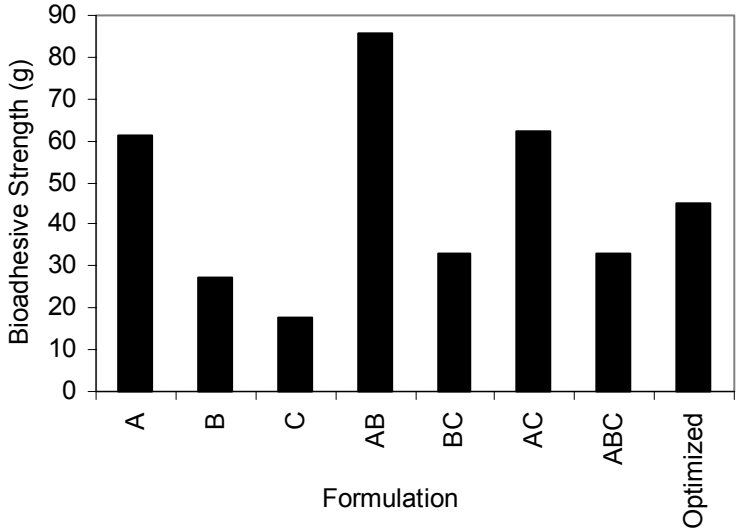

Fig. 4. Bioadhesive strength of formulations prepared as per simplex centroid design

HPMC K4 M is useful to reduce irritation of buccal mucosa which may be caused by carbopol, it also acts as release retardant, maintains tablet integrity. The swelling characteristics are important for adhesion, considering that main physical mechanism of bioadhesion is the interpenetration of the chains of polymer and mucus to a sufficient depth to create a semi permanent adhesive bond. Three constituents HPMC, carbopol and PVP from formula F5 were mixed according to mixture design, with multiple constraints on the component proportions, using fixed intervals, as stated in Table-2. The total amount of excipients was maintained at 50 mg and the miconazole content was 10 mg. The coordinates of the 7 design points were generated and the respective tablet formulations are described in Table-2.

Optimization is applied for finding a factor combination matching an optimal response profile. The design supporting a linear model is useful when the experimental objective is screening, whereas, the design supporting quadratic or special cubic models are relevant for optimization. We constructed a design for investigating the influence of polymers on the responses (mucoadhesion force and % drug release). With three factors, the lead number of experiments n = 7 was constructed and six runs were randomly set. After producing and analyzing the formulations, responses were applied to fit the appropriate model (linear or quadratic). The model was tested for goodness of fit (R^2) and analysis of variance (Anova) was applied to verify the adequacy of the regression model in terms of a lack-of-fit test.

TABLE-5
ANALYSIS OF VARIANCE OF THE LINEAR AND QUADRATIC MODELS FOR THE RESPONSES

Model	Bioadhesion force	% Drug Release (6 h)
Linear	Not Significant	Not Significant
R^2	0.4254	0.2827
F value	0.0112	0.2839
Quadratic	Not Significant	Not Significant
R^2	0.5624	0.2859
F value	0.3091	0.2595
Special cubic	Significant	Significant
R^2	0.9984	0.9458
F value	0.9368	0.7082

It was found that, linear or quadratic models were not significant as presented in Table-5 Consequently, special cubic model was used.

$$\text{Bioadhesion} = 61.16X_1 + 27.16X_2 + 17.61X_3 + 186.16X1X_2 + 42.6X_2X_3 + 91.96X_1X_3 - 1725.2\,X_1X_2X_3 \quad (3)$$

This equation shows negative value for combined effect of carbopol, HPMC and PVP on bioadhesion. Special cubic model was also obtained for % drug release and the equation calculated from the regression data was:

$$\% \text{ Release} = 81.23X_1 + 78.33X_2 + 68.23X_3 + 0.8\,X_1X_2 + 42.00X_1X_3 + 40.80X_2X_3 + 223.05X_1X_2X_3 \quad (4)$$

Based on the fitted regression models, optimal factor settings were selected by Design-Expert® in order to identify experimental settings in which all desirabilities were met as well as possible. An optimum formulation was generated by the software, which was produced and analyzed for desired response variable. The optimized formula calculated thus contains miconazole 10 mg, carbopol 20 mg, HPMC 20 mg, PVP 10 mg, mannitol 37 mg and talc 3 mg to make tablet weight 100 mg. The predicted and observed results for the optimized tablet formulation are given in Table-6 and it is that the model predicted the responses well.

TABLE-6
PREDICTED AND OBSERVED RESPONSES FROM OPTIMIZED TABLET FORMULATION (n = 3)

Test	Predicted	Observed
Bioadhesion Force	45.15	42.32 ± 2.3654
% Drug release (6 h)	91.35	96.44 ± 3.6781

Thus with the aid of this design it was possible to meet all the official specifications, demonstrating that the experimental planning of mixture can supply trustworthy results, reducing the spent time and the number of experiments.

Conclusion

An optimized formulation of tablets by direct compression was found to have good bioadhesion and drug release. A formulation providing 96 % release of the drug over 6 h was produced. The bioadhesion was also good (21.23 g). Design and analysis of experiments were used as good tools to obtain the optimal formulation.

REFERENCES

1. N.A. Peppas and P.A. Buri, *J. Control Rel*., **2**, 257 (1985).
2. K. Morimoto, H. Katsumata, T. Yabuta, K. Iwanaga, M. Kakemi, Y. Tabata and Y. Ikada, *Eur. J. Pharm. Sci.*, **13**, 179 (2001).
3. P. Bottenberg, R. Cleymaet, C. deMuynck, J.P. Remon, D. Coomans and D. Slope, *J. Pharm. Pharmcol.*, **44**, 684 (1993).
4. N.A Nafee, F.A. Ismail, N.A. Boraie and L.M. Mortada, *Int. J. Pharm.*, **264**, 1 (2003).
5. K. Goud, H. Desai and T.M.P. Kumar, *AAPS Pharm Sci Tech.*, **5**, 35 (2004).
6. P. Bottenberg, R. Cleymaet, C. deMuynck, J.P. Remon, D. Coomans, Y. Michotte and

D. Slope, *J. Pharm. Pharmacol.*, **43**, (1991).
7. B. Singh and S.A Singh, *Indian J. Pharm. Sci.*, **60**, 358 (1998).
8. R. Franz, D.C. Cooper, J. Browne and A.R. Lewis, in eds.: H.A. Liberman and L. Lachman, Disperse Systems, Marcel Dekker, Inc., Vol. 2, pp. 437-513.
9. The United States Pharmacopoeia-24/National Formulary-19, Asian Edn., US Pharmacopoeia convention, Inc., Rockville MD, p. 1942 (2000).
10. G.S. Banker and G.R. Anderson, in eds.: L. Lachman, H.A. Liberman and J.L. Kanig, The Theory and Practice of Industrial Pharmacy, Varghese Publishing House, Mumbai, edn. 3 pp. 293-343 (1987).
11. L. Eriksson, E. Johansson and C. Wikstrom, *Chemomet. Intell. Lab. Syst.*, **43**, 1 (1998).

(*Received*: 24 February 2007; *Accepted*: 4 October 2007) AJC-5975