

## PRELIMINARY SCREENING AND DEVELOPMENT OF FORMULATION DESIGN SPACE FOR BUCCAL THIN FILMS OF ISRADIPINE

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### ABSTRACT

The drugs which are susceptible to acid hydrolysis in the stomach or extensively metabolized in the liver can be protected successfully by getting absorbed directly into systemic circulation through buccal route. Isradipine is used to treat hypertension and undergoes extensive hepatic first pass metabolism and have low oral bioavailability. Immediate effect by buccal drug delivery system depends on its ability to deliver an adequate amount of drug immediately. The preliminary screening of the formulation variables was attempted in this work with aim of releasing not less than 50% of drug in 5 min. The experimentation was done by taking levels of isradipine, HPMC and acetone as independent variables and percent drug release in 5 min as dependent variable. The fabrication of mucoadhesive buccal thin films of isradipine was achieved by using casting and solvent evaporation method. The water soluble plasticizer, PEG 400 was used. The prepared buccal thin films were tested for various physicochemical and performance characteristics, and release kinetic studies. The contour plots, response surface diagrams and design space were drawn. The developed formulation design space can be used during the subsequent stages of process development, scale up, validation and risk management as part of quality by design perspective. Drug and solvent levels were showed directly proportional and polymer showed inversely proportional relationship with percent drug release. The linear equation was presented to find the numerical relationship between dependent and independent variables.

**Keywords:** Buccal thin films, Isradipine, Immediate release formulations, Robust screening design, Response surface, Design space.

### INTRODUCTION

The current perspective of USFDA is to introduce the concept of design space as part of quality by design framework<sup>1</sup>. The proper design of experimentation is the basis for formulating the design space<sup>2</sup>. The central composite design was used in the present work to draw the design space. To reduce the extent of experimentation, the robust screening design was adopted for the empirical approach to get the linear prediction equations for finding the relationship between the factors and responses. Subsequently, the computer simulation techniques were used to predict the responses for given set of factors within the experimental range.

Isradipine is a water insoluble drug, used in the treatment of hypertension. The fast releasing buccal drug delivery systems release the drug without delay and produce immediate relief<sup>3</sup>. The immediate release of drug can be achieved by preparing the buccal thin film (BTF) formulations<sup>4</sup>. Buccal route is a suitable site for drugs, which are susceptible to acid hydrolysis in the stomach or extensively metabolized in the liver<sup>5</sup>. Isradipine undergoes extensive hepatic first pass metabolism and have oral bioavailability of 15-24%<sup>6</sup>. Buccal delivery of such drugs bypasses hepatic first pass metabolism and expected to produce the similar effect as that of oral route at lower doses<sup>7</sup>.

BTF formulations can be prepared by melting and congealing, compression, molding or film casting and solvent evaporation. The casting and solvent evaporation method was selected as it is simple, does not require complex equipment and high temperatures, and hence formulation related parameters can be assessed<sup>8</sup>. The buccal films can be easily accepted by patients if they are flexible by using correct polymer and plasticizer in comparison to rigid buccal tablets<sup>9</sup>. Initially, the films were prepared without using the plasticizer but the films were brittle and not getting removed from borosilicate glass substrate and hence plasticizer was used. The feasibility studies with different polymers and plasticizers were conducted to select the polymer and plasticizer. As the drug is hydrophobic in nature and hence water soluble, hydrophilic polymer hydroxyl propyl methyl cellulose (HPMC) of low viscosity grades 5 cps was selected for immediate delivery. The usage of water as solvent takes longer period of time for drying and hence not possible to dry at atmospheric conditions. Hence non-toxic, organic volatile solvent acetone was selected, as it is readily get evaporated and films can be dried faster. Finally buccal films of isradipine were planned by using hydroxyl propyl methyl cellulose as polymer, PEG 400 as plasticizers and acetone as solvent to achieve not less than 50% of drug release in 5 min.

### MATERIALS AND METHODS

Isradipine was received as gift sample from Matrix Laboratories Limited and hydroxyl propyl methyl cellulose 5 cps polymer was generously gifted by Aurobindo Pharma limited, Hyderabad. All the other materials used are of analytical grade.

#### Preparation of buccal thin films

The films were casted on plain borosilicate glass substrate. During casting, the glass plates were suitably leveled with surface plates such that the films of uniform thickness were formed<sup>10</sup>. In open film casting method, the thickness of films and subsequent drug release depend on the consistency of dispersion before casting which depends on the level of casting solvent used. Hence the level of acetone was taken as one of the independent variable. In addition, the effect of varying concentrations of drug and polymer on drug release was studied while maintaining the plasticizer concentration constant. The experiments were designed to find the effect these three independent variables, drug, polymer and solvent levels on the dependent variable such as % drug released in 5 min (D% in 5 min). The care has been executed during the design of experiments such that the total numbers of batches were as low possible to reduce the time and material consumption for screening. The independent variables with their levels were mentioned in Table 1. The effect of these three independent variables was tested by taking these variables at two levels. Hence the full factorial design with three variables and two levels would require taking minimum of 8 runs in 2<sup>3</sup> factorial design. By choosing the fractional factorial robust screening design, the total number experiments were reduced to four. By varying the independent variables and maintaining the concentration of plasticizer constant, the master formula was tabulated as shown in Table 2.

**Table 1: Experimental variables with their levels for isradipine BTF**

Run No	Isradipine level (coded) actual, gm X1	HPMC level (coded) actual, gm X2	Acetone level (coded) actual, ml X3
1	(-1) 0.1	(+1) 1.0	(-1) 9
2	(+1) 0.2	(-1) 0.8	(-1) 9
3	(-1) 0.1	(-1) 0.8	(+1) 15
4	(+1) 0.2	(+1) 1.0	(+1) 15

Table 2: Master formula of isradipine BTF, gm

Ingredients	BTF1	BTF2	BTF3	BTF4
Isradipine	0.1	0.2	0.1	0.2
HPMC 5 cps	1	0.8	0.8	1.0
PEG 400	0.2	0.2	0.2	0.2
Acetone, ml	9	9	15	15
Drug polymer ratio	1:10	1:4	1:8	1:5

The plasticizer, PEG 400 was dissolved in acetone and then the weighed quantity of isradipine was added and dissolved. The weighed polymer was added to drug blend and mixed thoroughly. The prepared drug excipient blend was poured into a plain borosilicate glass substrate and covered with porous tray made of aluminum foil to avoid direct exposure of wind currents. The films were kept at room temperature for 12 hours for drying. The dried films were cut into 1×1 cm<sup>2</sup> films and preserved in aluminum foil and kept in desiccator until further use.

### Evaluation of Buccal Films

#### Physical characteristics study

Films were evaluated for the physical characteristics of dosage forms. The thickness of each film was measured using screw gauge at five different positions of the film and the average was calculated.

#### Uniformity of weight of the Films

The weights of 10 films of size of 1x1 cm<sup>2</sup> were taken, and the average weight and weight variation was calculated.

#### Folding Endurance

Folding endurance of the films was determined by repeatedly folding one film (2x2 cm<sup>2</sup>) at the same place till it broke or folded up to 300 times manually. The number of times, the film could be folded at the same place without breaking gave the value of the folding endurance. The folding endurance not less than 300 was considered as satisfactory to possess good film properties<sup>11</sup>.

#### Assay of buccal films

The assay of films was performed by placing the cut film of size 1×1 cm<sup>2</sup> in a 10 ml flask. Five ml of methanol was added. The flask was kept in ultra sonic bath for 30 minutes and then stirred in a cyclomixer to dissolve the film and then volume was made up to the mark. The absorbance of the filtered suitably diluted solution was measured against the corresponding blank solution at 326 nm.

#### Swelling studies<sup>12</sup>

##### Increase in weight due to swelling

A film of 1x1 cm<sup>2</sup> was weighed with a pre-weighed cover slip. It was kept in a petridish and 50 ml of simulated saliva fluid, SSF pH 6.75 was added. After every five min, the cover slip was removed and weighed up to 30 min. The increase in weights gives the weight increase due to absorption of water and swelling of film.

##### Increase in area due to swelling

The film of 1x1 cm<sup>2</sup> size was cut and placed in a petridish. A graph paper was placed beneath the petridish, to measure the increase in the area. Fifty ml of simulated saliva fluid, pH 6.75 was poured into the petridish. An increase in the length and breadth of the film was noted at five min intervals for 60 min and then area was calculated. The percent swelling, %S was calculated using the equation 1.

$$\%S = \frac{X_t - X_0}{X_0} \times 100 \quad (1)$$

Where X<sub>t</sub> is the weight or area of the swollen film after time t and X<sub>0</sub> is the original film weight or area at zero time.

#### In vitro mucoadhesion test of the films

The mucoadhesion test of films was performed by using modified physical balance method<sup>13</sup>. In this method the physical balance was modified to measure the weight required to detach the film from mucosal membrane. The mucosal side of goat intestinal membrane was used to study the mucoadhesion. The goat intestine was collected from the local slaughter house and preserved in 0.9% w/v sodium chloride solution at 4° C and used within 24 hours. The buccal film of size 1×1 cm<sup>2</sup> was taken for the studies.

#### In vitro residence time

In-vitro residence time was determined using modified disintegration test apparatus. The medium consisted of 900 ml of SSF pH 6.75, maintained at 37±2°C. The goat intestinal membrane was cut and attached at the open end of a test tube with mucosal surface facing out. The test tube was inverted and vertically fixed to the apparatus. The mucoadhesive film of each formulation was hydrated and attached from bottom on the mucosal surface. The setup was dipped into the medium in such a way that the film was completely immersed in the medium at the lowest point and out of the medium at the highest point. The test tube was allowed to move up and down. The time required for complete erosion or detachment of the film from the mucosal surface was recorded<sup>5</sup>.

#### Surface pH

Buccal films were left to swell for 1 h on the surface of the agar plate, prepared by dissolving 2% (w/v) agar in warmed water under stirring and then poured the solution into the petridish and allowed to stand till gelling at room temperature. The surface pH was measured by means of pH paper placed on the surface of the swollen film<sup>10</sup>.

#### In vitro release studies of isradipine films

USP dissolution apparatus type II was used throughout the study. One film was fixed to the flat side of paddle with help of 10 micro liter of SSF pH 6.75. The dissolution medium consisted of 300 ml of simulated saliva fluid pH 6.75. The drug release study was performed at 37±0.5° C at a rotation speed of 50 rpm for 30 min<sup>14</sup>. After every 5 min, the sample was withdrawn from the dissolution medium and the same volume of fresh medium maintained at 37±0.5° C was replaced. Each withdrawn sample was filtered and analyzed spectrophotometrically at 326 nm.

### RESULTS AND DISCUSSION

The films were translucent, yellow in color, having smooth surface visually. Thickness uniformity of films had shown that the thickness of films was varying from 47.3 μm to 128 μm. The consistency of polymer blend before casting was the determinant factor for the thickness of film formed. The uniformity of weight of isradipine formulations had shown that the average weight of films was varying from 4.8 mg to 13.1 mg. The average weight of isradipine was found to be dependent on drug-polymer ratio. The data of physical characteristics of films was shown in Table 3.

Table 3: Physical characteristics of BTF

B. No.	Weight Variation, mg, n=10 Avg± sd	Thickness, μm, n=5 Avg± sd	Max. % Increase in weight, n=3, Avg± sd	Time for maximum increase in weight min, n=3 Avg± sd	Max. % increase in area, n=3, Avg± sd	Time for Max. increase in area. min, n=3, Avg± sd
BTF 1	13.1 ± 0.27	128.0 ± 4.0	274.3 ± 11.84	5 ± 0	293.3 ± 11.55	41.7 ± 2.9
BTF 2	7.4 ± 0.24	76.7 ± 1.15	231.7 ± 13.70	5 ± 0	194.3 ± 10.12	41.7 ± 2.9
BTF 3	7.6 ± 0.68	78.0 ± 2.0	128.9 ± 8.33	5 ± 0	130.0 ± 8.66	36.6 ± 2.9
BTF 4	4.8 ± 0.13	47.3 ± 1.15	302.6 ± 10.15	5 ± 0	73.3 ± 7.50	31.6 ± 2.9

### Swelling studies of the films

The time taken for maximum increase in weight due to swelling was 5 min for all films. The swelling studies were indicating that the % increase in weight during swelling was polymer concentration and thickness dependent. The high increase in weight due to swelling

was found in thick films with high polymer content. The similar observation was found with increase in area due to swelling study also. But some discrepancy in results i.e. non-correlation of swelling with polymer concentration may be attributed to dissolution of film before swelling.

**Table 4: Performance characteristics of isradipine BTF**

B. No.	Assay, mg/cm <sup>2</sup> film, (n=3), Avg± sd	Surface Ph	Folding Endurance	In-vitro mucoadhesion, gms, n=3 Avg± sd	In-vitro residence time, min, n=3, Avg± sd	% drug dissolved in 5 min, (D% 5 min)
BTF 1	0.68 ± 0.05	Neutral	>300	28.3 ± 0.6	18.8 ± 0.35	16
BTF 2	1.01 ± 0.03	Neutral	>300	19 ± 0.0	13.8 ± 0.40	33
BTF 3	0.46 ± 0.084	Neutral	>300	25 ± 0.00	15.5 ± 0.57	56
BTF 4	0.504 ± 0.01	Neutral	>300	13 ± 0.0	11.7 ± 0.58	64

### Surface pH

The surface pH of film is critical a parameter for the prediction of *in vivo* performance as it is prone to cause irritation when pH is drastically deviated to acidic or basic side. The surface pH studies indicated that the film surface was neutral and hence no irritation can be expected during *in vivo* utilization. The performance characteristics of films were shown in Table 4.

### Folding endurance

The folding endurance of film provides assurance that the films have enough strength to withstand shocks during handling. The acceptance criterion for folding endurance greater than 300 was set for satisfactory handling and packing. The folding endurance studies showed that all films were having folding endurance greater than 300.

### In vitro mucoadhesion test

The mucoadhesion is desired feature to retain the dosage forms in buccal pouch and avoiding the accidental consumption. To get the same function, the mucoadhesive polymers were chosen. In order to know the strength of mucoadhesion, *in vitro* mucoadhesion test was conducted. This gives the weight necessary to be added to detach the film in opposite arm of modified physical balance. The mucoadhesion values were indicated that all formulations were mucoadhesive and the values ranging from 13 gm to 28.3 gm. The studies indicated that the mucoadhesion strength was polymer concentration dependent.

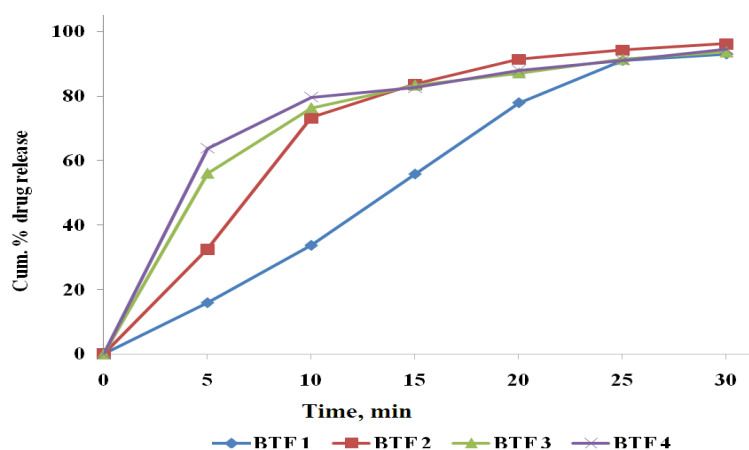
### In vitro residence time

*In vitro* residence time test was conducted to evaluate the dosage form to predict the retention power during the stress due to mastication, swallowing and speaking while the dosage is in buccal pouch. This test gives the time taken to detach from mucus membrane after application of stress in the form of up and down movements in modified disintegration test apparatus. *In vitro* residence times were varying from lowest 11.7 min to highest 18.8 min for BTF 1 (drug polymer ratio 1:10). *In vitro* residence time was also dependent on polymer concentration and thickness of film.

### In vitro drug release studies

*In vitro* release studies were conducted to compare the drug release from prepared formulations at various time intervals. To study the effect of drug, polymer and solvent levels on drug release BTF 1 to BTF 4 were studied. Even though the initial release was drastically varying from film, but after 20 min all release patterns were found to be same, which was shown in Fig 1.

Most of formulations released 90% of drug within 25 minutes except BTF 1 with drug polymer ratio of 1:10, showed 30 min. The drug release data was subjected to kinetic analysis by using different models such as zero, first order, Higuchi diffusion and Hixson Crowell cube root kinetics. The release kinetic data was presented in Table 5. All formulations followed first order release kinetics with diffusion mechanism.



**Fig. 1: Cumulative percent drug release plots of isradipine BTF formulations**

**Table 5: The release kinetic data of buccal thin films**

B. No	Zero Order		First Order		Higuchi Diffusion		Hixson Crowell Cube Root	
	R	K	R	K	R	K	R	K
BTF 1	0.976	3.381	0.983	-0.042	0.958	18.876	0.888	-0.133
BTF 2	0.899	3.075	0.993	-0.049	0.972	19.098	0.775	-0.120
BTF 3	0.841	2.587	0.979	-0.038	0.963	17.022	0.709	-0.108
BTF 4	0.809	2.476	0.970	-0.038	0.946	16.630	0.690	-4.492

R= correlation coefficient, K= release rate constant

The response data of D% 5min was plotted as contour plots as shown in Fig 2 by using DOE wisdom software to find the unknown independent variable levels for getting the same response. Design

expert software was used to plot response surface diagram to predict the responses at known independent variables as shown in Fig 3 and Fig4.

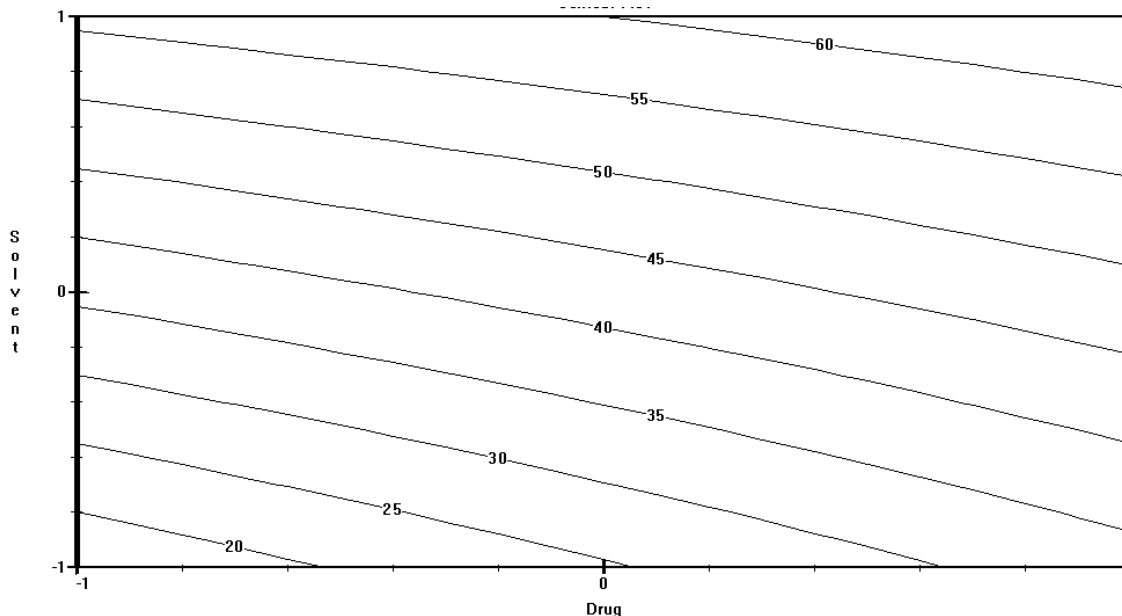


Fig. 2: Contour plot of response D% 5min for isradipine and acetone

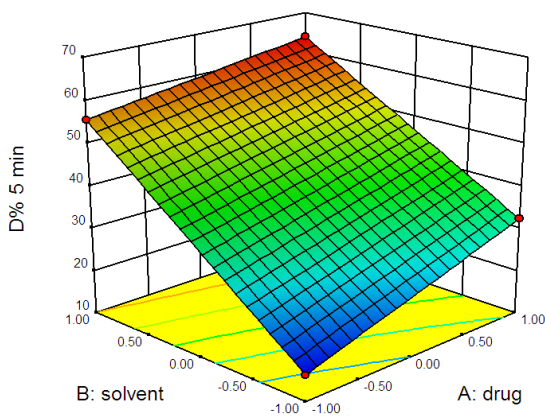


Figure 3: Response surface of D% 5 min for isradipine and acetone coded variables (HPMC at 0.8 gm)

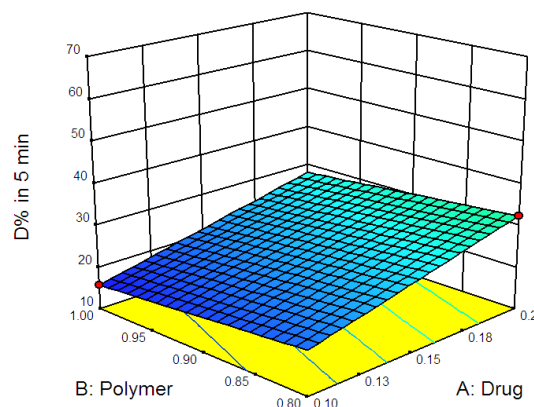


Figure 4: Response surface of D% 5 min for isradipine and HPMC actual variables (acetone at 9 ml)

The response data of percent drug release in 5 min (D% 5 min) presented in Table 4 was used to calculate linear equation of the response, by using Sigmatech software and the equation was found to be in the form of equation 2

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 \tag{2}$$

Where,

Y is the dependent variable

X1, X2 and X3 are the independent variables

b0 is constant and b1, b2, b3 are coefficients,

X1 is level of isradipine

X2 is level of HPMC 5cps

X3 is level of acetone

Y is % of drug release in 5 min, D% 5 min

With the help of Sigmatech software the constant and coefficient values for the above equation had been determined and shown the Table 6 along with their contributory effect in form of SS ratio (the ratio of square of individual effect to total sum of squares of all effects).

Table 6: Contributory effect of independent variables in effervescent technology along with the SS ratio values

Sl. No	Combinations	Coefficient	SS ratio %
1	b0	42.25	-
2	b1	6.25	10.9
3	b2	-2.25	1.4
4	b3	17.75	87.7

The above coefficient data showed that independent variables, drug and solvent levels had the directly proportional relationship and whereas polymer showed inversely relationship with the dependent variable D% 5min. In addition the positive effects of

drug and solvent are more predominant than negative effect of polymer. Hence the drug and solvents were considered as critical variables for immediate release effect when compared to polymer concentration.

This linear equation can be used to predict the D% 5 min at unknown independent variables. In order to check the accuracy of calculate equation the experimental levels of BTF 4 (Run 4) was substituted in the equation 2 and the response was calculated as follows.

$$Y = b_1 + b_1X_1 + b_2X_2 + b_3X_3$$

$$Y = 42.25 + 6.25X_1 - 2.25X_2 + 17.75 X_3$$

$$= 42.25 + 6.25(+1) - 2.25(+1) + 17.75 (+1)$$

$$= 42.25 + 6.25 - 2.25 + 17.75 = 64\%$$

The above calculated data was matching with the experimental data of BTF 4 indicated that the predicted response by using linear equation was correct.

Hence the equation 2 can be used to calculate the responses of unknown independent variables. In order to draw the design space which is used to predict the correct independent variable levels to achieve the desired response, the central composite design can be used. The central composite design for two critical independent variables drug and solvent would require at least 9 runs along with base run at zero levels. Hence the previous design report was modified by changing the +1 and -1 levels of used fractional factorial design into +2 and -2 levels in the central composite design. The central points from extreme 2 levels to midpoint were taken as +1 and -1 levels. Accordingly, the experimental unit of critical variables in central composite design was reduced to half as shown in Table 7.

By using the above experimental conditions, the central composite design was planned by using Sigmatech software. The responses for the central composite design were calculated by simulation technique. The design report for central composite design with calculated response was shown in the Table 8.

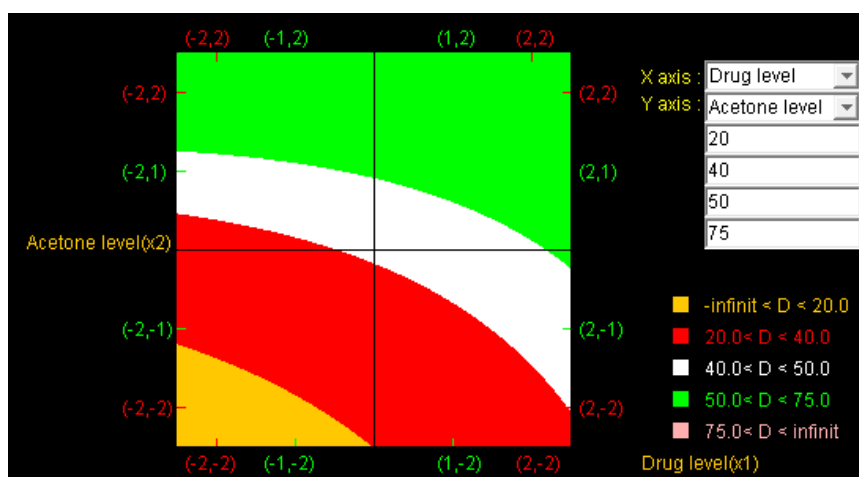
**Table 7: Modified central composite experimental design of critical variables for drawing design space**

Variables	-2	-1	0	+1	+2	Experimental unit, e. u
Isradipine level gm, X1	0.1	1.25	1.5	1.75	0.2	0.25
Acetone, ml X2	9	10.5	12	13.5	15	1.5

**Table 8: The design report for central composite design with calculated responses**

Run No.	Combinations	Isradipine level, gm, X1	Acetone level, ml, X2	D% 5min, (%)
1	1	0.125	10.5	27
2	X1	0.175	10.5	37
3	X3	0.125	13.5	49
4	X13	0.175	13.5	54
5	MID POINT	0.15	12.0	42
6	X1 at -2L	0.1	12.0	36
7	X1 at +2L	0.2	12.0	49
8	X3 at -2L	0.15	9.0	25
9	X3 at +2L	0.15	15.0	60

By using the data mentioned in Table 8, the design space was plotted by using Sigmatech software as shown in Fig 5. With the help of design space one can predict the concentration ranges of independent variable for achieving the desired response variable, percent drug release in 5 min.



**Fig. 5: Design space of isradipine buccal thin films**

The quadratic equation of the response Y (D% 5 min) to drug level (X1) and solvent level X2 was calculated by using Sigmatech software and it was showed in equation 3.

$$Y = 41.6 + 3.4(X_1) + 9.1(X_2) - 1.25(X_1X_2) + 0.21(X_1)^2 + 0.21(X_2)^2 \quad (3)$$

The equation 3 showed the negative interaction between the two variables even though it is less when compared to the main effects.

This implied that both variables should not be used at high levels for fast drug release.

In Fig 5, the level of isradipine was plotted on the X axis and levels of acetone were plotted on Y axis while maintaining the polymer level constant. As there was no pink zone in design space, D% in 5 min would not be achieved greater than 75% under the experimental conditions employed in the study. But green zone can be used to

achieve 50-75% of drug release in 5 min meets the objectives of study. The red zone region can be used to achieve the D% in 5 min of 20-40%. Whereas the white zone indicated 40 to 50% of drug release in 5min. Hence the formulation variables of acetone and drug in green space can be used to achieve not less than 50% of drug release in 5 min while maintaining the polymer at low level of experimental design.

#### CONCLUSION

The studies showed that immediate release of water insoluble drug isradipine was made feasible by formulating the drug in form of thin films for buccal delivery. Drug and solvent showed predominant positive effect over negative effect of polymer on drug release. The design space can be used for further optimization and scale up studies.

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