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Development, evaluation and optimization of extended release buccal tablets prepared using progressive hydration technology

Amit Gupta[1]*, Ram S. Gaud[1], S. Ganga [1]

***Corresponding author:**
Amit Gupta
[1]School of Pharmacy and Technology Management
SVKM's NMIMS Deemed University
Mumbai- 400056
Maharastra, India
Telephone number: +91-22-64521148/49/50
Fax: +91 22 26185422
E-mail:
amitopgupta@gmail.com
rsgaud@nmims.edu
gangach@rediffmail.com

Abstract:

Extended release Buccoadhesive buccal tablet for delivery of Nisoldipine were developed using Progressive hydration technology. Technology involves Carbopol 972P (CP), Hypromellose K15M (HPMC) and Polycarbophil (PC) in different amounts. Experiments were designed based on 3^2 full factorial design to explore effects of CP and HPMC on buccoadhesive strength (BAS) and drug release. Both polymers were found to have effect on swelling index, BAS and drug release which was confirmed by level of significance ($p < 0.05$). Using quadratic terms a linear second order model that describes a twisted plane of responses were also drawn for elucidation of effect of polymers. Three check points were also taken into account to validate the polynomial equation. Results show that polymers drastically change the drug release mechanism which was confirmed by model fitting into dissolution profile. By customizing the formulation by optimizing the ratio of polymers, desired release (90%) was obtained in the sixth hour and good BAS were obtained for batch F10.

Keywords: Buccoadhesive; Nisoldipine; Factorial design; Polynomial equation

Introduction

The oral route of drug administration is the most preferred route for systemic drug delivery by physicians and patients. Though, oral route offers distinct advantages over other conventional drug delivery routes like topical and parenteral. Peroral administration of certain drugs has disadvantages such as unpredictable, erratic and incomplete absorption, degradation of drug in stomach and hepatic metabolism resulting in reduced bioavailability. Thus, several alternative routes are constantly being studied for better delivery. Buccal route has long been shown as possible route of delivery of drugs having poor oral bioavailability because of high first pass metabolism or degradation in the gastrointestinal tract. This route is well vascularized draining to the heart directly via the internal jugular vein [1]. In the oral mucosal cavity, drug can be delivered either by sublingual route or by buccal route. Novel dosage forms for buccal delivery may be either conventional tablets or sustained release systems. These are intended to release the drug within a specified period of time including buccoadhesive, biodegradable or chewing gum systems. Adhesive sustained delivery systems like tablets, gels, and patches, have been recommended for buccal drug delivery.

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Prerequisites of such delivery systems are adhesion to mucosa for retention and extension of drug delivery. Variety of polymers are available for such type of delivery system like Chitosan , gelatin, cellulose and its derivatives from natural origin, Carbopol, HPMC, HPC, PVP , Polycarbophil, Polyoxyethylene and thiolated polymers from semisynthetic and synthetic origin. Buccoadheisve formulations are available in the form of tablets, patches, wafers, lozenge, gels, ointment and suspensions. For those drugs that penetrate the oral mucosal membranes slowly or incompletely, formulation with a penetration enhancer have been recommended.

Nisoldipine is a calcium channel blocker used in the treatment of hypertension. It has high and variable hepatic clearance with a bioavailability of only 5% and elimination half life 7-12 hrs [2]. Drug has low molecular weight of 324 D, optimal log P, 3.2 [3] indicating it's delivery is best suited via buccal extended release formulations where its bioavailability can be enhanced and side effects can be reduced.

For Extended release buccal formulation, very few technologies are found to be commercially viable. Buccoadhesive "Progressive hydration technology" is the only technology which has been employed for tablets and has been successfully commercialized [4,5]. This technology provides a bioadhesive tablet that progressively hydrates, whereby the inner core of the tablet remains protected from moisture and the surrounding environment. It involves Carbopol, HPMC, Polycarbophil, and Starch as function excipients. This study is an attempt to aiming development of Buccal adhesive tablet of Nisoldipine using Progressive hydration technology studying effects of its functional components on BAS and drug release.

Materials and Methods

Materials

Nisoldipine (NS) (99.15% purity) was procured from Shandong Boyuan Chemical co, Ltd (Jinan, China), Carbopol, Polycarbophil and HPMC were obtained as gift samples from Lubrizol Advanced Materials India Pvt. Ltd and Colorcon, Goa, India. Directly compressible lactose (DCL 11) was obtained from Wockhardt Research centre (Aurangabad, India), Talc, Sodium lauryl sulphate, Starch, Aerosil 200 and Magnesium stearate were procured from S.D.Fine chemicals (Mumbai, India). Porcine buccal piece was obtained from Deonar abattoir (Mumbai). All other reagents and chemicals used were of analytical reagent grade.

In vitro drug permeation studies

The in vitro buccal drug permeation study of NS through the porcine buccal mucosa was performed using Keshary-Chien type glass diffusion cell at 37°C ± 0.2°C [6]. Fresh porcine buccal mucosa was mounted between the donor and receptor (surface area 3.14 cm^2) compartments. The suspension of NS in 2 ml of simulated salivary fluid, pH 6.8 containing 10 mg of NS was placed in the donor compartment, while receiver compartment contained 25 ml of 2.0% Sodium lauryl sulphate. Two compartments were clamped tightly. Solution hydrodynamics in the receptor compartment was maintained by stirring with a magnetic bead at 50 rpm. One milliliter sample was withdrawn at predetermined time intervals and analyzed for drug content at 238 nm, after suitable dilution using a UV-spectrophotometer (PerkinElmer-Lambda 25, USA).

Design of experiments: preparation of buccoadhesive buccal tablets

Depending upon the evaluation of prototype formulation (data not shown) two polymers were found to be having predominant effect on BAS and drug release. A central composite design (CCD) for these two factors at three levels each (with a = 1) was selected to optimize the varied response variables. Both factors were varied as required by the experimental design and the factor levels were suitably coded (Table 1). The amounts of other excipients were kept constant and directly compressible lactose (DCL) was taken in a sufficient quantity to maintain a constant tablet mass of 100 mg.

Preparation of buccoadhesive tablets

Buccoadhesive tablets were prepared by a direct compression procedure involving two consecutive steps. The buccoadhesive drug/polymer mixture was mixed homogeneously by sifting through sieve 60 ASTM. The mixture was then compressed using an 8-mm, round-shaped flat punch in a single-stroke, multistation tablet machine (Karnavati, Mumbai). The

tablets were prepared using compositions as given in Table 2.

Table 1. Formulation variables and their levels

Formulation variables and levels	
HPMC (X_1)	CP (X_2)
-1	-1
0	-1
1	-1
-1	0
0	0
1	0
-1	1
0	1
1	1
-1 = 0 mg	-1 = 0 mg
0 = 15 mg	0 = 15 mg
+1 = 30 mg	+1 = 30 mg

Tablet characterization and evaluation

Ten tablets were powdered and a quantity equivalent to 10 mg of NS was extracted with 30 mL of methanol. The resultant suspension was shaken for 15 minutes and contents diluted to 50 mL with methanol and filtered through 0.45micron filter. Absorbance of the filtrate was measured at λ_{max} of 238 nm spectrophotometrically.

Tablets were also evaluated for hardness (n = 6) using a Monsanto type hardness tester (Labline, India), friability (n = 10) using a Roche Friabilator (Eletrolab, India), weight variation (n = 10) using an electronic balance (Shimadzu) and thickness (n = 10) using Vernier Callipers (Mitutoyo, India).

Swelling studies

The swelling properties of the tablets were evaluated using swelling index by determination of % swelling [6,7]. Each tablet was weighed (W1) and immersed in a simulated saliva fluid at pH6.8 for predetermined times. After immersing the formulation for specified time, the tablets were wiped off to remove excess of surface water by using filter paper and weighed (W2) [8]. Swelling index was calculated using equation 1:

$$Swelling\quad Index = \frac{(W2 - W1)}{W1} \times 100 \qquad (1)$$

Ex Vivo Buccoadhesive Strength

A modified balance method was used for determining the ex vivo buccoadhesive strength [9]. Fresh porcine buccal mucosa was obtained from a local slaughterhouse and used within 2 hours of slaughter. The mucosal membrane was separated by removing underlying fat and loose tissues. The membrane was washed with distilled water and then with phosphate buffer pH 6.8 at 37°C. The mucosa was cut into pieces and washed with phosphate buffer pH 6.8. A piece of buccal mucosa was tied to a lower teflon block which was placed in a beaker filled with phosphate buffer pH 6.8 touching mucosal surface at 37°C ± 1°C. The buccal tablet was stuck to the upper Teflon block with cyanoacrylate glue. The two sides of the balance were made equal before the study, by keeping a weight on the right-hand pan. A weight of 5 g was removed from the right-hand pan, which lowered the pan along with the tablet over the mucosa. The balance was kept in this position for 5 minutes contact time. The water (equivalent to weight) was added slowly with a burette (100 drops/min) to the right-hand pan until the tablet detached from the mucosal surface. This detachment force gave the buccoadhesive strength of the buccal tablet in grams. Force of adhesion and bond strength parameters were calculated from BAS [10] using equation 2 & 3.

$$Force\ of\ \ Adhesion\,(N) = \frac{Bioadhesive\ \ Strength \times 9.8}{1000} \qquad (2)$$

$$Bond\ \ \ Strength\ \ (Nm^{-2}) = \frac{Force\ \ of\ \ Adhesion}{Surface\ \ \ Area} \qquad (3)$$

In vitro drug release

An in house dissolution method was developed and validated. Paddle method (USP XXIII) was used in study. The dissolution medium consisted of 500 mL of 1.0% Sodium Lauryl Sulphate. The release was performed at 37°C ± 0.5°C, with a rotation speed of 60 rpm. Samples (5 mL) were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through 0.2-µm Whatman filter paper (Whatman, Brentford, UK) and analyzed without dilution by UV spectrophotometry at 238 nm.

Table 2. Composition of Nisoldipine extended release tablet

Composition	F1	F2	F3	F4	F5	F6	F7	F8	F9
Nisoldipine	10.1	10.1	10.1	10.1	10.1	10.1	10.1	10.1	10.1
HPMC 15K	0	0	0	15	15	15	30	30	30
Corn Starch	15	15	15	15	15	15	15	15	15
DCL 11	67.9	52.9	37.9	52.9	37.9	22.9	37.9	22.9	7.9
Aerosil	2	2	2	2	2	2	2	2	2
PC	3	3	3	3	3	3	3	3	3
CP	0	15	30	0	15	30	0	15	30
Talc	1	1	1	1	1	1	1	1	1
Mag stearate	1	1	1	1	1	1	1	1	1

*HPMC indicates hypromellose; DCL 11, directely compressible lactose monohydrate; CP, carbopol 974P; PC, polycarbophil

Stability studies in human saliva

The stability study of optimized tablets was performed in natural human saliva. The human saliva was collected from subjects ranging between 18-30 years [11]. Buccal tablets were placed in separate petri dishes containing 5 mL of human saliva and placed in a temperature-controlled oven (Dolphin, India) at 37°C ± 0.5°C for 7 hours. Tablets were physically examined for changes in color and shape, collapsing of the tablets, and drug content at regular time intervals of 0, 1, 2, 3, and 6 hours.

Optimization and data analysis

For the studied design, the multiple linear regression analysis (MLRA) method was applied using the SPSS software version 16 (SPSS Inc. USA) to fit the full second-order polynomial equation with added interaction terms. Polynomial regression results were demonstrated for the studied responses [12], using equation 4:

$$Y = b_1 + b_2X_1 + b_3X_2 + b_4X_1X_2 + b_5 X_1^2 + b_6X_2^2 \qquad (4)$$

Where, Y is the dependent variable, b_1 is the arithmetic mean response of the 9 trials. Coefficient b_2 is the estimated coefficient for the factor X_1 and b_3 is the estimated coefficient for the factor X_2. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when 2 factors interact. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity. The values of correlation coefficients were set to be statistically significant at 5% confidential interval.

Finally, the prognosis of optimum formulation was conducted in two stages; first, a feasible space was located and second, an exhaustive grid search was conducted to predict the possible solutions using Surface and contour plot drawn using and Statistical 6.1 (StatSoft Inc. USA) software.

Results and Discussion

Drug content and physical evaluation

The assay of NS in tablets varied between 97.1 and 100.2 % (mean ± SD = 98.6 ± 1.2 %). Tablet weight varied between 97 and 102 (99.5 ± 2.5 mg), thickness between 1.15 and 1.22 mm (1.185 ± 0.035 mm), hardness between 3.5 and 5 kg cm^{-2} (4.25 ± 0.75 kg cm^{-2}), and friability ranged between 0.41 and 0.80 % (0.605 ± 0.195 %). Hence all physical parameters of the compressed matrices were within the permissible limits of USP XXIII.

In vitro drug permeation studies

In-vitro drug permeation studies were conducted to find possibility of drug permeation through porcine buccal mucosa. Porcine mucosa owing to its most resembling nature to human buccal mucosa in terms of lipid content and composition; membrane morphology and permeability barrier functions; composition and structure; and being nonkeratinized similar to human buccal mucosa [13] was selected as a model for this

study. There was no significant lag time found followed by permeation coefficient steady state varying from 0.433 to 0.179 cm/sec (Figure 1) with average value 0.303 cm/sec. Throughout the study NS permeation was found to be in the steady state region.

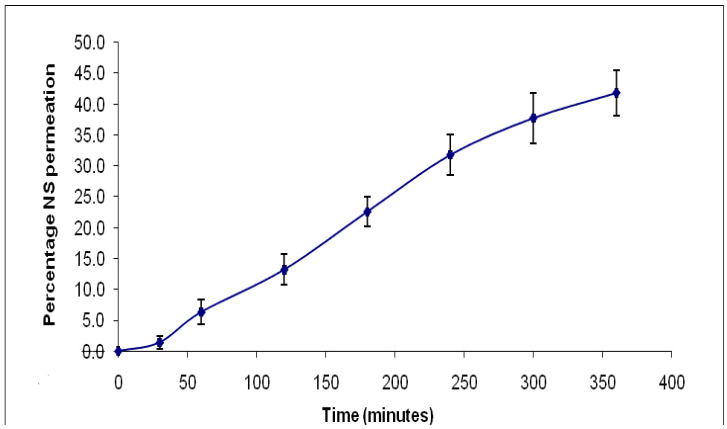

Figure 1. Permeation profile of NS through porcine buccal mucosa (n=3)

Selection of polymers and technology with suitable experimental design

A numbers of polymers have been used in buccoadhesive systems like HPMC, HPC, PVP, Polycarbophil, Polyoxyethylene, thiolated polymers, Chitosan, gelatin, sodium alginate and other celluloses and its derivatives. Amongst all, HPMC and CP have been used most widely. Progressive hydration technology also uses the same set of polymers [4]. HPMC is a non-ioninc polymer and CP is ionic. Such combination of polymers is known to provide the formulation with controlled drug release along with desired buccoadhesive properties [14,15]. Selected polymers were also non-toxic, non-irritant, stable at buccal and GI pH and compatible with the drug.

A central composite design (CCD) for two factors for CP and HPMC at three levels with a = 1, equivalent to 3^2 factorial design was chosen as the experimental design. This is an effective second-order experimental design associated with minimum of experiments to estimate the influence of individual variables (main effects) and their second-order effects [14,16,17]. Further, this design has an added advantage of determining the quadratic response surface, not estimable using a factorial design (FD) at two levels [18].

Ex vivo buccoadhesive strength

The *ex vivo* buccoadhesive strength with porcine buccal mucosa varied from 1.3 g (F1) to 40.2 g (F9). Similarly other parameters of bioadhesion were calculated and were found to vary between 0.0125 N (249 Nm-2) to 0.394 N (7849 Nm-2) as mentioned in Table 3. Since selected polymers belong to hydrogel group, increase in buccoadhesive strength may be attributed to the formation of a strong gel that penetrates deeply into the hydrated mucin membrane [19]. Hydrogels exist in glass-rubbery transition state which has high plasticization property. This property provides high surface for maximum contact with mucin along with flexibility for interpenetration. Figure 2 shows that the ex-vivo buccoadhesive strength increased linearly with increasing concentration of CP or HPMC which may attribute to high interpenetration, augmenting high buccoadhesive strength. Such observations are concurrent to the observation by Singh et. al. and Ponchel et. al. who attributed this phenomena to high interpenetration resulting in gelling, augmenting high buccoadhesive strength [14,19,20]. The results also indicate that the effect of X2 (concentration of CP) was more significant than the effect of X1 (concentration of HPMC). Moreover, a synergistic effect was found by interaction of CP and HPMC which are similar to that obtained by Singh et. al. and Nur et. al. [14,15].

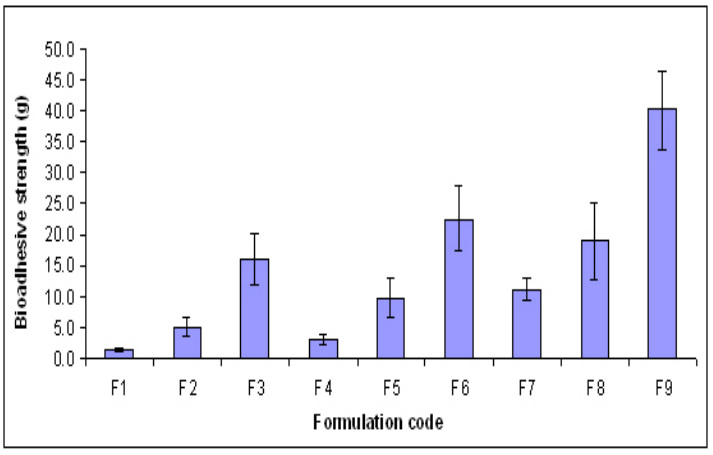

Figure 2. Buccoadhesive strengths of Nisoldipine buccal tablets (F1 to F9) prepared as per centre composite design (n=3)

Table 3. Buccoadhesive parameters of buccoadhesive Nisoldipine buccal tablets

Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Buccoadhesive strength (g)	1.3	5.1	16.0	3.0	9.8	22.6	11.1	18.9	40.2
force of adhesion (N)	0.01256	0.05003	0.15696	0.02943	0.09614	0.22171	0.10889	0.18541	0.39436
Bond strength (Nm-2)	249.936	995.84	3124.2	585.788	1913.57	4412.94	2167.42	3690.47	7849.56

Results are in mean ±SD (n=3)

Swelling and erosion studies

Swelling and erosion studies help in analysis of important parameters involving drug release mechanism in a matrix system, possibility of water penetration for drug release, lag time of drug release of insoluble drug in matrix system and requirement to remove residual tablet on complete erosion [21]. Swelling and erosion data for formulation F8 is shown in Figure 3 which shows that an initial increase in swelling occurred till 4 hours followed by comparatively steep swelling curve. Matrix erosion was also observed to play a role in controlling the drug release with an initial lag phase followed by significant erosion. Such observation is in concurrence with dissolution behavior of F8.

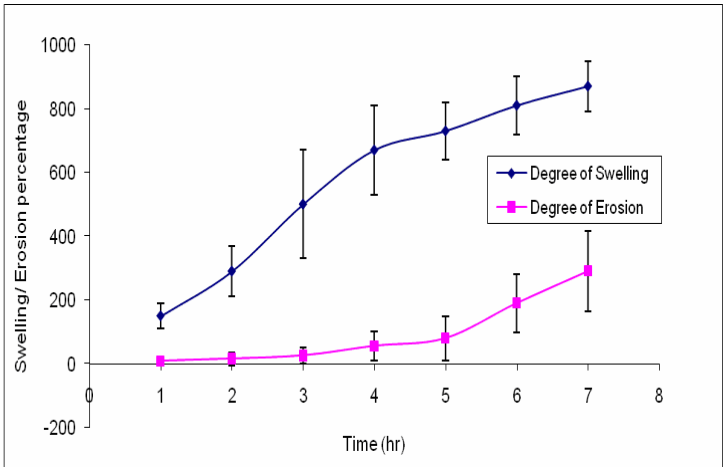

Figure 3. Degree of swelling and erosion for formulation F8

In vitro drug release studies

Dissolution profiles obtained are shown in Figure 4. As evident from the degree of swelling and erosion (Figure 3), the influence of polymer levels are found to be vital in regulating the drug release. Drug release profiles of formulations show an initial phase of spontaneous release of the drug for formulation having insufficient polymer amounts to spread network of hydrophilic chain around matrix system, demonstrated by batches F1 and F4. [14,20,22]. Formulation F2. F3, F5, F6, F7, F8 and F9 shows development of hydrophilic gel layer surrounding the matrix which control the release of drug. In these batches drug is entrapped in the swollen matrix and it releases only when matrix starts eroding.

Several drug release models were used to characterize release mechanism. Summary of the drug release models used and their correlation coefficients are mentioned in Table 4. Correlation coefficient can be utilized to find a suitable model. Formulations F1, F6 and F8 predominantly follow Hopfenberg model, applicable for slab shaped matrices. In this model rate limiting step for drug release is erosion of matrix itself and time dependent internal or external resistances do not influence the release of the drug [23]. This may be attributed to thin shape of the formulation because of which release may happen via erosion mechanism. This model has been employed by Katzhender at. Al. and Munasur et. al.for thin formulations [24,25]. Formulation F2, F3 and F7 follow Higuchi model which is most common for homogeneous polymer matrices. It describes drug release process based on Fick's law and release being dependent on square root of time [26]. Formulation F2 and F9 follow Bankers-Lonsdale model indicating high polymer amount in matrices which swells to great extent and may behave structurally close to spheres [27]. Formulation F5 has equal amount of CP and HPMC where polymer neither swells nor erodes as in case of low polymer containing matrices, hence it follows Hixson-Crowell model which assumes that tablet may take spherical shape and

Table 4. Drug release model fitting to various models and their correlation coefficients

	Correlation coefficient (R^2)								
Model	F1	F2	F3	F4	F5	F6	F7	F8	F9
Zero order	0.9195	0.9195	0.9360	0.9921	0.8994	0.9224	0.9365	0.9426	0.6509
First order	0.7393	0.7182	0.7771	0.2498	0.7578	0.8946	0.7606	0.9496	0.9565
Higuchi	0.9334	0.9471	0.9657	0.9614	0.8382	0.7973	0.9613	0.8341	0.7325
Hixson-Crowell	0.7478	0.7132	0.6853	0.7926	0.9296	0.3096	0.7698	0.8635	0.9202
Banker-Lonsdale	0.8670	0.9470	0.8870	0.8280	0.8930	0.6780	0.8370	0.6830	0.9890
Hopfenberg	0.9690	0.9390	0.9300	0.9630	0.9150	0.9790	0.9270	0.9780	0.9180
Weibull	0.9280	0.9900	0.9760	0.9020	0.9960	0.9760	0.9940	0.7950	0.7420
Release model	Hopfenberg	Higuchi/ Banker	Higuchi	Zero oredr	Hixson-Crowell	Hopfenberg	Higuchi	Hopfenberg	Banker

dissolution can occur equally from all sides [28]. Only batch F4 followed zero order kinetics where the entire drug released in less than 4 hours.

Further drug release profiles were analysed using Korsmeyer-Peppa's model to analyse drug transport mechanism based on their release exponent (n) using single equation 5:

$$\frac{M_t}{M_\infty} = at^n \qquad (5)$$

Where, M_t is amount of drug released in time t, M_∞ is amount of drug released in infinite time, a is constant, t is time and n is release exponent. When n approximates 0.5, a Fickian/diffusion-controlled release is implied, where n = 0.5 to 1.0 a non-Fickian transport/ anomalous transport happen, n = 1 for zero-order (case II transport) and n > 1 super case II. In the case of a cylinder, n=0.45 instead of 0.5, and 0.89 instead of 1.0 [29].

The n varies from 0.0227 to 1.2475 representing huge change in drug transport mechanism by change in polymer concentration (Table 5). Formulations F1, F2, F3, F6 and F7 were found to follow Fickian transport; however anomalous transport was observed for batches F4, F8 & F9 and Super Class II for F5. None of the formulation was found to have unit value for n (Zero order kinetic) as it was not observed in multimodel analysis. Also Single formulation F5 showed Super Class II concurrent to the above result of multimodel analysis having dominating Hixson-Crowell model.

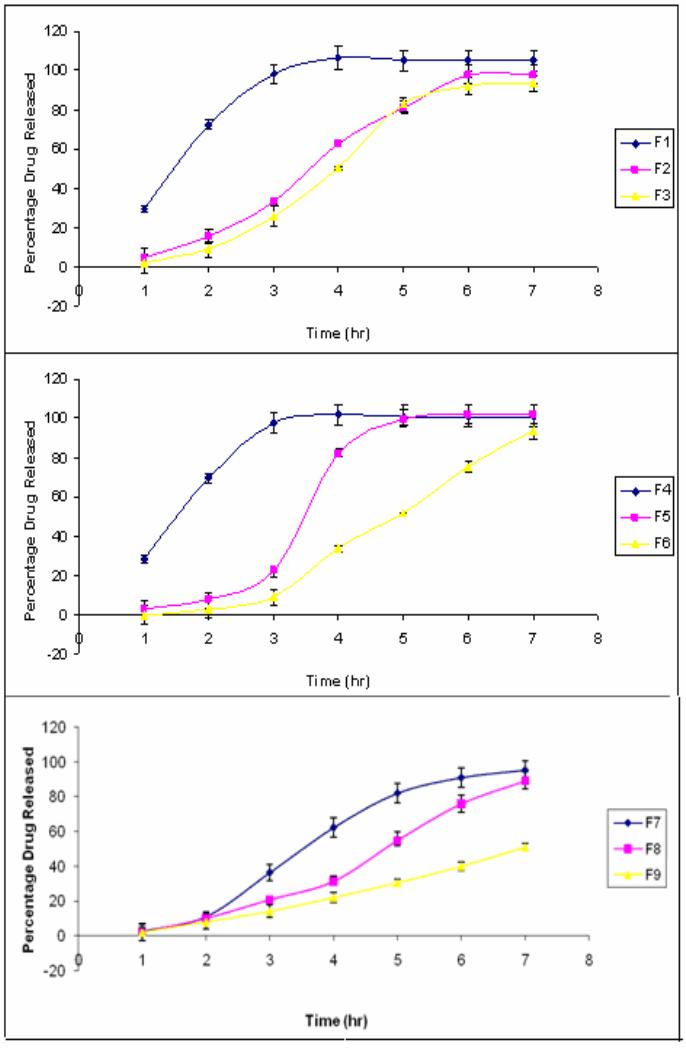

Figure 4. Dissolution profile of Nisoldipine buccal extended release tablets (F1-F9)

Table 5. Drug release model fitting to Korsmeyer-peppas's and correlation coefficients

Korsmeyer-peppas's Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Release exponent (n)	0.0227	0.0434	0.2648	0.7548	1.2475	0.069	0.4325	0.5353	0.7503
Kinetic constant (k)	0.9539	0.9204	0.6308	0.2659	0.1069	0.8890	0.4779	0.3805	0.2148
Correlation coefficient (R^2)	0.8635	0.8499	0.8235	0.847	0.8189	0.597	0.6878	0.8482	0.9423
Transport mechanism	Fickian	Fickian	Fickian	Anomolous	Super Class II	Fickian	Fickian	Anomolous	Anomolous

Values of the kinetic constant (k) showed a declining trend with an increase in the level of each polymer, construing an appreciable change in the polymer matrix with a change in the polymer composition attributed by both polymers. Table 5 reveals that the overall rate of drug release tends to decrease with an increase in concentration of HPMC or CP.

Formulations having high CP amount were found to have initial phase with insignificant drug release. Several research findings have supported the fact that a mixture of HPMC with CP causes reduced hydration of the matrix followed by insufficient channel formation for drug release or absence of significant erosion in initial phase [14,29,30].

Experimental design approach

A complete 3^2 randomized full FD was used in present study to evaluate effect of CP and HPMC on buccoadhesive strength and drug release in 6 hours. Applied 3^2 FD yields coefficient for one factor and for two factors as well. Coefficient for more than one factor represents interaction of both factors. Coefficient may be positive or negative for synergistic or antagonistic effect respectively [32]. A backward elimination with statistically significant model was generated for buccoadhesive strength and drug release in 6 hours. From the model it is evident that both synergistic and antagonistic effects on buccoadhesive strength and drug release persist. All coefficients were found to be significant, having *p* value less than 0.05 for buccoadhesive strength while only significant synergistic interaction was observed in controlling the release on coefficient owing to interaction of CP and HPMC (-0.036* HPMC*CP, p = 0.036)

Based on significant coefficient in the above studies polynomial equations obtained (full model) are:

For BAS,

BAS = 1.978 – (0.193*HPMC) – (0.127*CP) + (0.016*HPMC*CP) + (0.016*HPMC*HPMC) + (0.020*CP*CP) (6)

For drug release in sixth hour

% DR = 101.444 - (0.049*HPMC*CP) (7)

Equation 6 shows that ex-vivo BAS increased linearly with increasing concentration of CP and HPMC with overall significance of 0.002 (Table 6). Figure 5 represents closeness of observed response value to that of predicted obtained by polynomial equation. Further combined effect of CP and HPMC can be elucidated with the help of 3D response surface plot and contour plot (Figure 6). A zone lowest of BAS exist closer to HPMC than CP elucidating higher BAS imparted by CP. A zone of highest BAS exists where CP and HPMC are used in high amount.

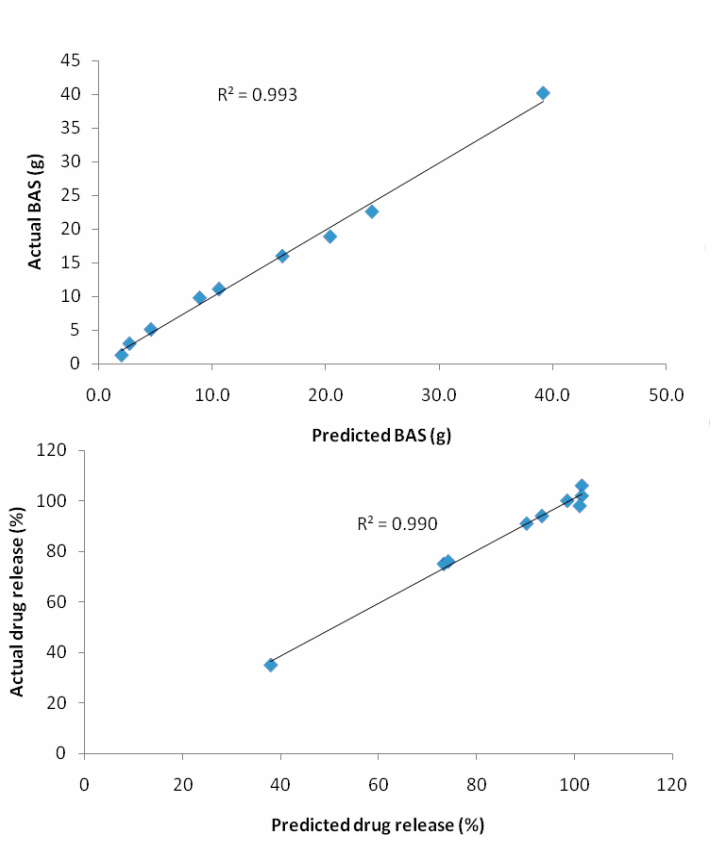

Figure 5. Corelation between actual and predicted values of buccoadhesive strength and drug release

Equation 7 for drug release demonstrates possible effect of individual polymer and their combination. A significant synergistic effect is seen when CP and HPMC are used together with overall significance of 0.015 (Table 6). Figure 8 represents observed response value to that of predicted obtained by polynomial equation. Further combined effect of CP and HPMC can be drawn with the help of 3D response surface plot and contour plot (Figure 7).

Validation of polynomial equation and selection of optimum formulation

Derivation of polynomial equation depends upon the input variables given into it. Further its workability to next formulations and reproducibility is to be validated. Validation of the polynomial equation was done by random scattering of check points analysis by developing three formulations within the experimental composition range. Upon comparison of the observed responses with those of predicted one (Table 7) a percentage variation was identified. Percentage variation was within the acceptable range ± 5% for BAS while ± 2% for drug release. The optimal formulation was needed to have 90% drug release and sufficient BAS to be adhered to buccal mucosa. Such composition was obtained by putting random values of independent variables, keeping CP at higher level for higher BAS. An optimum formulation of HPMC/ CP keeping 13/ 23 was formulated which was found to be having acceptable percentage variation from predictable responses.

Table 6. Coefficients from central composite design for BAS and drug release on 6th hour

	Buccoadhesive Strength (g)		Drug release (%)	
Coefficients	Value	p Value	Value	p Value
b	1.978	0.251	101.444	0.000
b1	-0.193	0.316	0.644	0.378
b2	-0.127	0.489	1.078	0.183
b3	0.016	0.019	-0.049	0.036
b4	0.016	0.045	-0.034	0.17
b5	0.020	0.027	-0.045	0.097
R2	0.994		0.972	
Significance	0.002		0.015	

Table 7. Composition of check points and optimal formulation and variation in predicted and actual response

Formulation type	Formulation composition		Responses					
			Bioadhesion (g)			Drug release (%)		
	HPMC	CP	Actual*	Predicted	Percentage variation	Actual*	Predicted	Percentage variation
Check points	5	25	12.4	12.7	2.36	97.1	96.5	-0.62
	25	15	15.9	15.7	-1.27	83	83.9	1.07
	25	25	25.1	26.5	5.28	63.1	64.5	2.17
Optimal (F10)	13	23	15.2	14.5	-4.83	89.6	90.4	0.88

* mean ±SD (n=3), significance level p=0.05

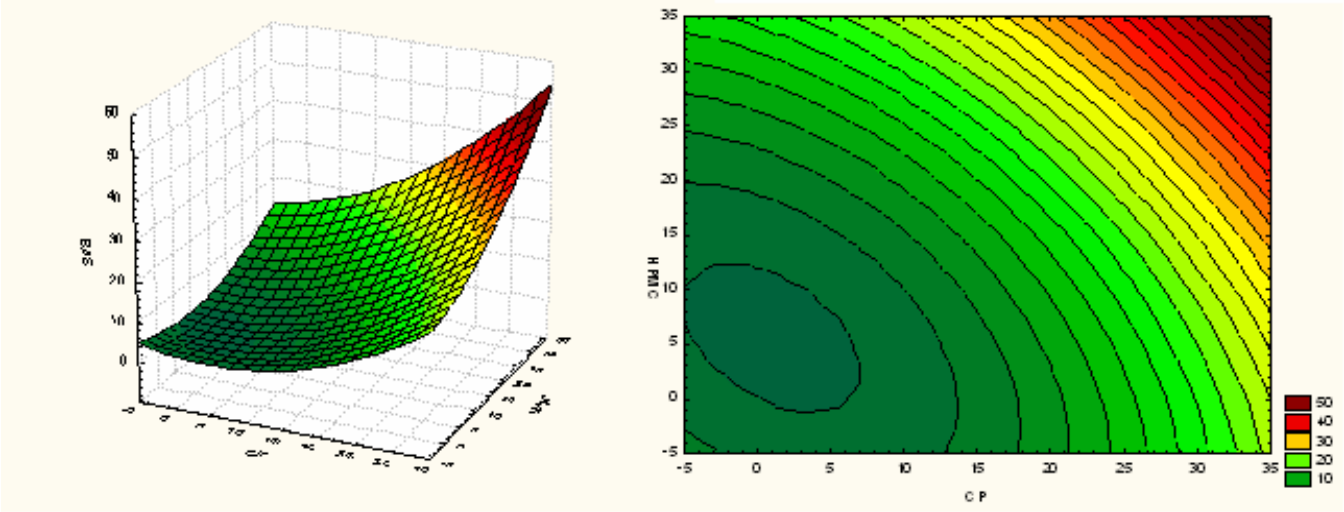

Figure 6. Response surface and Contour plot showing effect of CP and HPMC on buccoadhesive strength

Conclusion

Present work included development of extended release Buccal tablet for Nisoldipine. Progressive Hydration technology was employed utilising HPMC and Carbopol as buccoadhesive and release rate controlling polymers. Effect of formulation variables were evaluated by 3^2 full FD. High polymer contribution was able to control the release and retain sufficient BAS. The polynomial equations developed for the studies were able to reproduce the responses. Finally, it can be concluded that by application of 3^2 full FD, experimental studies can be designed and optimized, limiting the number of experiments for target release and sufficient BAS.

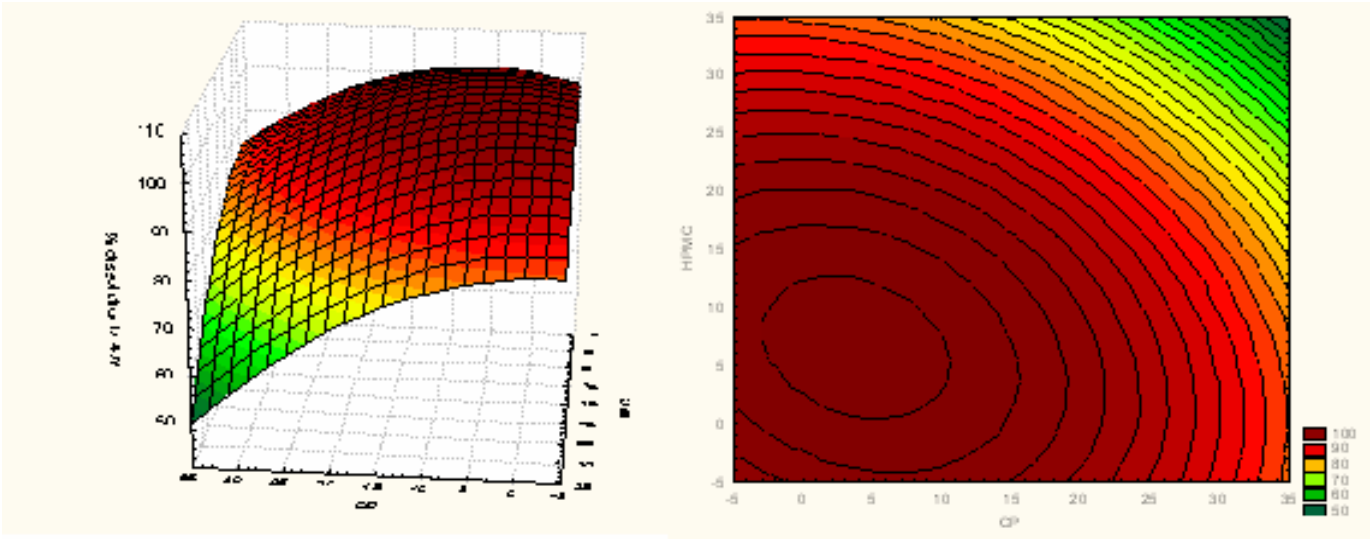

Figure 7. Response surface and Contour plot showing effect of CP and HPMC on drug release in 6 hours

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