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Effect of formulation parameters on Sumatriptan succinate Buccal Mucoadhesive Tablet: Quality by Design approach

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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 migraine drug, Sumatriptan succinate to circumvent the first pass effect and to provide sustained release. Risk assessment of critical material and process parameters are linked to critical quality attributes (CQAs) of the product with respect to obtain total quality product profile (TQPP). The effect of critical parameters (polymer: drug ratio, carbopol: HPMC E5 ratio and diluent quantity) were investigated by executing design of experimentation (DoE) using Box-Behnken statistical model. DR10 hr (drug release after 10 hrs), mucoadhesive strength and mucoadhesion time were considered critical quality attributes (CQAs). Sumatriptan succinate buccal mucoadhesive (SBM) tablets were prepared by direct compression method and were evaluated as per pharmacopoeia procedure. Multiple regression analysis and ANOVA were employed to identify and 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 the region of design space. FDS graph, 3D response graph and Overlay plot were successfully implemented to interpret effects and selection of significant parameters on CQAs. Hence, it can be concluded that formulation parameters affects the SBM tablet and can be successfully optimized using the QbD a novel approach resulting into the SBM tablets which could provide sustained effect and avoid first pass effect.

INTRODUCTION

Sumatriptan succinate is a selective serotonin (5-HT $1_{B,}$ 1_{D} receptor) agonist drug used to treat migraine. It has low oral bioavailability (15%) due to high first-pass metabolism as it rapidly and incompletely absorbed followed by oral administration (Singh *et al.,* 2012; Shivanand *et al.,* 2011). Also, half life of Sumatriptan succinate is about 2.5 hr. These constraints and low molecular weight of Sumatriptan makes it suitable candidate to deliver drug delivery through buccal route (Singh *et al.,* 2012). Among the various transmucosal routes, buccal mucosa is suitable for administration of retentive dosage form as its excellent accessibility for expansion of smooth muscle and relatively immobile mucosa (Sudhakar *et al.,* 2006). Also, buccal delivery avoid high first pass metabolism, drug degradation in harsh gastrointestinal environment as buccal route provide direct access to the systemic circulation through jugular vein which leads to high bioavailability (Biyani *et al.,* 2011). Bioadhesive polymers used to prolong the residence time of dosage form on the mucosal membrane and for localized drug targeting (Hassan *et al.,* 2011). Carbopol is lightly cross-linked (Allyl ethers of pentaerythritol) polymer. Carbopol 971P NF is the most efficient grade for controlling drug release (Hassan *et al.,* 2011). The application of quality-by-design (QbD) approach to formulation development has provided an opportunity for a harmonized pharmaceutical quality system based on continuous quality improvement which can yield safer, more efficacious product (Cobb *et al.,* 2012; Awotwe *et al.,* 2012; Rathore *et al.,* 2009; Verma *et al.,* 2009; Wu *et al.,* 2009; Charoo *et al.,* 2011; Mennini *et al.,* 2012). To conduct 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 (Rathore *et al.,* 2009). In this paper, we used QbD

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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 as model drug. Sumatriptan succinate buccal mucoadhesive (SBM) tablets were prepared using Carbopol 971P, HPMC E5, lactose and mannitol by direct compression techniques. Based on risk assessment understanding for SBM tablets, high risk variables were selected and Box- Behnken model was employed for design of experimentation as we want to conduct optimization study on three high risk formulation variables at their three levels with objective to estimate pure error in optimum number of experiments as compared to general factorial design. SBM tablets were evaluated for *in vitro* drug release, swelling study, *Ex-vivo* 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 TQPP. Based on effects of critical formulation variables on TQPP, we proposed design space to obtain robust formulation.

MATERIALS AND METHODS

Materials

Sumatriptan succinate provided by Cipla Pharmaceuticals Ltd, Mumbai, India as gift sample, Carbopol 971P and HPMC E5 procured from Vergo Pharma Research lab, Goa India as gift sample. All other chemicals are of analytical grade.

Risk assessment of Critical material and process attributes

Risk assessment for the experiment was carried out by basic risk management facilitation method as shown in table 1. Drug: Polymer, Carbopol 971 P: HPMC E5 ratio and Diluent quantity were considered for design of experimentation of the Sumatriptan succinate buccal mucoadhesive (SBM) tablet.

Formulation of Sumatriptan succinate Buccal Mucoadhesive (SBM) tablet using Experimental design

Sumatriptan succinate Buccal Mucoadhesive tablet were prepared by direct compression method using different grades of polymer with varying concentration of excipients (Narmada *et al.,* 2009; Patel *et al.,* 2012) as shown in table 2. Drug, carbopol 971P, HPMC E5 polymer and other excipients were screened (Mesh # 40), mixed thoroughly and lubricated with talc and magnesium stearate and were directly compressed into tablets using conventional rotary tablet machine; equipped with round-shaped, flat faced 8 mm punches and a die. The tablet tensile strength was ranged from 70 to 150 N for all formulation batches. In the present study, Box Behnken design was employed to see effect of 3 formulation variables at 3 levels by the 17 experimental trials; criteria for selection of design were number of variables, their levels in experiment, and minimum number of runs to estimate main effects, 2FI and pure error.

Determination of Physicochemical Parameters

Sumatriptan buccal mucoadhesive tablets were evaluated for hardness, weight variation, friability and drug content as per Pharmacopoeial specifications.

Surface pH

The surface pH of the tablets was determined in order to investigate the possibility of any side effects *in vivo* (Patel *et al.,* 2012). As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was determined to keep the surface pH as close to neutral as possible. The tablet was allowed to swell by keeping it in contact with distilled water (pH 6.5 ± 0.05) for 2 hours at room temperature. The pH was measured by bringing the electrode in contact with the surface of the tablet and allowing it to equilibrate for 1 minute. The average pH of three determinants was reported in table no 3.

Swelling Study

Swelling properties of Sumatriptan succinate buccal mucoadhesive tablet were evaluated by determination of the percentage of hydration (Agarwal *et al.,* 1999; Saleem *et al.,* 2011). The experiment was performed in triplicate and further swelling index (percent hydration) calculated according to the following formula and given in table no 3,

% Swelling index = (W2-W1)/W1 X 100

W1 = initial weight of tablet,

W2 = weight of swollen tablet

Bioadhesive Strength

Bioadhesive strength of SBM tablets were measured on a modified physical balance using fresh sheep buccal mucosa as model mucosal membrane (Singh *et al.,* 2012; Mario, 2004). The mucosal membrane was washed with phosphate buffer pH 6.8. A double beam physical balance was taken and to the left arms of balance a thick thread of suitable length was hanged and to the bottom side 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 50 ml glass beaker which was placed in a 500 ml beaker filled with phosphate buffer pH 6.8 kept at 37º C such that the buffer reaches the surface of mucosal membrane and keeps it moist. The SBM tablet was stuck to glass stopper using cyanoacrylate adhesive. The two sides of the balance were made equal before the study, by keeping a weight on right hand pan. A weight of 5 g was removed from the right hand pan, which lowered the glass stopper along with the tablet over the mucosal membrane with a weight of 5 g. The balance was kept in this position for 5 min. Then, the weights were increased on the right pan until tablet just detached from mucosal membrane. The weight in grams required to detach the SBM tablet from mucosal surface provided the measure of mucoadhesive strength. The experiment were performed in triplicate and mean ± SD values were reported. The force of adhesion was calculated by following formula;

Force of Adhesion (N) = Mucoadhesive strength × 9.8 / 1000

Ex-vivo Mucoadhesion Time

The *ex-vivo* mucoadhesion time of SBM tablets were evaluated using freshly excised sheep buccal mucosa (Singh *et al.,* 2012; Patel *et al.,* 2012; Mario, 2004). The fresh sheep buccal

mucosa was stuck on the glass slide and buccal tablet was placed on sheep buccal mucosa by applying a light force for 30 seconds. The glass slide was immersed in the beaker containing 200 ml of phosphate buffer pH 6.8 at 37±1º C. After 2 min, stirring was applied by magnetic stirrer solely to simulate buccal cavity environment. The time necessary for complete detachment of SBM tablet from mucosal surface was recorded.

***In vitro* Drug release study**

The *in vitro* study for SBM tablets was carried out in USP Dissolution test apparatus (Apparatus II paddle type) (Singh *et al.,* 2012). 500 ml phosphate buffer pH 6.8 was used as dissolution medium at 37±0.5ºC, and rotation speed of 50 rpm. The SBM tablet stuck to glass cover slip with cyanoacrylate adhesion and kept at bottom of dissolution vessel. Aliquots of 5 ml sample were withdrawn at predetermined time interval and replaced with fresh medium to maintain the sink condition. The samples were filtered through 0.45 µm filter (Millipore) and were analyzed at 283 nm by UV Visible spectrophotometer. The experiments were performed in triplicate. The PCP-Disso-Ver. 2.0 software, Pune, India used to calculate cumulative percent drug release.

Differential Scanning Calorimetry Study

Thermograms of samples (drug, physical mixture of drug and excipients in the final ratio and tablet) were obtained by differential scanning calorimetry study (Shimadzu, DSC 60, University of Pune, Pune). Drug, physical mixture and tablet powder (2 mg) was accurately weighed into aluminum pan and then sealed with aluminum lids. The thermograms of the samples were obtained at a scanning rate of 5°C/min over temperature range of 50 to 320°C.

Validation of optimized formulations of SBM tablets:

Three optimized formulations were selected (B1-B3) from yellow shaded region i.e. design space. The composition of the checkpoints, the predicted and experimental values of all the response variables as shown in table no 5 (Drug Release 10 hr, Mucoadhesive strength, Mucoadhesion time) and the percentage error in prognosis were determined to validate the selected statistical model.

RESULT AND DISCUSSION

Based on QbD approach, risk assessment was carried and 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 on prior knowledge and preliminary studies. The independent variables considered for SBM tablet formulations were polymer: drug ratio, Carbopol 971P: HPMC E5 ratio and diluent quantity since they were considered critical in determining responses DR10 hr, Mucoadhesive strength and Mucoadhesion time. Based on the nature of variables, number of formulation variables, levels of variables, optimization study, to estimate the main as well as interactive effects of variable and minimum number of experimental trials, Box Behnken design with ‘12 runs and 5 center points’ was selected to see the effect of formulation variables on Sumatriptan Buccal Mucoadhesive (SBM) tablet. SBM tablets were prepared by direct compression method using Carbopol 971P and HPMC E5 in different concentration. All prepared SBM tablets were evaluated for thickness, hardness, friability, weight variation, surface pH, swelling study etc. The hardness of SBM tablets were from 5.4 - 6.4 kg/cm^2 and increased due to increasing weight of the tablet. The average thickness of the SBM tablets was observed in the range of 1.62 - 2.33 mm. All the SBM tablets complies the Indian Pharmacopoeia standard for weight variation and friability. The surface pH of all the SBM tablet formulation was in the range of 6.8 - 7.3, which was nearest to salivary pH (6.5-7.5) suggesting that the prepared SBM tablets can be used without the risk of mucosal irritation. The content uniformity of the SBM tablets was evaluated. Results of all physicochemical parameter are presented in table 3. It can be concluded that all the formulations are falling within the pharmacopoeial limits. When the goal of experiment is optimization, FDS graph gives interpretation of sizing and precision of design. We obtained FDS value 0.99 or 99% as shown in figure 1 for selected Box- Box Behnken design indicating good size and precise design to see effect of formulation parameter on the selected CQAs.

Swelling Study

The swelling studies were conducted for SBM tablet formulations and the results were shown in table 3. From results, it can be concluded that swelling index is proportional to polymer concentration. Matrices in which high concentration of Carbopol 971P showing high swelling value could be due to higher and faster swelling of Carbopol 971P whereas matrices containing HPMC E5 demonstrated lower swelling values as compare to Carbopol 971P.

Statistical design and analysis

SBM tablet formulations were evaluated in a randomized order for Mucoadhesive strength, Mucoadhesion time and Drug release after 10 hrs. Analysis of variance (ANOVA) was applied for testing the significance and validity of the postulated model, using a 1% significance level (Lewis *et al.,* 1999; Rath *et al.,* 2011). ANOVA results shown in table 4 indicated that the assumed regression model was significant and valid for the examined responses.

Effect on Mucoadhesive strength

The mucoadhesive strength study was performed using fresh sheep mucosa on the modified physical balance and measured the force (N) required to detach the tablet; results are shown in the table 2. From design of experiment (Stat-ease,

Design Expert 8.0.7.1) generated reduced polynomial equation (1) showing quadratic correlation for mucoadhesive strength.

Mucoadhesive Strength =

$24.36 + 3.31X_1 + 3.55X_2 - 1.15X_3 - 2.33X_1X_2 - 3.87X_1^2 - 2.07X_2^2 - 4.73X_3^2$

The positive value for the coefficient of X_1 and X_2 in the equation (1) indicates increase in the mucoadhesive strength with increase in the concentration of polymer blend and carbopol concentration whereas negative value of X_3 diluents quantity respectively. The same effects can be depicted from the 3D surface response graphs as shown in figure 2. It was observed that mucoadhesive strength of formulation was based on different factors including molecular weight, swelling behavior, concentration of polymer and proportion of polymer blend and diluents quantity. The SBM tablets containing Carbopol 971P, HPMC E5 had mucoadhesive strength between 7.8 - 24.6 g. As Carbopol 971P concentration increased mucoadhesive strength was increased, might be due to ionization of Carbopol at salivary pH, which leads to the formation of secondary bioadhesion bonds with mucin and interpenetration of the polymer chains in the interfacial region (Hassan *et al.*, 2009). Thus the mucoadhesive strength exhibited by the SBM tablet with middle level of formulation variables can be considered satisfactory to maintain tablet in the oral cavity.

Effect on Mucoadhesion time

The mucoadhesion time study performed on sheep buccal mucosa, time was observed in the range of 6.30 - 14.7 hrs. Reduced polynomial equation (2) obtained from ANOVA showing quadratic model.

Mucoadhesion time =

$13.90 + 1.69\ X_1 + 1.25\ X_2 + 0.50\ X_1X_3 - 2.08\ X_1^2 - 0.70\ X_2^2 - 2.58\ X_3^2$ … 2.

The positive value for the coefficient of X_1 and X_2 in the equation indicates the mucoadhesive time increases with increase in the polymer blend: drug ratio and concentration of Carbopol971P in polymer blend, whereas X_3, diluent quantity showed non-significant effect on mucoadhesion time hence removed in reduced equation. This might be due to bioadhesive nature of the polymers and interpenetration of polymeric chains into the mucus membrane. The effect of two independent variables was found as quadratic in 3D surface response of mucoadhesive time as shown in figure 3.

Effect on *in-vitro* Drug Release

The *in-vitro* drug release after 10 hr of SBM tablets was presented in table 2 and figure 5. Drug release from SBM tablets varied according to the polymer blend: drug ratio, ratio of matrix–forming polymer and diluents quantity. From quadratic model polynomial equation (3) it was observed that drug release was decreased with increase in polymer: drug ratio and Carbopol 971P concentration in polymer blend as it has excellent gelling properties which controlled drug release from SBM tablet. Positive value of coefficient X_3 indicates increase in drug release with high level of diluent quantity, might be due to formation of pores at higher level of MCC and Lactose as compared to low level which might helped to swell Carbopol at their low level. 3D surface response graph shown in figure 4 helped diagrammatically to understand the effect.

Drug release after 10 hr (Y1) =

$98.87 - 1.60\ X_1 - 1.53\ X_2 + 0.78\ X_3 - 0.71X_1^2 - 1.65\ X_2^2$ 3

Differential Scanning Calorimetry Study

The drug, physical mixture of drug with excipients and SBM tablets were characterized by DSC, to confirm the physical compatibility of drug in physical mixture and tablet after compression as shown in figure 6. Sumatriptan succinate exhibits sharp melting endotherm at 173^0C and physical mixture of drug also in the same vicinity but with reduced intensity as compared to pure drug. For SBM tablet endotherm was observed at 174^0C indicating absence of any drug-polymer interactions

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 process characterization studies. Whereas, "design space" is space within which desired quality of product can be built. Regulatory point of view changes within design space are not considered as changes, but changes outside design space would normally initiate regulatory post approval process. Polymer: drug ratio, carbopol: HPMC E5 and diluent quantity were found to be critical on responses DR10 hr, 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 95 % DR10hr, mucoadhesive strength more than 20 gm and mucoadhesion time minimum of 10 hr. This study lead to the design space from multidimensional combination of polymer: drug ratio, polymer blend and diluent quantity leads to the acceptable operating ranges for formulating SBM tablet 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 7, also called as overlay plot which is shaded region with yellow color indicates that region of successful operating ranges.

Validation of optimized formulations of Sumatriptan succinate buccal mucoadhesive (SBM) tablets:

The composition of the checkpoints, the predicted and experimental values of all the response variables (Drug Release 10 hr, Mucoadhesive strength, Mucoadhesion time) and the standard error in prognosis 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 Box-Behnken model to conduct design of experimentation. We could conclude that, if we keep the selected parameters within design space we would be able to achieve desired QTPP for Sumatriptan succinate buccal mucoadhesive tablets.

Table. 1: Risk assessment parameters to identify variables affecting product quality.

Drug product CQAs	Polymer: Drug ratio	Carbopol 971P: HPMC E5 Concentration	Diluent Quantity	Compression force	Blending time
Mucoadhesive Strength	Medium	High	High	Medium	Medium
Mucoadhesion Time	High	High	Low	Medium	Medium
Drug Release	High	High	Medium	Medium	Medium

Table. 2: Box Behnken design for Sumatriptan succinate Buccal Mucoadhesive tablets.

Formulation Code	Independent Variables			Dependent response		
	X1 (Polymer:Drug ratio)	X2 (Carbopol: HPMC E5)	X3 (Diluent quantity)	Mucoadhesive Strength (gm)**	Mucoadhesive Time (Hr)***	DR10hr (%)*
F-1	-1	-1	0	7.4±0.97	7.5±0.30	100.58±1.2
F-2	1	-1	0	20.1±1.22	11.5±1.25	95.68±2.03
F-3	-1	1	0	21.4±0.60	11±0.40	96.91±1.8
F-4	1	1	0	24.8±0.40	14.5±0.50	93.19±1.67
F-5	-1	0	-1	14.12±1.07	8.5±0.75	98.13±1.46
F-6	1	0	-1	19.56±0.90	10.5±1.30	96.23±1.57
F-7	-1	0	1	12.23±1.50	7±1.20	100.13±1.61
F-8	1	0	1	17.14±0.71	11±0.7	97.82±1.52
F-9	0	-1	-1	16.12±1.24	9.5±1.0	97.81±1.4
F-10	0	1	-1	21.42±1.43	11.5±1.2	95.12±1.6
F-11	0	-1	1	14.13±1.39	10±0.5	99.49±1.8
F-12	0	1	1	18.56±1.41	11.5±0.4	96.12±1.2
F-13	0	0	0	24.91±1.21	14±0.5	98.28±1.6
F-14	0	0	0	24.52±1.32	13.5±1.2	97.61±1.5
F-15	0	0	0	24.13±1.08	14.5±1.3	99.43±1.9
F-16	0	0	0	25.41±1.10	13.5±1.2	99.83±1.5
F-17	0	0	0	22.85±1.32	14±1.3	99.5±1.1

Each SBM tablet contains 3 mg Magnesium Stearate and 2 mg of Talc; *, **, *** n = 3

Table. 3: Physicochemical Parameter of SBM tablets.

Batch Code	Thickness (mm)	Avg. Weight (mg)	Hardness (Kg/cm^2)	Content Uniformity (%)	Friability (%)	Surface pH	Swelling Study (%)
F1	1.64±0.04	142.7±1.13	5.4±0.14	98.12	0.463	7.2±0.15	120.12±2.4
F2	2.26±0.01	155.2±1.00	6.4±0.20	99.98	0.403	7.3±0.20	135.16±2.37
F3	2.24±0.04	154.8±1.21	5.9±0.32	97.52	0.363	7.1±0.1	132.82±1.95
F4	2.32±0.04	161.2±1.43	5.5±0.23	98.91	0.449	7.1±0.15	150.62±2.31
F5	1.58±0.02	137.1±0.97	6.2±0.18	96.23	0.411	6.9±0.2	140.12±2.64
F6	1.75±0.05	146.9±1.18	5.7±0.25	98.10	0.272	7.2±0.1	142.51±2.16
F7	1.87±0.02	155.3±1.26	6.0±0.18	97.07	0.453	6.8±0.2	131.62±2.89
F8	1.73±0.03	164.2±1.19	5.8±0.17	96.82	0.372	7.0±0.2	148.13±1.64
F9	1.57±0.12	137.6±0.84	5.7±0.84	98.82	0.473	6.7±0.1	126.81±2.68
F10	1.59±0.14	138.2±1.26	6.2±0.60	98.58	0.693	7.1±0.1	139.21±3.12
F11	1.68±0.08	147.3±1.41	5.8±0.74	98.42	0.563	7.2±0.2	131.62±2.78
F12	2.33±0.1	161.4±1.32	5.8±0.93	99.41	0.891	6.9±0.2	143.31±2.47
F13	1.67±0.1	142.6±1.37	6.3±0.58	98.63	0.751	6.8±0.2	138.42±2.61
F14	1.65±0.04	141.3±0.86	5.9±0.65	98.81	0.712	6.9±0.15	134.62±1.76
F15	1.68±0.1	143.5±0.94	6.4±0.68	98.67	0.547	6.7±0.1	140.10±2.57
F16	1.68±0.04	142.5±1.7	5.9±0.37	98.92	0.756	6.9±0.15	142.57±1.86
F17	1.65±0.1	140.6±1.56	6.3±0.80	99.14	0.812	7.0±0.15	143.62±2.43

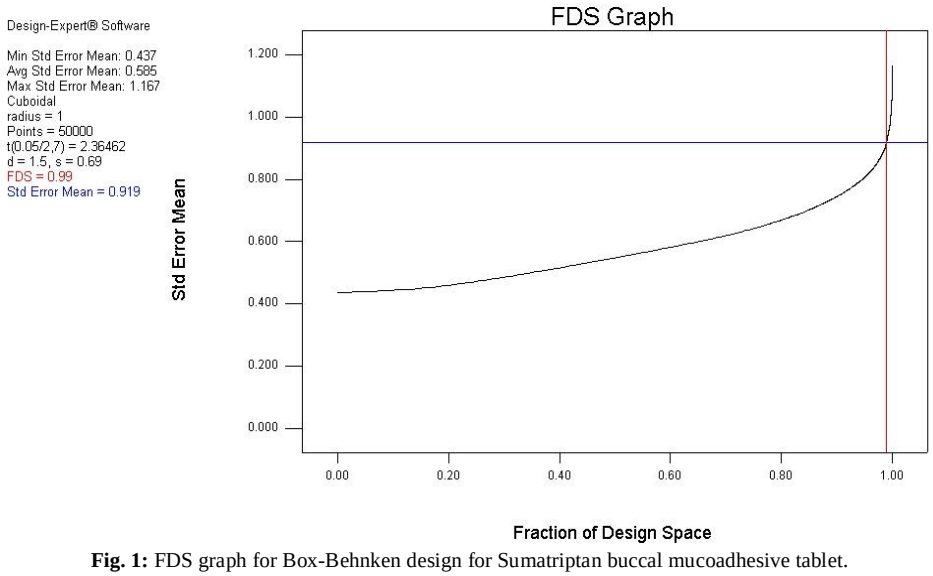

Fig. 1: FDS graph for Box-Behnken design for Sumatriptan buccal mucoadhesive tablet.

Table. 4: ANOVA results for formulation variables of Sumatriptan succinate buccal tablets.

Response	Source	Sum of Squares	df	Mean square	F value	P value Probe ⟩ F	Comments
Response (Y1)= Mucoadhesive strength	Model	414.05	7	59.15	29.17	0.0001	Significant
	A-Polymer Blend: Drug Ratio	87.45	1	87.45	43.13	0.0001	Significant
	B: Carbopol concentration	101.03	1	101.03	49.82	0.0001	Significant
	C: Diluent quantity	10.49	1	10.49	5.17	0.0490	Significant
	AB	21.26	1	21.62	10.66	0.0098	Significant
	A^2	62.69	1	62.96	31.05	0.0003	Significant
	B^2	18.08	1	18.08	8.91	0.0153	Significant
	C^2	94.38	1	94.38	46.54	0.0001	Significant
	Residual	18.25	9	2.03			
	Lack of Fit	14.49	5	2.90	3.08	0.1492	Not Significant
	Pure Error	3.79	4				
	Cor total	432.30	16	0.94			
Response (Y2)= Mucoadhesion Time	Model	88.72	6	14.79	58.13	0.0001	Significant
	A: Polymer: Drug	22.78	1	22.78	89.56	0.0001	Significant
	B: Carbopol concentration	12.50	1	12.50	49.14	0.0001	Significant
	AC	1	1	1	3.93	0.0755	Not Significant
	A2	18.13	1	18.13	71.27	0.0001	Significant
	B2	2.06	1	2.06	8.11	0.0173	Significant
	C2	27.92	1	27.92	109.75	0.0001	Significant
	Residual	2.54	10	0.25			
	Lack of Fit	1.84	6	0.31	1.76	0.3049	Not Significant
	Pure Error	0.70	4	0.17			
	Cor total	91.26	16				
Response (Y3)= Drug Release 10 Hr	Reduced Quadratic Model	58.34	4	11.67	19.18	0.0001	Significant
	A: Polymer: Drug ratio	20.58	1	20.58	33.83	0.0002	Significant
	B: Carbopol concentration	18.67	1	18.67	30.69	0.0160	Significant
	C: Diluent Quantity	4.91	1	4.91	8.08	0.0028	Significant
	A^2	2.11	1	2.11	3.47		
	B^2	11.49	1	11.49	18.88		
	Residual	6.69	11	0.61			
	Lack of Fit	3.14	4	0.45	0.51	0.7975	Not Significant
	Pure Error	3.55	4	0.89			
	Cor Total	65.03	16				

Table. 5: Validation of Box-Behnken model for Design of Experimentation of SBM Tablets.

Formulation Code	Composition (mg/tab) X1 (Polymer: Drug ratio)	X2 (Carbopol: HPMC E5)	X3 (Diluent quantity)	Response	Predicted Value	Experimental Value	Standard Error
B1	- 0.35	0.30	- 0.68	Mucoadhesive strength	22.87	23.61	0.37
				Mucoadhesion Time	12.54	13.91	0.685
				Drug Release 10hrs	97.81	96.15	0.83
B2	0.03	- 0.34	- 0.68	Mucoadhesive strength	22.83	23.5	0.335
				Mucoadhesion Time	12.54	11.3	0.62
				Drug Release 10hrs	97.81	98.9	0.545
B3	0.42	- 0.25	- 0.68	Mucoadhesive strength	22.4	21.59	0.405
				Mucoadhesion Time	12.28	13.65	0.685
				Drug Release 10 Hrs	98.24	99.87	0.815

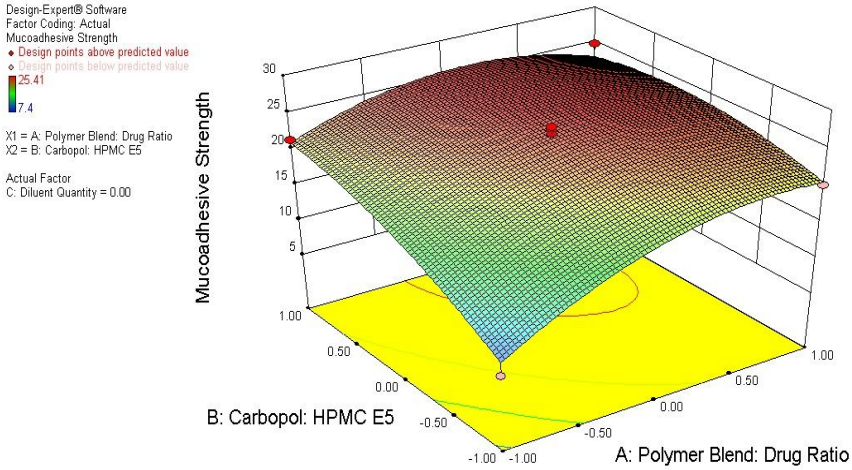

Fig. 2: 3D Surface response plot demonstrating influence of Polymer blend: drug ratio and polymer ratio (Carbopol: HPMC E5) on the mucoadhesive strength.

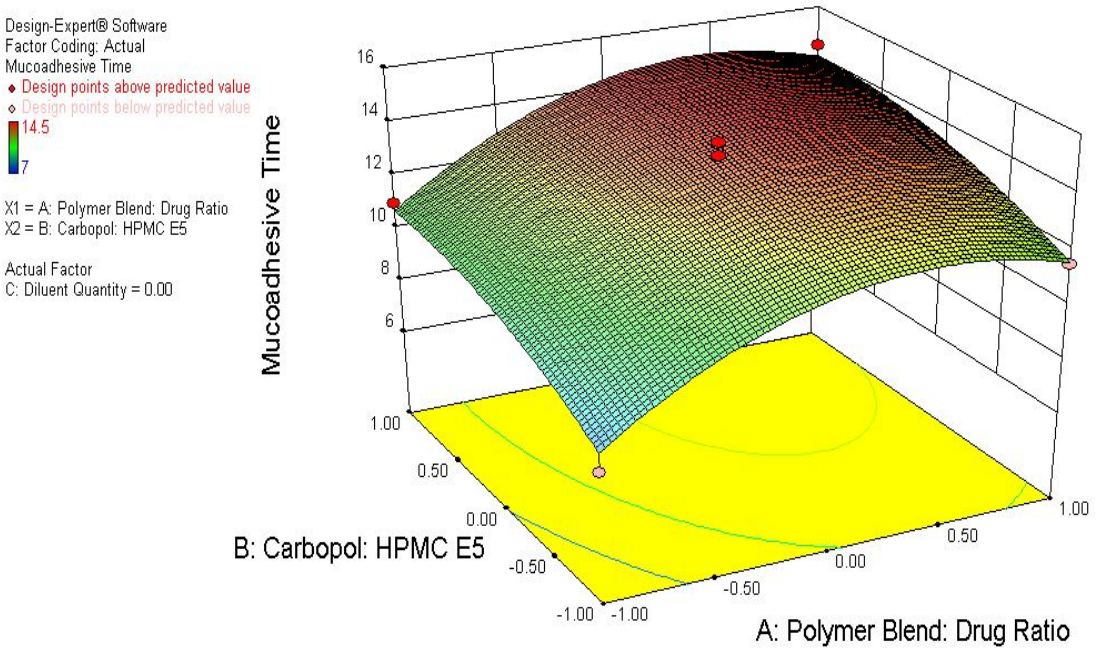

Fig. 3: 3D Surface response plot demonstrating influence of polymer blend: drug ratio and polymer ratio (Carbopol: HPMC E5) on mucoadhesion time.

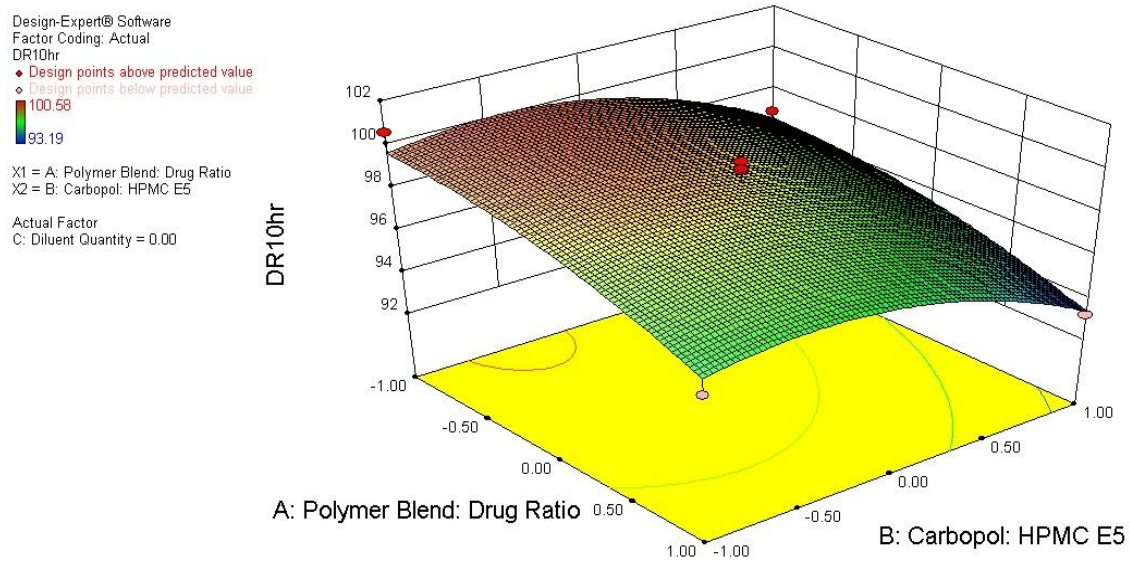

Fig. 4: 3D Surface response plot demonstrating influence of polymer blend ratio and polymer: drug ratio on drug release after 10 hr.

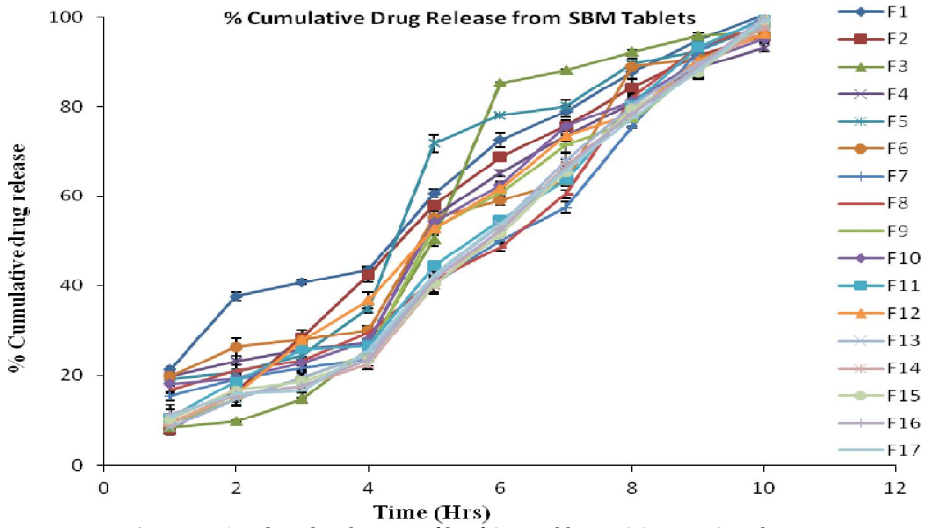

Fig. 5: *In-Vitro* drug dissolution profile of SBM tablets in 6.8 pH PBS medium.

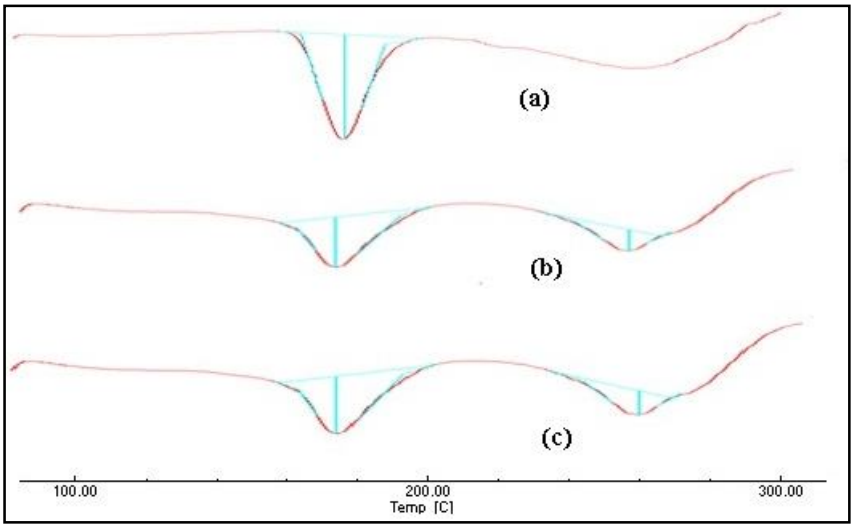

Fig. 6: DSC thermographs of (a) Sumatriptan succinate, (b) physical mixture of drug and excipients, (c) SBM tablet.

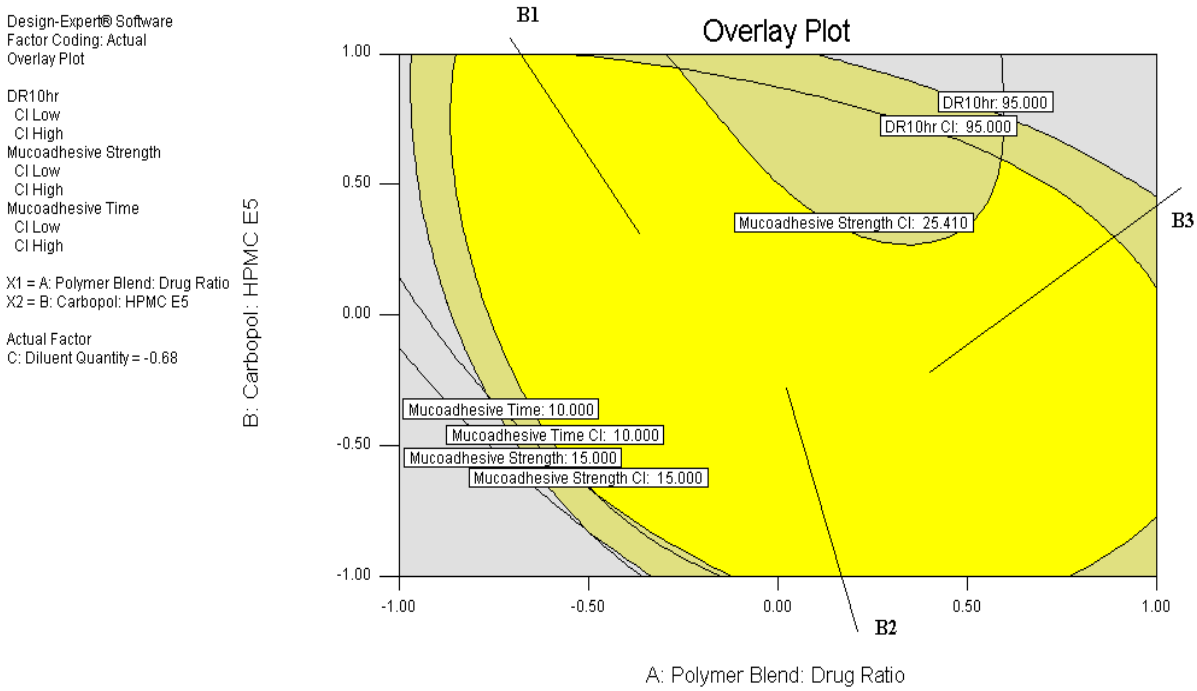

Fig. 7: Design space for SBM tablet formulation.

CONCLUSION

It can be concluded that QbD approach can be successfully implemented to see the effect of formulation parameters on SBM tablet formulation with predictable drug release, mucoadhesive strength and mucoadhesion time. All Critical parameters ranked as high risk in the initial risk assessment were included in the design of experimentation. Polymer: drug ratio, carbopol: HPMC E5 and diluent quantity (Lactose: Mannitol) were identified as critical parameters to achieve desired QTPP. Based on selection criteria, Box-Behnken design (RSM) design was employed to conduct design of experimentation. Polynomial equations, ANOVA, different statistical values were utilized to interpret significance of formulation parameters on responses and design space was proposed with desired QTPP. From the experiments, it can be concluded that if formulation parameters were operated within the proposed design space, high risk can be lowered to low level of risk. From this study it can be concluded that formulation prepared within design space can produce formulation with acceptable *in vitro* drug release, mucoadhesive strength and mucoadhesion time. Also we could conclude that SBM tablets can be one of the alternative routes of administration to avoid first pass effect and could provide prolonged release. Further research on pharmacokinetic study can give better insight about bioavailability for buccal mucoadhesive tablet, but it was beyond the current research. It can be expected that this application of the DoE tools in QbD approach could be useful for further formulation studies

especially related to process parameters which contribute significantly to the product quality, but these are beyond the current experimental work.

ABBREVIATIONS

SBM	= Sumatriptan succinate Buccal Mucoadhesive
HPMC E5	= Hydroxypropyl methylcellulose E5
MCC	= Microcrystalline cellulose
PBS	= Phosphate buffer solution
QbD	= Quality by Design
CMAs	= Critical Process Parameters
CPAs	= Critical Process Parameters
CQA_S	= Critical Quality Attributes
QTPP	= Quality Target Product Profile
DR 10 hr	= Drug release after 10 hr
USP	= United State Pharmacopoeia
ANOVA	= Analysis of Variance
ICH	= International Conference Harmonization

REFERENCES

Agarwal V, Mishra B. Design development and biopharmaceutical properties buccoadhesive compact of Pentazocine. Drug Dev Ind Pharm. 1999; 701–709.

Awotwe OD, Agarabia C, Wub GK, Casey E, Read E, Lute S, Brorson KA, Khan MA, Shah RB. Quality by Design: Impact of formulation variables and their interactions on quality attributes of a lyophilized monoclonal antibody, Int J Pharm, 2012; 438:167– 175.

Biyani KR, Shahzad M, Shaikh SR, Khan TZ. Buccal mucoadhesive tablets of Carvedilol: characterization and optimization. Int J Pharm Res Dev. 2011; 3(8):30-36.

Charoo NA, Shamsher AA, Zidan AS, Rahman Z. Quality by design approach for formulation development: a case study of dispersible tablets, Int J Pharm. 2011; 423 (2): 167–178.

Cobb J, Brett RJ, Ruff MD, Berry A, Epps R. Using Quality by Design (QbD) for Process Optimization of a Novel oral solid dosage form. Metrics, 2012; 1-7.

Hassan N, Khar RK, Ali M, Ali J. Development and Evaluation of buccal bioadhesive tablet of an anti-emetic agent Ondansetron. AAPS PharmSciTech, 2009; 10 (4): 1085-1092.

Lewis GA, Mathieu D, Phan-Tan-Luu R. Pharmaceutical Experimental Design, Marcel Dekker, New York 1999.

Mario J. Influence of hydroxylpropyl cyclodextrin complexation on piroxicam release from buccoadhesive tablets. Eur J Pharm Sci. 2004; 2: 251-260.

Mennini N, Furlanetto S, Cirri M, Mura P. Quality by design approach for developing chitosan-Ca-alginate microspheres for colon delivery of celecoxib hydroxypropyl-<beta>-cyclodextrin-PVP complex, Eur J Pharm Biopharm. 2012; 8: 67-75.

Narmada GY, Mohini K, Prakash Rao B, Gowrinth DXP, Kumar KS. Formulation and evaluation and optimization of fast dissolving tablets containing Amlodipine Besylate by sublimation method. ARS Pharmaceutica. 2009; 50: 129-144.

Patel AA, Patel K, Patel M, Patel N. Formulation and *in vitro* evaluation of mucoadhesive buccal tablet of Venlafaxine hydrochloride. Ame J Pharm Tech Res. 2012; 2(3): 1081-1100.

Rath S, Gupta BJ, Bala NN, Dhal HC. Formulation and optimization of immediate release Telmisartan tablets using full factorial design. Int J Appl Pharm. 2011; 3(3): 20-24.

Rathore AS. Roadmap for implementation of quality by design (QbD) for biotechnology products, Trends Biotech. 2009; 27 (9): 546-553.

Saleem MA, Pange SS, Umair SA, Singh VK. Formulation and evaluation of mucoadhesive buccal tablets of Sumatriptan succinate. Int J Novel Drug Deliv Tech. 2011; 105-113.

Shivanand K, Raju SA, Nizamddin S, Jayakar B. In vivo bioavailability studies of Sumatriptan succinate buccal tablets. DARU, 2011; 19(3): 224-230.

Singh S, Savaliya D, Shah S. Design, development and evaluation of buccal tablets of Sumatriptan succinate. Asian Pac J Trop Biomed, 2012; 1-8.

Sudhakar Y, Ketousetuo K, Bandyopadhyay AK. Buccal bioadhesive drug delivery- A promising option for orally less efficient drugs. J Control Rel. 2006; (114): 15-40.

Verma S, Lan Y, Gokhale R, Burgess DJ. Quality by design approach to understand the process of nanosuspension preparation, Int J Pharm. 2009; 377:185–198.

Wu H, Tawakkul M, White M, Khan MA. Quality-by-Design (QbD): An integrated multivariate approach for the component quantification in powder blends, Int. J. Pharm. 2009; 372: 39–48.

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