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QBD APPROACH IN FORMULATION AND EVALUATION OF SUMATRIPTAN SUCCINATE BILAYER BUCCAL TABLETS

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ABSTRACT

The present investigation was focused on application of QbD approach to see the effect of formulation variables on buccal mucoadhesive tablets containing anti-depressant drug, Sumatriptan succinate to circumvent the first pass effect. Risk assessment of critical material and process parameters are linked to critical quality attributes (CQAs) of the product with respect to obtain target quality product profile (TQPP). The effects of critical parameters (concentration of HPMC K100LV, Carbopol 974P) were investigated by executing design of experimentation (DoE) using 3^2 factorial designs. Drug release, mucoadhesive strength and mucoadhesion time were considered critical quality attributes (CQAs). Sumatriptan succinate buccal mucoadhesive tablets were prepared by direct compression method and were evaluated as per pharmacopoeia procedure. Multiple regression analysis and ANOVA were employed to identify and to estimate the effect of important parameters and establish their relationship with CQAs and to obtain design space for optimization purpose. The best in-vitro drug release profile, mucoadhesive strength, Mucoadhesion time and desired product quality was achieved with the formulation prepared in theregion of design space.3D response graph and Overlay plot were successfully implemented to interpret effects and selection of significant parameters on CQAs. Formulation parameters which affect the Sumatriptan succinate buccal mucoadhesive tablets can be successfully optimized.

KEYWORDS: Sumatriptan succinate, Buccal tablets, HPMC K100LV, Carbopol 974P, Mucoadhesive.

INTRODUCTION

Buccal delivery of drug, as an alternative to the oral route of drug administration, is a subject of growing interest because of its numerous advantages such as good accessibility, robustness of epithelium, facileremoval of dosage form in case of need, relatively low enzymatic activity, prevent drug degradation in gastrointestinal tract and avoid hepatic first-pass metabolism. Buccal route provides potential routes fortypically large, hydrophilic, unstable proteins, oligonucleotides and polysaccharides as well as smalldrug molecules. Among the various transmucosal sites available, mucosa of the buccal cavity was found to be the most convenient and easily available site for delivery of therapeutic agents for both local and systemic delivery as retentive dosage forms, because it has expanse of smooth muscle which is relativelyimmobile, abundant vascularization, rapid recovery time after exposure to stress.

Sumatriptan succinate is an antimigraine and pain inhibitory drug. Sumatriptan succinate has half-life of 2.5 hrs. Its total bioavailability in the body is 06% due to first pass metabolism. Also Sumatriptan succinate is an acid sensitive that is readily reacts in the gastric environment thus reduces its oral bioavailability. Transmucosal administration of drugs that undergo first pass metabolism can improve the bioavailability and reduce the dosing frequency compared with the oral route, while maintaining the antimigraine profile for a longer period of time.

The application of quality-by-design (QbD) approach in formulation development has provided an opportunity for a harmonized pharmaceutical quality system based on continuous quality improvement which can yield safer, more efficacious product. Design of experimentation, selection of appropriate model is important and criteria for selection can vary based on number and type of factors, number of levels for factor, type of study, time and cost for experiments. In this paper, we used QbD approach for better understanding of relationship of critical formulation and process parameters to CQAs relating to quality product profile of buccal mucoadhesive tablet of Sumatriptan succinate. Tablets were prepared using HPMC K100LV and Carbopol 974P by direct compression techniques. Based on risk assessment understanding for tablets, high risk variables were selected and 3^2 factorial designs was employed for design of experimentation. Tablets were evaluated for in-vitro drug release, swelling study, mucoadhesion time and strength etc. We presented different graphs, polynomial equations, ANOVA and P (Probe >F) value

to understand correlation and significance of critical parameters on QTPP. Based on effects of critical formulation variables on QTPP, Proposed design space to obtain robust formulation.

MATERIALS AND METHOD

Sumatriptan succinate was received as gift sample from Lupin Ltd, Aurangabad. HPMC K100LV and Ethylcellulose were procured as gift samples from colorcon ltd, Goa, India. All other reagents and chemicals used of analytical grade.

Risk assessment of Critical material and process attributes

Risk assessment for the experiment was carried out by basic risk management facilitation. Polymer concentration (HPMC K100LV and Carbopol 974P) were considered for design of experimentation of the Sumatriptan succinate buccal bilayer tablets[19-20]

Formulation of unidirectional, bilayered, buccoadhesive tablet of Sumatriptan succinate

All the ingredients including drug, polymer and excipients were weighed accurately according to the batch formula (Table:3), the ingredients except lubricant were mixed in the order of ascending weights and blended for 10 min in a glass mortar. After uniform mixing of ingredients, lubricant was added and again mixed for 2 min. The prepared blend (150 mg) of each formulation was pre-compressed, on a rotary tablet punching machine (Karnavati mini press, India) to form single layered flat-faced tablet of 8 mm diameter. Upper punch was raised, the backing layer of ethyl cellulose powder (50 mg) was placed on the above compact and two layers were compressed with a total weight of 200 mg/tablet.

Evaluation of bilayered buccal tablets[28,29]

Thickness

The thickness of tablet was determined using micrometer screw gauge. Tablets from each batch of formulation were measured and mean thickness value and standard deviation were calculated for each formulation.

Weight variation

The weight variation test was performed as perprocedure of IP. The weight (mg) of each of 20 individual tablets, selected randomly from eachformulation was determined by dusting each tablet offand placing it in an electronic balance. The weight datafrom the tablets were analyzed for sample mean and percent deviation.

Friability

Twenty tablets were weighed and subjected tofriability test in Roche friabilator. The pre-weighedsample was placed in friabilator which revolves at 25rpm for 4 min. dropping the tablets through a distanceof 6 inch with each revolution. This process was repeated for all formulations and the percentagefriability was calculated.

$$F=(W_{initial}-W_{final})/W_{initial} \times 100$$

Where,

$W_{initial}$= Weight of tablet before test

W_{final}= weight of tablet after test

% Friability of tablets less than 1% is considered acceptable.

Hardness

Tablets require a certain amount of strength, orhardness and resistance to friability, to withstandmechanical shocks of handling in manufacture, packaging and shipping. The hardness of the tabletswas determined using Monsanto Hardness tester. It isexpressed in Kg/cm2. Three tablets were randomly picked from each formulation and the mean andstandard deviation values were calculated.

Content uniformity

Ten tablets were weighed and grounded in a mortarwith pestle to get fine powder. Powder equivalent to the mass of one tablet was dissolved in ethyl alcoholand filtered through a 0.45-µm filter paper. The filtrate was diluted with phosphate buffer (pH 6.8).The drug content was analyzed spectrophotometrically at 227.0 nm using an UV spectrophotometer using a referenceto a standard calibration curve of the Sumatriptan succinate.

Swelling index

The formulated tablets were weighed (W1) and placedin petri dishes with 5 mL of phosphate buffer of pH 6.8.At the time interval of 1hr tablets were removed and excess water was removed carefully using filter paper.The swollen tablets were reweighed (W2) and thepercentage hydration were calculated using the following formula:

$$\text{Percentage hydration} = (W2 - W1)/ W1 \times 100$$

Determination of surface pH of tablet

A combined glass electrode was used for this purpose.The tablet was allowed to swell by keeping them incontact with 2 mL of phosphate buffer pH 6.8 in a test tube for 2 hrs. The pH was then noted by bringing the electrode in contact with the surface of the formulation and allowing it to equilibrate for 1 min.

Mucoadhesion time

The in-vitro residence time for buccal tablet was determined using a locally modified USP disintegrationapparatus. The medium was composed of 500 mL of phosphate buffer pH 6.8 maintained at 37°C . A segment of sheep buccal mucosa 3 cm length was glued to glass slab. The tablet surface was hydrated using phosphate buffer pH 6.8 and then the hydrated surface was brought into contact with the mucosal membrane.The glass slab was vertically fixed to the tablet was completely immersed into the buffer solution at thelowest point and was out at the highest point. The time necessary for complete erosion or detachment of the tablet from the mucosal surface was recorded.[28-30]

Mucoadhesive strength

Mucoadhesion strength of the tablet was measured on a modified physical balance. Fresh sheep buccal mucosa was obtained from a local slaughter house and it is used within 2 hrs of slaughtering. The mucosal membrane was washed with distilled Water and then with phosphate buffer pH 6.8. A double beam physical balance was taken and to the left arm of balance a thick thread of suitable length was hanged and to the bottomside of thread a glass stopper with uniform surface was tied. The buccal mucosa was tied tightly with mucosal side upward using thread over the base of inverted 50mL glass beaker which was placed in a 500 mL beakerfilled with phosphate buffer pH 6.8 kept at 37°C. Such that the buffer reaches the surface of mucosal membrane and keeps it moist. The buccal tablet was then stuck to glass stopper from one side membrane using an adhesive. The two sides of the balance were made equal before the study, by keeping a weight on the right hand pan. Aweight of 5 g was removed from the right hand pan,which lowered the glass stopper along with the tabletover the mucosal membrane with a weight of 5 g. Thebalance was kept in this position for 3 min. Then, the weights were increased on the right pan until tablet just separated from mucosal membrane. The excessweight on the right pan i.e. total weight minus 5 gmwas taken as a measure of the mucoadhesive strength. The mean value of three trials was taken for each set offormulations. After each measurement, the tissue wasgently and thoroughly washed with phosphate bufferand left for 5 min before placing a new tablet to get appropriate results for the formulation.[28,29]

In vitro drug release study

In-vitro drug release studies of the prepared tablets were conducted for a period of 8 hrs using an eightstation USP XXII type 2 apparatus (Labindia, Mumbai, India).The dissolution medium was 500 mL ofphosphate buffer pH 6.8 and the study was performed at 37 ± 0.5°C, with a rotation speed of 50 rpm. The backing layer of buccal tablet was attached to the glassslide with instant adhesive. The slide was placed on thebottom of the dissolution vessel. Then 5 mL samples were withdrawn at predetermined time intervals andreplaced with fresh medium. The samples were filtered through Whatman filter paper and analyzed after appropriate dilution by UV spectrophotometry at227.0 nm.[21-23]

Validation of optimized formulations

Two optimized formulations were selected from yellow shaded region i.e. design space. The composition of the checkpoints, the predicted and experimental values of all the response variables (%Drug Release, Mucoadhesive strength, Mucoadhesion time) are shown in table: 5.

RESULTS AND DISCUSSION

Based on QbD approach, risk assessment was carriedand high risk parameters, based on their strong correlation to Critical Quality Attributes (CQAs) were considered for Design of experimentation to ensure a predefined quality of the product. In order to define the ‘‘design space’’ the critical formulation variables (independent variables) and the responses able to measure the product quality were defined based onprior knowledge and preliminary studies. The independent variables considered for tablet formulations are concentration of HPMC K100LV and Carbopol 974Psince they were considered critical in determining responses i.e. % Drug release, mucoadhesive strength and mucoadhesion time. Based on the nature of variables, number of formulationvariables, levels of variables, optimization study, to estimate the main as well as interactive effects of variable and minimum number of experimental trials,3^2 factorial design with 9 runs was selected to see the effect of formulation variables on Sumatriptan succinate bilayer buccal tablets. The tablets were prepared by direct compression method using HPMC K100LV and Carbopol 974P in different concentration. All prepared tablets were evaluated for thickness, hardness, friability, weight variation, surface pH, swelling study etc. The hardness of tablets were from 5.17-5.57kg/cm2. The average thickness of the tablets was observed in the range of 2.13-2.51 mm. All the tablets complies the standard for weight variation and friability. The surface pH of all the tablet formulation was in the range of 6.33-6.73, which was nearest to salivary pH (6.5-7.5) suggesting that the prepared tablets can be used without the risk of mucosal irritation. The content uniformity of the tablets was evaluated. The in-vitro drug release profile of bilayered tablet of Sumatriptan succinate show variation in %Drug release according to concentration of matrix forming polymer. The F5 batch show highest % Drug release i.e. 94.9% in 12 hrs (Figure: 1). Results of all physicochemical parameter are presented in table: 4. It can be concluded that all the formulations are falling within the pharmacopoeial limits.

Statistical design and analysis

Prepared tablet formulations were evaluated in arandomized order for %Drug release, mucoadhesive strength and mucoadhesion time. Analysis of variance (ANOVA) was applied for testing the significance, P value 0.0363 indicated that the assumed regressionmodel was significant and valid for the examined responses.

Establishing Design Space and Control Strategy

In general, the knowledge space within the QbD approach represents the whole range of interactions between critical parameters and their effects on CQAs that has been examined during processcharacterization studies. Whereas, “design space” is space within which desired quality of product can be built. Regulatory point of view changes within designspace are not considered as changes, but changes outside design space would normally initiate regulatory post approval process. Concentration of Polymer (HPMCK 100LV and Carbopol 974P) were found to be critical on responses Drug release, mucoadhesive strength and mucoadhesion time. The variables ranked as high risk in the initial risk

assessment are included in the control strategy. Based on the requirement of product quality the criteria considered for responses were minimum of 85%Drug release, mucoadhesive strength more than 12 gm and mucoadhesion time minimum of 8 hrs. This study lead to thedesign space from multidimensional combination of polymer leads to the acceptable operating ranges for formulating Sumatriptan succinate buccal bilayer tablets with respect to target product profile. When critical variables operated within the established design space compliance to CQAs would be assured. Design space shown in figure: 5, also called as overlay plot which is shaded region with yellow color indicates that region of successful operating ranges.

Validation of optimized formulations

The composition of the checkpoints, the predicted and experimental values of all the response variables Drug Release, mucoadhesive strength, and mucoadhesion time were as shown in table: 5. This indicates statistical equivalence between experimental and predicted values, demonstrating the validity of the selected formulation variables, their levels and applied 32 factorial design to conduct design of experimentation. We could conclude that, if we keep the selected parameters within design space wewould be able to achieve desired QTPP for Sumatriptan succinate buccal mucoadhesive tablets.

Table 1: Risk assessment of the drug

Drug product CQA's	Impact of HPMCK100LV	Impact of Carbopol 974P
Drug Release	High	Medium
Mucoadhesive Strength	Low	High
Mucoadhesion Time	High	High

Table 2: Risk assessment of the drug product CQAs

Formulation Variables	CQA's	Justification
HPMC K100LV level	Assay	Polymer can impact the flow properties ofthe blend. This, in turn, can impact tablet CU. The risk is high. Occasionally, poor CU can also adversely impact assay. The risk is medium.
	Dissolution	Release of drug from tablet depends on the amount of polymer in formulation so the risk is high
Carbopol 974P Concentration	Swelling index	Carbopol 974P level may influence the %swelling index of tablet, the risk is medium
	Mucoadhesive Time	Change in concentration may have impact on mucoadhesive time

Table 3: Formulation of factorial batches

	Factorial batches								
Ingredients (mg) / batch	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Sumatriptan Succinate	10	10	10	10	10	10	10	10	10
HPMC K100LV	15	30	15	30	22.5	30	22.5	15	22.5
Carbopol 974	11.25	7.5	15	11.25	11.25	15	7.5	7.5	15
SLS	4	4	4	4	4	4	4	4	4
MCC (pH 102)	92.75	81.5	89	77.75	85.5	74	89	96.5	81.5
Mg. stearate	2	2	2	2	2	2	2	2	2
Mannitol	15	15	15	15	15	15	15	15	15
Ethyl cellulose (backing layer)	50	50	50	50	50	50	50	50	50
Total weight of tablet(mg)	200	200	200	200	200	200	200	200	200

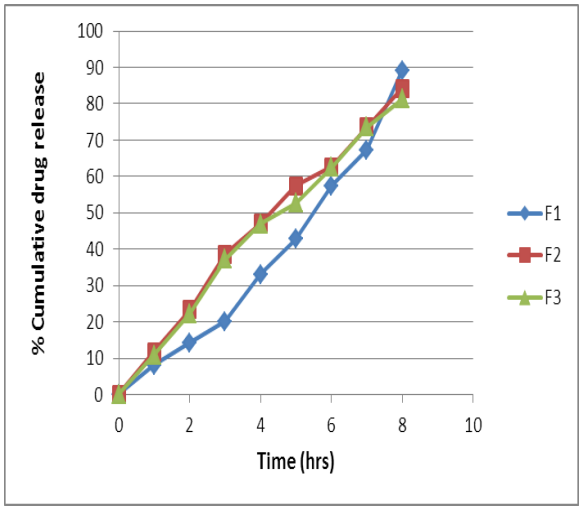

Figure 1% drug release of F1-F3 batches

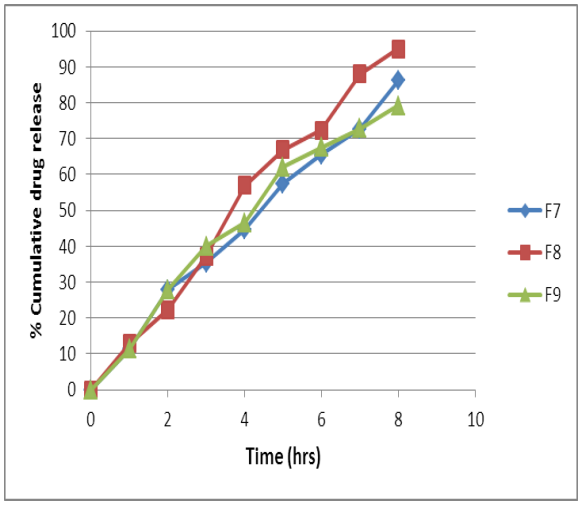

Figure 3:% drug release of F7-F9 batches

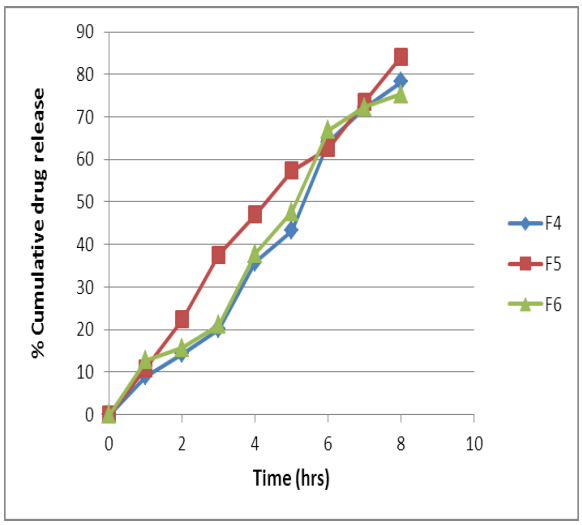

Figure 2:% drug release of F4-F6 batches

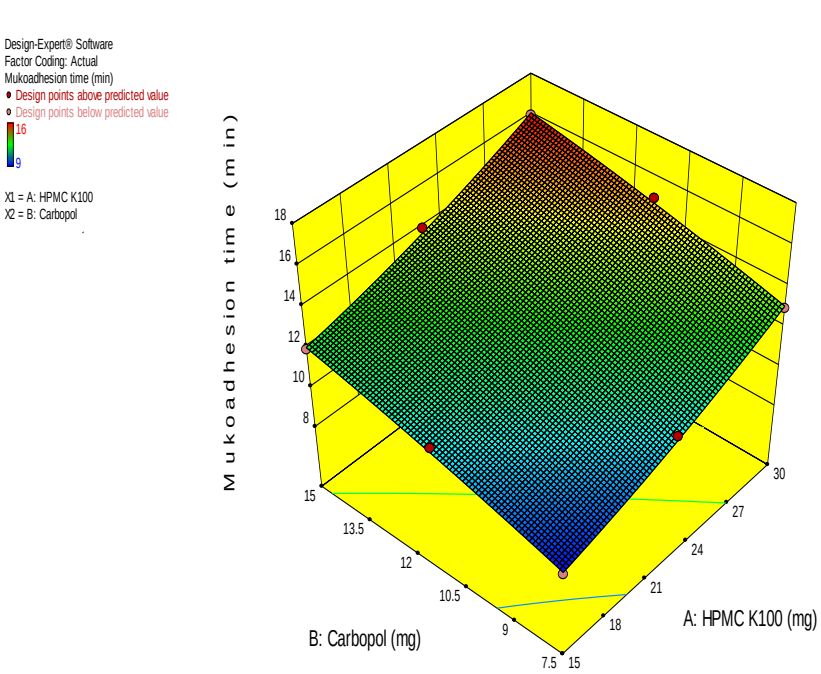

Figure 4: Response surface plot for mucoadhesive time

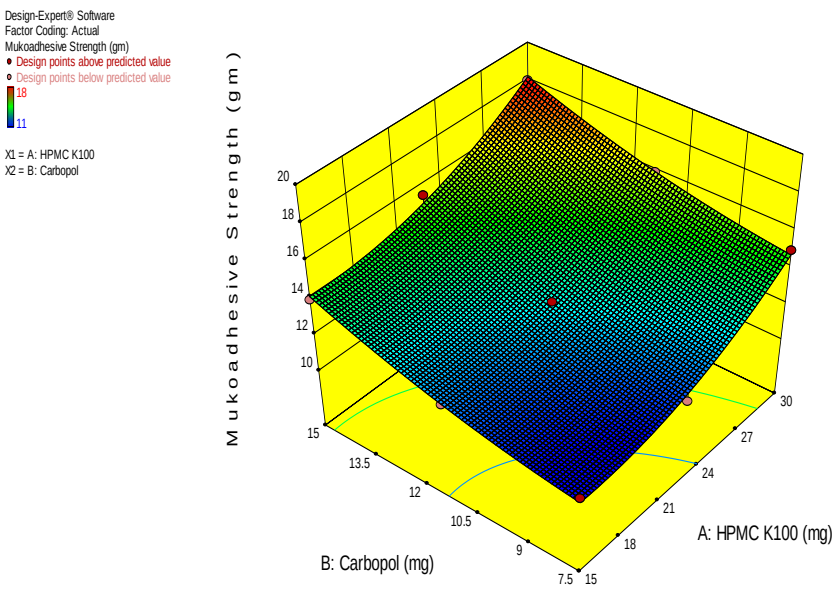

Figure 5: Response surface plot for mucoadhesive strength

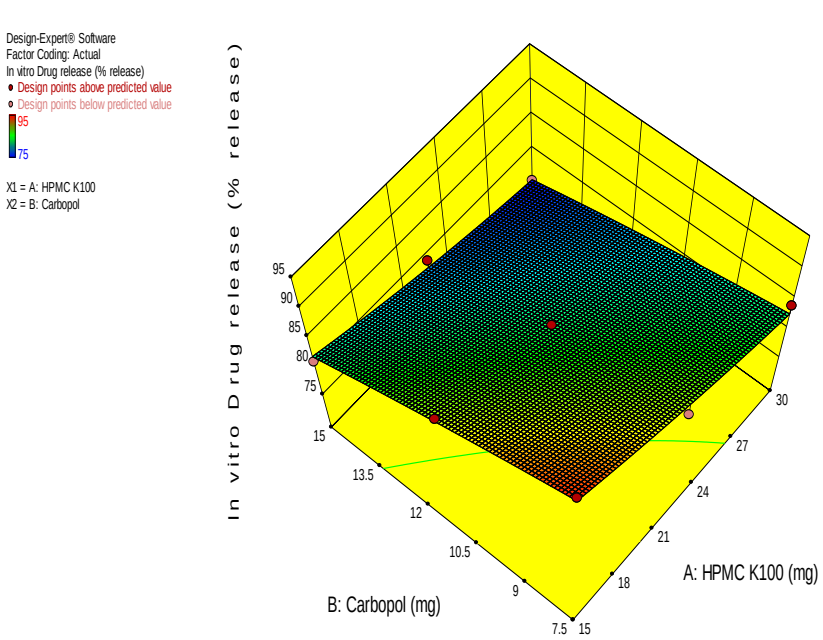

Figure 6: Response surface plot for %drug release

Table 4: Evaluation of bilayer buccal tablets

Evaluation parameters of factorial batches									
Evaluation Parameter	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Thickness (mm)	2.13±.02	2.16±0	2.29±0.01	2.46±0.01	2.37±0.02	2.13±0.1	2.48 ±0.1	2.24 ±0.2	2.51 ±0.23
Tablet Hardness (kg/cm2)	5.17±0.153	5.13±0.058	5.37±0.15	5.30±0.3	5.40±0.1	5.10±0.1	5.83 ±0.5	5.23 ±0.3	5.57 ±0.15
Friability (%)	0.45±0.036	0.32±0.11	0.32±0.02	0.35±0.03	0.72±0.02	0.63±0.2	0.53 ±0.3	0.54 ±0.1	0.43 ±0.15
Swelling index (%)	25.7±0.265	35.63±0.13	42.83±0.25	54.7±0.15	57.43±0.15	60.4±0.2	62.4 ±0.2	63.57 ±0.2	65.33 ±0.05
Content	99.3±0.275	95.63±0.25	99.5±0.2	99.3±0.26	100.0±0.07	99.5±0.3	100	99.5	98.56

uniformity (%)							±0.1	±0.1	±0.08
Surface PH	6.63±0.058	6.5±0.1	6.37±0.153	6.43±0.115	6.53±0.231	6.33±0.2	6.73 ±0.2	6.33 ±0.1	6.47± 0.306
Weight variation (mg)	199.6±0.46	199.33±0.2	199.23±0.1	200.17±0.1	198.3±0.3	199.5±0.1	200.3 ±0.2	199.4 ±0.26	199.4 ±0.26
Mucoadh esion time(min)	8±0.1	8±0.5	9±0.2 9	9±0.2	10.00±0.2	10.00±0.3	11.00 ±0.3	11.00 ±0.4	12.00 ±0.6
Mucoadh esive Strength (gm)	11±0.44	12.5±0.2	12.5±0.53	13±0.53	13.6±0.78	16.20±0.26	14.00 ±0.2	15.00 ±0.2	18.00 ±0.1

Table 5: Comparison of predicted and experimental values of O.F.3

Responses	O.F.3	
	Predicted	Experimental
Drug Release (%)	92.458	92.00
Mucoadhesive Strength (gm)	11.013	10.085
Mucoadhesive Time (min)	9.690	9.750

Table 6: evaluation parameterof formulation O.F.3

Code	Thickness (mm)	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%)	Content Uniformity (%)
O.F.3	2.1±0.3	199.1±0.01	5.1±0.2	0.1±0.5	99.5±0.1

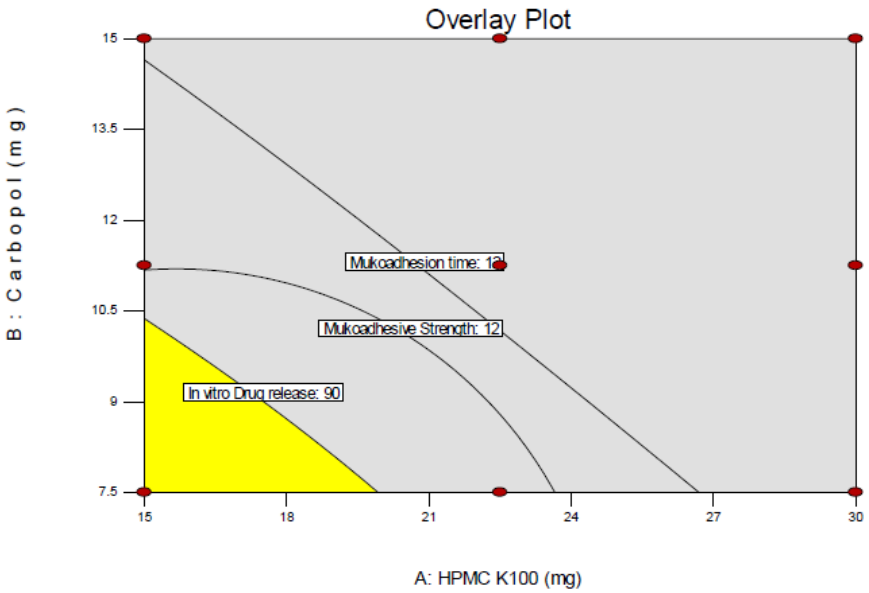

Figure 7: Overlay plot showing design space

CONCLUSION

It can be concluded that QbD approach can be successfully implemented to see the effect offormulation parameters on tablet formulation with predictable % Drug release, mucoadhesive strength and mucoadhesion time. All Critical parameters rankedas high risk in the initial risk assessment were included in the design of experimentation. Amount of HPMCK100 and Carbopol 974P were identified as criticalparameters to achieve desired QTPP. Based on selection criteria, 3^2 factorial design (RSM) was employed to conduct design of experimentation.

Polynomial equations, ANOVA, different statistical values were utilized to interpret significance offormulation parameters on responses and designspace was proposed with desired QTPP. From theexperiments, it can be concluded that if formulationparameters were operated within the proposed designspace, high risk can be lowered to low level of risk.From this study it can be concluded that formulationprepared within design space can produce formulationwith acceptable in-vitro drug release, mucoadhesive strength and mucoadhesion time. Also we could conclude that Bilayer buccal tablets can be one of thealternative routes of administration to avoid gastricirritation and first pass effect.

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