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DESIGN, OPTIMIZATION AND EVALUATION OF BUCCAL DRUG DELIVERY SYSTEM OF PROPRANOLOL FOR HYPERTENSION TREATMENT

Pankaj Sharma [*1] and Mukul Tailang [2]

Department of Pharmaceutics [1], Shri Ram College of Pharmacy, Morena - 476444, Madhya Pradesh, India. Department of Pharmacognosy [2], S.O.S. Pharmaceutical Science, Jiwaji University, Gwalior - 474011, Madhya Pradesh, India.

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Correspondence to Author:
Mr. Pankaj Sharma

Assistant Professor,
Department of Pharmaceutics,
Shri Ram College of Pharmacy,
Morena - 476444, Madhya Pradesh,
India.

E-mail:pankajsharma223@gmail.com

ABSTRACT: The main objectives of the present study were to design, optimization and evaluation of buccal drug delivery system of propranolol for hypertension treatment. Propranolol is non-selective β-adrenergic blockers. It shows first-pass metabolism so its bioavailability is decreased and its absolute bioavailability is only about 26%. The buccal tablets of propranolol formulated, by using different mucoadhesive polymers such as sodium crosscarmilose sodium, PVP K30, and HPMC K15M. F8 was containing 18.18% PVPK30, 10.90% HPMC K15M showed desired drug release within 6 h to above batches. The dissolution profile of formulated batch F1 to F8 at the end of 6 h was found in the range of 83.03 to 94.69% in phosphate buffer pH 6.8. From the results, it was found that formulation F8 was shown most similar dissolution profile because the similarity value was found to be above 90%. The swelling index was found higher in formulation F9 80.15% swelling observed because of higher concentration of PVP K30 and HPMC K15M. The results indicate that out of two bioadhesive polymers PVP k 30 along with HPMC K15M in different concentration with fraction batches code F1 to F9 having PVP K30 have shown more bioadhesive strength than HPMC K15M. Statistical optimization of propranolol tablet was done by design expert software, version 8.0.7.1. No significant changes were observed in the physical appearance, mucoadhesive strength and drug content of the formulations kept both at room temperature (RT) and accelerated conditions (45 °C, 75% RH) for 1 month.

INTRODUCTION: Over the last few decades' research, researchers are trying to deliver drugs *via* transmucosal and transdermal routes as an alternative to parenteral rout [1]. By these formulations, drugs can be applied onto the body with low vascularisation when targeting local administration, or with high vascularisation, when systemic delivery is required; in against to the oral formulations, whose pharmacological effects depends upon the absorption and systemic distribution [2].

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The main beneficiary effect of buccal drug delivery systems is increased bioavailability, easy release pattern, drug targeting, increased residence time in the buccal mucosa, and decreased prime adverse effects [3]. The oral mucosa provides unique environment for delivery of drugs.

Drugs which show the effect of first-pass metabolism and sensitive to acid hydrolysis in stomach are good candidate for oral mucosal delivery because high blood supply in that region. This type of drug delivery system includes delivery of drugs through buccal mucosa to systemic circulation [4, 5]. For the development of these type buccal drug delivery formulations, mucoadhesion of the formulation is a prime element. The mucin layer of biological membrane act as support system for binding of materials, this phenomenon is known

as "mucoadhesion" [6]. For targeting systemic circulation *via* oral mucosa, many types' mucoadhesive polymers are utilized in buccal drug delivery formulations [7]. There is very challenging task for buccal tablets to maintain their shape, solidarity, and attitude during the application. Precise dosing control and visually seen during the treatment can be achieved by buccal tablets. Direct compression method for buccal tablets formulation can be used because it is very easy method, economically good and less time consuming [8].

Propranolol is generally used to treat hypertension and migraine. It is non-selective β-adrenergic blockers. It shows first-pass metabolism so its bioavailability is decreased and its absolute bioavailability is only about 26%. Buccal tablets of propranolol may be best option to treat hypertension as well as migraine [9]. For designing traditional formulation, there are single variable changes required every time and perpetuate other factors unchanged. Since this consideration is time taking and needs to conduct a large number of experiments to determine optimum conditions. So we can use statistical optimization techniques to define key parameters with minimum number of trials. This whole process is known as design of experiments (DoEs) [10]. Response surface methodology (RSM) is widely used for the designing and optimization of formulations. This statistical method shows the interaction between predefined factors and their effects on required responses that are very important to final formulation [11, 12]. Buccal drug delivery technology has great importance but quite complex process, the present study aims to design, evaluate and optimize, from a sequential review with meta-analysis, the evaluation of physicochemical property and advancement for this technology applied to the surface of the buccal mucosa.

MATERIALS AND METHODS:

Materials: Propranolol as a gift sample was provided by Cadila healthcare Ltd., Ahmadabad, Gujarat. All other polymers and chemicals were analytical grade and provided by Shri Ram College of pharmacy, Banmore, Morena.

Methods:

Compatibility Analysis (FTIR): The Fourier transform infrared spectroscopy was performed to check compatibility between drug and additives. In this method we used a moisture-free powder sample of 1:1 ratio of Propranolol with excipients and spectra was recorded on IR spectrophotometer by the using of potassium bromide (KBr) pellet method [13].

Calibration Curve Preparation for Propranolol: From the stock solution aliquot of 0.4, 0.8, 1.2, 1.6 and 2.0 ml was taken and diluted up to 10 ml with phosphate buffer ph 6.8 to get 4, 8, 12, 16 and 20 µg/ml concentration solution. The absorbance of each solution was measured at maximum wavelength (λ_{max}) of 289 nm against of phosphate buffer ph 6.8. The λ_{max} of propranolol was performed in triplicate and mean absorbance was considered.

Dose Calculation: The pharmacokinetic parameters of propranolol were utilized for the calculation of theoretical drug release profile for the developed dosage form. The loading dose and maintenance dose of propranolol were calculated using formula:

$$\text{Loading dose (X0L)} = (\text{Css} \times \text{Vd}) / (\text{S} \times \text{F})$$

$$\text{Maintenance dose (X0M)} = (\text{Css} \times \text{CL}) / \text{F}$$

Where Css is steady-state plasma concentration, Vd is volume of distribution, CL is the clearance, S is a salt fraction and F is fraction of bioavailability.

From the above equation:-

Loading dose and maintenance dose was found 22.7 mg and 7.7 mg respectively. The amount of drug should be released within one hour equivalent to X0L and X0M. The maintenance dose is depending on the elimination rate while the loading dose depends on Css.

Using the value of X0L and X0M for propranolol calculated dissolution profile at each time interval to predict the similarity in drug release profile from each developed formulation with theoretically developed release profile.

Development and Optimization of Buccal Formulations by using Experimental Design:

Formulation of Buccal Tablets of Propranolol by combining different Polymer Concentration: Direct compression method was used for the

preparation of buccal tablets. PVP K30, HPMC K15M were used as a mucoadhesive polymer. 60# sieve was used for sieving all the ingredients individually. Drug, polymers and other additives were mixed uniformly with gentle trituration using mortar and pestle to get a uniform mixture.

Finally, magnesium stearate, talc was added and mixed well to provide lubricant effect. The tablets were compressed using 6 mm punch on the eight-station rotary punching machine. And total tablet weight was 110 mg.

Optimization of Buccal Tablets Formulations by using Experimental Design: It is an essential step to develop an acceptable pharmaceutical formulation in shortest possible time using minimum number of man-power and raw materials. Although, it is difficult to develop an ideal formulation using these classical techniques since the joint effects of independent variable are not considered. A statistical model was used to evaluate, the response of polynomial and interactive.

The number experiments required for designing these studies, which is dependent on the number of independent variables selected. The response (Y_1) is measured for each trial.

$$Y= b_0 + b_1X_1+b_2 X_2+b_{12} X_1 X_2+b_{11} X_1^2+b_{22} X_2^2$$

Where Y is dependent variables, b_0 is the arithmetic mean response of the nine runs, b_1 is the estimated coefficient for the factor X_1, and b_2 is the estimated coefficient for the factor X_2.

The main effect (X_1 and X_2) represents the average result of changing one factor at a time from its low to high value.

A 3^2 randomized full factorial design method was used in this study. In present design- two factors are selected for evaluation, each at three levels, and experimental work was carried out at all nine possible combinations. The design layout detail and coded value of independent variables are shown below in **Table 1**. The selected factors were based on preliminary study. The amount of PVP K30 (X_1) and the amount of HPMC K 15M (X_2) were studied as an independent variable.

ANOVA provision in the Microsoft software was used for the establishment of statistical polynomials validity. Level of significance was considered at $p< 0.05$. For the comparison of several statistical parameters, best fitting mathematical model was selected- including the coefficient of variation (CV), the multiple correlation coefficient (R^2), the adjusted multiple correlation coefficient (adjusted R^2), and the predicted residual error sum of square (PRESS), provided by the software.

PRESS indicates how well the model fits the data, and for the chosen model, it should be small relative to the other models under consideration. The significant approach was used to produce the optimum setting for the formulation.

TABLE 1: INDEPENDENT VARIABLE CODING

Formulation code	Independent variable X_1	Independent variable X_2
F1	-1	-1
F2	-1	0
F3	-1	+1
F4	0	- 1
F5	0	0
F6	0	+1
F7	+1	-1
F8	+1	0
F9	+1	+1

TABLE 2: TWO INDEPENDENT VARIABLE AND THREE LEVELS

Independent variable	Low (-1)	Medium (0)	High (+1)
PVP K30	4	12	20
HPMC K15M	4	12	20

TABLE 3: FORMULATION OF 3^2 FACTORIAL DESIGNS

Ingredients (in mg)	Factorial design batch								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Propranolol	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25
PVP K30	4	4	4	12	12	12	20	20	20
HPMC K15M	4	12	20	4	12	20	4	12	20
Mannitol	92.75	84.75	76.75	84.75	76.75	68.75	76.75	68.75	60.75
Mg. Stearate	1	1	1	1	1	1	1	1	1
Talc	2	2	2	2	2	2	2	2	2

Evaluation Parameters:

Preformulation Study:

Physical Appearance Study: It includes test the state, colour, odour, taste and melting point of propranolol drug and compare with pharmacopeia limit of pure propranolol drug.

Micrometric Evaluation:

Angle of Repose: The angle of repose of powder blend was determined by the funnel method. The accurate weight powder blend was taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on the surfaces. The diameter of the powder cone was measured and angle of repose was calculated using following equation.

$$\text{Tan } \theta = h/r$$

Where h and r are the height and radius of the powder cone respectively.

Bulk Density: The granules fill in measuring cylinder called a bulk volume of powder and measure mass. Bulk density is ratio of mass of powder of bulk volume of powder. It is measure used to describe a packing of powder. The equation for determine bulk density is

$$\rho b = m/vb$$

Where, ρb = Bulk density (gm/ml), m = Mass of powder (gm) and vb = Volume of powder (ml)

Tapped Density: It is the ratio of total mass of powder to the tapped volume of powder. Tapped density was determined by the tapped density tester by taking the granules in a measuring cylinder and measure the volume of tapped after 100 tapings and weight of the mass. The equation for determining tapped density is

$$\rho t = m/vt$$

Where, ρt = Tapped density (gm/ml), m = Mass of powder (gm), vt = Tapped volume

Compressibility Index: The compressibility index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the ρb and ρt of a powder and the rate at which it packed down. The formula for Carr's index is as below:

$$\text{Carr's compressibility index (\%)} = (\rho t - \rho b) / \rho t \times 100$$

Where, ρb = Bulk density, ρt = Tapped density

Hausner's Ratio: It is the ratio of bulk volume to tapped volume or tapped density to bulk density. It is a measure used to describe the compressibility of granules.

$$\text{Hausner's ratio} = \rho t / \rho b$$

Where, ρb = Bulk density, ρt = Tapped density

Post-Compressional Evaluation Parameters:

Hardness Test: The tablet hardness was determined by using Pfizer and Monsanto Hardness tester. It is expressed in kg/cm^3. Three tablets are randomly picked as a sample for each formulation and the average and standard deviation were calculated.

Thickness: Vernier calipers were used for determination of the thickness of each formulation. From each formulation, three tablets were taken as sample and average values were calculated.

Friability: Initially twenty tablets were weighed and placed in the Roche friabilator. The tablets were explored for rolling and allowed for shocks, resulting from free falls within the apparatus. After 100 revolutions the tablets were de-dusted and weighted again. The friability was determined as the percentages loss in weight of the tablets

$$\text{\% Friability} = W_{initial} - W_{final} / W_{initial} \times 100$$

% Friability of tablets less than 1 % is considered as pass [14].

Weight Variation: This test was performed as per the procedure of IP/BP. Twenty tablets were taken randomly as sample and weighed individually each tablet. The data of individual tablets weight were analyzed for sample mean and percent deviation.

TABLE 4: WEIGHT VARIATION ACCORDING TO IP/BP

Average weight (mg)	Maximum % Deviation
<80	10%
80-250	7.5%
>250	5%

Assay: Three tablets were randomly selected from each formulation and crushed to a fine powder in a mortar with pestle. Weigh accurately equivalent to

6.25 mg of propranolol from fine powder then transferred in 100 ml volumetric flask, 100 ml of phosphate buffer pH 6.8 was added to dissolve and sonicated for few minutes. After sonication, insoluble matter was allowed to settle. The sonication was diluted to get concentration about 20 µg/ml propranolol in phosphate buffer pH 6.8. The resulting solution was filtered through Whatman filter paper.

The absorbance of final solution was measured in UV spectrophotometer at 289 nm. This procedure was repeated three times to get accuracy in the result.

***In-vitro* Dissolution Study:** United States Pharmacopoeia type II apparatus was used for *in-vitro* dissolution study of the tablet for each formulation. The drug release study of tablets was performed by the rotating paddle method. Dissolution medium 900 ml of Phosphate buffer (pH 6.8) was placed in dissolution vessel. The release was evaluated at 37 ºC ± 0.5 ºC and rotational speed of paddle set on 50 rpm. Tablets were placed in each dissolution vessel. The 5 ml samples were withdrawn each time and time interval was one hour for 6 h. The withdrawn samples were filtered through Whatman filter paper and checked for drug content by UV Spectrophotometer.

The absorbance for each sample was recorded at 289 nm and the concentration of drug present was calculated using the calibration curve method for Propranolol. Then, the cumulative percentage amount of drug released at each time interval was calculated using the formula,

$$\text{Cumulative amount of drug release} = C \times DF \times DM$$

Where, C = Concentration of drug at each time interval (µg/ml), DF = Dilution factor is 1, DM = Dissolution medium (900 ml)

Drug Release Kinetics: Different type's models were used for the determination of kinetics of drug release. For the determination of mechanism of drug release kinetics of mucoadhesive dosage form, the obtained data were fitted into zero-order, first-order, Higuchi, Korsmeyer-Peppas release model, and Hixson-Crowell equation [15].

Swelling Index: The phosphate buffer 6.8 pH was used to evaluate the swelling index of the buccal tablets. The initial weight of buccal tablet was determining (W1). The (25 ml) in a Petri-dish kept in an incubator at 37 ± 1 ºC, and tablet was checked at different time interval (0, 1, 2, 3, 4, 5, 6 h), and excess water was removed using filter paper without pressing and reweighted (W2). The swelling index was calculated using the formula,

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

Where W_1 is initial weight of tablet, W_2 is final weight of tablet

Mucoadhesive Strength: The modified balance method was used for determination of *ex-vivo* mucoadhesive strength. Newly harvested sheep buccal mucosa was collected from a local butcher house and used within 2 h of slaughter. Then underlying fat and loose tissues were removed for separation of mucosal membrane. First of all, membrane was cleaned with distilled water and then with phosphate buffer pH 6.8 at 37 ºC [16].

A piece of buccal mucosa was tied to the glass, which was fixed on the plank, and the plank was assembled with little crown block placed in a right side balance pan. After wetting the sheep mucosa with distilled water, the tablet was kept in contact with the mucosa by applying the force for minute. After initial touch, the tablet was fringed by a thread which fastened a light plastic beaker through the crown block. Then, water was added into the beaker at a constant rate until the tablet and sheep mucosa were pulled apart by the gravity of water. The beaker filled with water was weighed and the minimum detachment force was calculated. The detachment force shows the mucoadhesive power of the buccal tablet in gm [17].

Stability Study: The aim of stability study is required for the collection of data on the quality of formulation or drug product which alters with time under the effect of different environmental factors such as temperature, humidity, and light. Formulations were selected for stability on the basis of the *in-vitro* drug release profile. The formulation was subjected to accelerated stability studies *i.e.* room temperature, 40 ºC / 75% RH in alu/alu foil for 1 month in thermostated ovens. The sample (n=3) were tested for 0-30 days. Tablets were evaluated for the different physicochemical parameters *i.e. in-vitro* dissolution study.

RESULTS AND DISCUSSION:

Compatibility Analysis (FTIR):

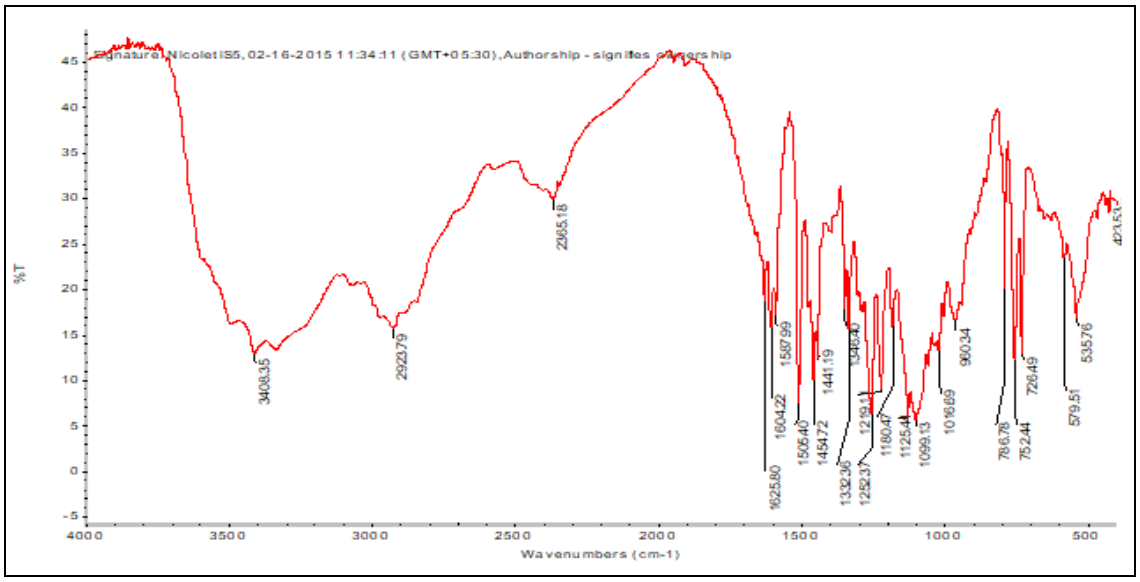

FIG. 1: COMPARISONS OF IR SPECTRA OF DRUG AND PHYSICAL MIXTURE

From **Fig. 1** it was observed that there were no changes in main peaks so the formulation mixture of drug and polymers, which show there is no chemical interaction between drug and polymer.

TABLE 5: IR SPECTRA INTERPRETATION FOR DRUG AND PHYSICAL MIXTURE

S. no.	Functional group	Peak for pure drug cm^{-1}	Peak for mixture cm^{-1}
1	-O-CH_3	2397.90	2365.18
2	-O-	1180.58	1180.47
3	2˚ Nitrogen	1625.47	1625.80
4	OH	1587.79	1587.99
5	Aromatic	726.19	726.49

Calibration Curve of Propranolol in Phosphate buffer 6.8 pH:

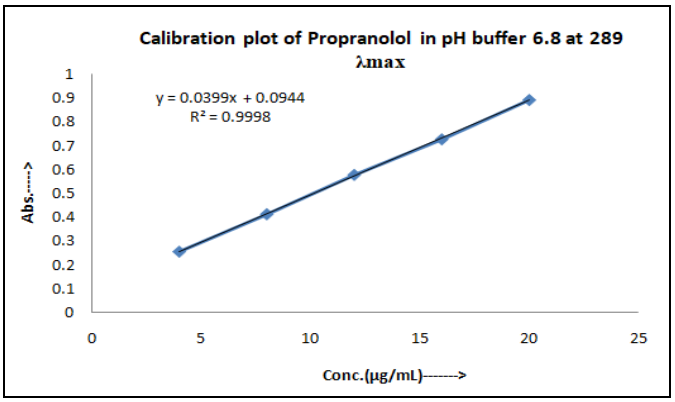

FIG. 2: CALIBRATION CURVE OF PROPRANOLOL IN PHOSPHATE BUFFER 6.8 pH

The linearity range of Propranolol was found between 4-20 µg/ml in phosphate buffer (pH 6.8) solution. Absorbance values of Propranolol in Phosphate buffer solution at 236 nm.

Dose Calculation: Theoretical dissolution profile was used for determination of propranolol dose, using the loading dose and maintenance dose is shown in **Table 6**.

TABLE 6: THEORETICAL DISSOLUTION PROFILE OF PROPRANOLOL

Time (h)	Amount of drug release (in mg)	% Drug release
1	1.418	22.7
1.5	1.899	30.4
2	2.38	38.1
2.5	2.861	45.8
3	3.342	53.5
3.5	3.823	64.2
4	4.304	68.9
4.5	4.786	76.9
5	5.266	84.3
5.5	5.747	92
6	6.228	99.7

Evaluation of Pre-Compressional Parameters of Tablets: The micrometric property of the polymer blend of all the formulation F1 to F9 were checked, wherein the angle of repose was found to be around 26 to 28º, which show good flowing property of the blend. The loose bulk density and the tapped bulk density were found to be between 0.61 to 0.70 gm/ml. The Carr's index was observed to be 15 to 20 % and Hausner's ratio was found to be between 1.19-1.36.

TABLE 7: PRE-COMPRESSION PARAMETER OF FACTORIAL BATCH

Batch	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's ratio	Angle of repose (ɵ)
F1	0.58 ± 0.029	0.70 ± 0.28	16.92 ± 1.18	1.21 ± 0.28	26.61 ± 0.56
F2	0.56 ± 0.032	0.69 ± 0.031	17.52 ± 1.11	1.29 ± 0.26	27.31 ± 0.31
F3	0.55 ± 0.030	0.65 ± 0.029	16.52 ± 1.09	1.28 ± 0.19	28.18 ± 0.29
F4	0.53 ± 0.033	0.65 ± 0.030	17.39 ± 1.12	1.32 ± 0.34	26.32 ± 0.18
F5	0.51 ± 0.038	0.64 ± 0.032	18.21 ± 1.14	1.34 ± 0.37	27.89 ± 0.16
F6	0.55 ± 0.034	0.68 ± 0.029	19.32 ± 1.19	1.36 ± 0.29	28.28 ± 0.20
F7	0.50 ± 0.035	0.61 ± 0.028	17.52 ± 1.16	1.20 ± 0.27	26.08 ± 0.23
F8	0.58 ± 0.036	0.69 ± 0.030	17.38 ± 1.17	1.19 ± 0.21	26.12 ± 0.22
F9	0.56 ± 0.029	0.69 ± 0.028	18.15 ± 1.10	1.28 ± 0.22	27.32 ± 0.19

Evaluation of Post Compressional Parameters of Tablets:

TABLE 8: POST COMPRESSION PARAMETER OF FACTORIAL BATCH

Batch no.	Weight variation (mg)	Diameter (mm)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Assay (%)
F1	Pass	6	3.0 ± 0.32	3.2 ± 0.11	0.22 ± 0.02	96.65 ± 1.18
F2	Pass	6	2.8 ± 0.46	3.3 ± 0.16	0.24 ± 0.06	94.48 ± 1.39
F3	Pass	6	3.2 ± 0.33	3.2 ± 0.13	0.26 ± 0.04	95.55 ± 1.35
F4	Pass	6	3.1 ± 0.37	3.4 ± 0.15	0.32 ± 0.09	101.21 ± 1.60
F5	Pass	6	3.1 ± 0.44	3.5 ± 0.18	0.28 ± 0.10	96.37 ± 1.55
F6	Pass	6	3.1 ± 0.29	3.4 ± 0.11	0.23 ± 0.08	104.89 ± 1.21
F7	Pass	6	3.1 ± 0.39	3.3 ± 0.17	0.24 ± 0.06	98.36 ± 1.78
F8	Pass	6	3.2 ± 0.41	3.3 ± 0.14	0.28 ± 0.07	97.37 ± 1.56
F9	Pass	6	3.0 ± 0.31	3.2 ± 0.11	0.25 ± 0.03	98.21 ± 1.43

All values are expressed as mean ± standard deviation, n=3 for thickness and hardness, n=20 for Wt. Variation, n=10 for diameter and % assay, n=5 for % friability.

The drug contain was in the range of 94.48 to 104.89%, which passes the official requirement. Weight variation data of the prepared tablets indicates no significant difference in the weight of individual tablets from the standard deviation. The hardness of the prepared tablets were observed within the range of 3 to 3.5 kg/cm^2. Thicknesses of all tablets were found in the range of the mm.

***In-vitro* Drug Dissolution Study of Tablets:** Dissolution profile of formulated batch F1 to F8 at the end of 6 h was found in the range of 83.03 to 94.69% in phosphate buffer pH 6.8. The cumulative drug release is compared with the theoretical dissolution profile. Calculate the similarity value (F2) for each formulation.

From the result, it was found that formulation F8 was shown most similar dissolution profile because the similarity value was found to be above 90%.

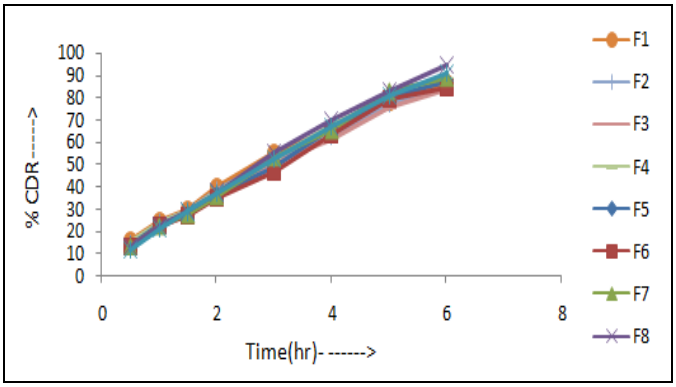

FIG. 3: DISSOLUTION PROFILE OF FORMULATED BATCH F1 TO F8

TABLE 9: *IN-VITRO* DRUG RELEASE STUDY OF FACTORIAL BATCH

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	15.74	14.21	12.89	14.89	14.12	13.22	12.99	13.04	11.45
1	24.75	23.78	21.85	23.68	23.2	22.91	22.08	22.48	21.13
1.5	29.45	28.71	27.22	28.58	27.85	26.71	27.31	28.83	28.61
2.0	39.81	38.23	37.68	37.42	36.52	35.21	35.45	37.45	36.78
3.0	54.92	52.45	51.23	52.3	48.89	46.78	52.85	55.45	52.12
4.0	65.78	62.98	61.01	67.89	65.91	63.48	64.93	69.78	66.89
5.0	78.04	77.12	75.45	80.12	79.89	79.45	82.45	83.32	81.02
6.0	86.72	84.66	83.84	88.03	86.98	84.32	88.39	94.69	91.03
Similarity factor (F2)	64.55	61.08	58.61	68.31	65.13	60.19	68.95	94.44	86.96

Drug Release Kinetic Studies for Buccal Tablet of Propranolol:

TABLE 10: DRUG RELEASE KINETIC STUDY

Code	Zero-order		First-order		Hixon Crowell		Korsmeyer Peppas			Higuchi plot	
	R^2	K_0	R^2	K_1	R^2	K_H	R^2	n	K_k	R^2	K_p
F1	0.987	13.09	0.925	0.146	0.993	-	0.992	-	0.705	0.987	41.54
F2	0.991	12.95	0.919	0.151	0.995	-	0.995	-	0.731	0.987	41.05
F3	0.991	12.98	0.910	0.157	0.993	-	0.996	-	0.767	0.987	40.88
F4	0.992	13.75	0.941	0.154	0.998	-	0.991	-	0.739	0.979	43.50
F5	0.993	13.68	0.943	0.156	0.997	-	0.990	-	0.748	0.972	42.92
F6	0.990	13.43	0.941	0.159	0.995	-	0.988	-	0.760	0.965	42.38
F7	0.991	14.25	0.936	0.166	0.997	-	0.993	--	0.798	0.974	45.17
F8	0.995	15.08	0.923	0.168	0.997	-	0.996	-	0.813	0.983	46.93
F9	0.995	14.61	0.906	0.173	0.998	-	0.999	-	0.846	0.987	45.72

Swelling Index (SI) Study of Tablets:

TABLE 11: SWELLING STUDY OF FACTORIAL DESIGN BATCH

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	22.38	25.59	27.89	27.65	29.54	31.97	34.74	35.32	39.10
1	31.21	32.15	33.21	32.34	35.48	36.48	41.28	45.78	47.06
2	34.12	36.48	38.45	37.64	4.059	44.58	48.79	49.78	53.47
3	38.29	41.58	43.25	45.78	47.89	49.75	54.79	55.49	61.07
4	44.32	48.75	51.74	49.85	52.49	55.79	58.79	65.71	69.04
5	52.75	54.24	57.14	55.45	58.92	60.84	66.04	68.98	75.49
6	55.48	56.78	60.45	58.48	61.48	64.78	69.16	73.45	80.15

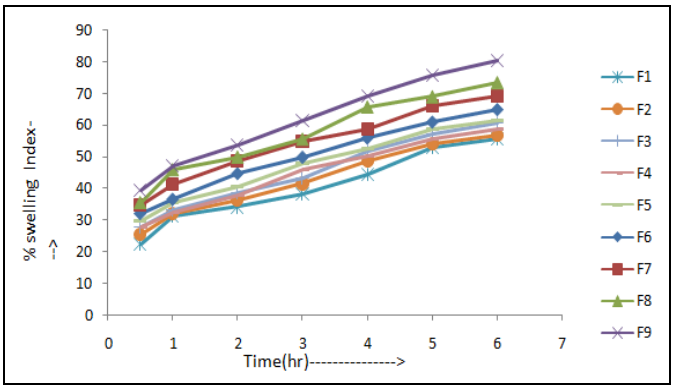

FIG. 4: SWELLING STUDY OF FACTORIAL DESIGN BATCH F1 TO F9

The swelling index was also measured for F1 to F9 as shown in **Table 11**. From the table it was found that as the concentration of both polymer increase, the value of swelling index increase. The swelling index was found higher in formulation F9 80.15% swelling observed because of higher concentration of PVP K30 and HPMC K15M.

Mucoadhesive Study (MS) of Tablets: The results indicate that out of two bioadhesive polymers PVP k 30 along with HPMC K15M in different concentration with fraction batches code F1 to F9 having PVP K30 have shown more bioadhesive strength than HPMC K15M. It was observed that increase in the concentration of PVP K30 increase mucoadhesive strength. The HPMC K15M also acts as bioadhesive strength. Increase of ratio of both polymers was found to increase mucoadhesive strength shown in **Table 12**.

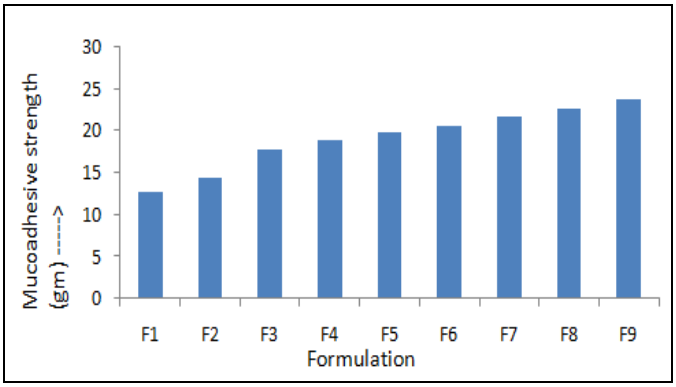

FIG. 5: MUCOADHESIVE STUDY OF FACTORIAL DESIGN BATCH F1-F9

TABLE 12: MUCOADHESIVE STUDY OF FACTORIAL DESIGN BATCH

Formulation	Mucoadhesive strength (gm)
F1	12.67
F2	14.52
F3	17.84
F4	18.89
F5	19.89
F6	20.70
F7	21.69
F8	22.78
F9	23.82

Statistical Optimization of Formulation: The results of all selected response variables for the selected independent variable, was statistically optimized as follow; the value of each response variable were summarized in **Table 13,** and it was statistically applied for multiple regression analysis using the best fitted quadratic model in design expert software version 8.0.7.1.

TABLE 13: THE RESULTS OF EACH RESPONSE VARIABLES AS PER 3^2 FULL FACTORIAL DESIGNS

Code	Code X_1	Code X_2	Actual X_1 (mg)	Actual X_2 (mg)	Mucoadhesive strength (MS) (gm)	*In-vitro* dissolution after 4h (T4) (%)
F1	-1	-1	4	4	12.67	65.78
F2	-1	0	4	12	14.52	62.98
F3	-1	+1	4	20	17.84	61.01
F4	0	-1	12	4	18.89	67.89
F5	0	0	12	12	19.89	65.91
F6	0	+1	12	20	20.70	63.48
F7	+1	-1	20	4	21.69	64.93
F8	+1	0	20	12	22.78	69.78
F9	+1	+1	20	20	23.82	66.89

Design Summary for Statistical Optimization: Statistical optimization of propranolol tablet was done by design expert software, version 8.0.7.1. The study type was response surface, 9 runs were applied to the design type central.

TABLE 14: DESIGN SUMMARY OF RESPONSE VARIABLE BY BEST FITTED QUADRATIC MODEL

Response	Name	Units	Analysis	Min	Max	Mean	SD	Model
Y_1	MS	Gm	polynomial	12.64	23.74	18.19	5.55	Quadratic
Y_2	T_4	%	polynomial	61.08	68.68	64.88	3.8	Quadratic
Y_3	SI	hr	polynomial	55.48	80.15	67.81	12.33	Quadratic

It was found linear model is best fitted to determine the effect of independent variable on response variables. There was considerable difference observed in minimum and maximum values of each response variables with respect to the independent variables by applying two-sided ANOVA with 94% confidants.

TABLE 15: % CONFIDENCE LEVEL OF EACH REGIME VARIABLE

Response	Name	Units	Obs.	analysis	p-values	Predicted value
Y l	MS	gm	9	Polynomial	0.0317	19.20
Y2	T4	%	9	Polynomial	0.0419	13.58
Y3	SI	hr	9	Polynomial	0.0010	00.68

Analysis of Variance (ANOVA) for Response Variables: Response 1- Mucoadhesive Strength: From **Table 16** it was revealed that F-value 45.99 implies the model is significant. There is only 0.49% chance that a "model F-value" this large could occur due to noise. The P-value is less than 0.0500 indicate the model is significant. Values greater than 0.1000 indicate the model terms are not significant. The value of R^2 was also suggested that the values were fit to the selected models.

TABLE 16: ANOVA RESPONSE FOR MUCOADHESIVE STRENGTH

Source	Sum of squares	DF	Mean square	F	P	R^2	Model
Regression	108.15	5	21.53				
Residual	1.41	3	0.47	45.99	0.049	0.9871	Significant
Total	109.57	8	22.10				
Regression coefficient equation							
$MS=19.69+3.88X1+1.52X_2+0.76X1X_2+0.94X1+0.20X2$							

Response 2- T4: From **Table 17**, it was found that the model F-value of 10.27 implies the model is significant. There is only a 4.19% chance that "Model F-value" this large could occur due to noise. A p-value less than 0.0500 indicates model terms are significant. Values greater than 0.1000 indicate model arms are not significant. The value of R^2 was also suggested that values were fit to the selected models.

TABLE 17: ANALYSIS OF VARIANCE FOR RESPONSE (T4)

Source	Sum of squares	DF	Mean square	F Value	P value	R^2	Model
Regression	22.48	5	4.50				
Residual	1.31	3	0.44	10.27	0.419	0.9448	Significant
Total	23.79	8	4.94				
T4=13.58+1.70X1+0.73X2+0.48X1X2+0.72X1+0.020X2							

The regression coefficient was found from the ANOVA study it is shown in **Table 17**. From the results, it was found that the positive effect of X1 and the positive effect of X2 coefficient at low level on the response variable but at high-level X1 coefficient opposite results were found. The X1 coefficient is more positive than the X2; coefficient was positive that concentration of HPMC Kl5M was created much impact on drug release when it compared with the concentration of PVP K30.

Response 3- Swelling Index: From **Table 18**, it is leveled that F-value of 138.40 implies the model is significant. There is only 0.10% chance that a Model F-value, this large could occur due to noise. The p-value is less than 0.0500 indicate the model is significant. Values greater than 0.1000 indicate the model terms are not significant, the value of R^2 was also suggested that the values were fit to the selected models.

TABLE 18: ANALYSIS VARIANCE RESPONSE FOR SWELLING INDEX

Source	Sum of squares	DF	Mean square	F Value	P-Value	R^2	Model
Regression	501 43	5	100 29				
Residual	2.17	3	0.72	138 40	0 0010	0 9957	Significant
Total	503.60	8	101.01				
MS=60.68+7.84X1+3.2IX2+2.26X1X2+4.83X1+1.33X2							

The regression efficient were found by ANOVA. The values of coefficient were found to be significant for the particular response. The coefficient for both variables was found positive at low level and in combination. At high-level X1 variable found opposite effect. Both variables might be affecting SI significantly but the effect of X1 variable was more predominant than X2 variable. The positive values of both indicate that as concentration of polymer increases, swelling index increases. So, it was found that the response value was increased by increasing the level of both variables (X1 and X2)

Stability Study: Stability studies for best formulation were carried out. Physical and chemical stability was determined for a period of 1 month. No significant changes were observed in the physical appearance, mucoadhesive strength and drug content of the formulations kept both at room temperature (RT) and accelerated conditions (45 °C, 75% RH) for 1 month.

TABLE 19: STABILITY DATE FOR THE FINAL FORMULATION F8

Parameter	Initial	After 1 month
MS(gm)	19 & 9	19.80
Assay (%)	98.78	98.25
% Drug Release (12 h)	94.43	93.38

Stability study was performed on the best formulation F8 by storing the samples at RT and 45 °C, RH 75 °C for 1 month. The samples were tested for any changes in physical appearance, drug content and mucoadhesive strength at monthly intervals indicated that there were no significant changes in physical appearance, mucoadhesive strength and drug content of the formulation during the storage.

CONCLUSION: The buccal tablets of propranolol were prepared by direct compression method. It was shown that with developed formulation, the propranolol release rate of the buccal tablet can be controlled by changing the polymer type and concentration. The buccal tablet of propranolol formulated by using different mucoadhesive polymers such as sodium crosscarmilose sodium, PVP K30, and HPMC K15M. F8 was containing 18.18% PVPK30, 10.90% HPMC K15M showed desired drug release within 6 h to above batches.

From this research study, it can be concluded that buccal tablet of propranolol prepared using combination of PVP K30 and HPMC K15M that increased in drug release compared to single mucoadhesive as well as bioadhesive polymer used to prepare buccal tablet.

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