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FORMULATION AND EVALUATION OF MUCOADHESIVE BUCCAL FILMS OF ITRACONAZOLE FOR ORAL CANDIDIASIS

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ABSTRACT

The present investigation was intended to formulate and evaluate of mucoadhesive buccal films of Itraconazole for oral candidiasis for local therapy and improving short residence time at the site of application. Buccal film of Itraconazole was formulated by using solvent casting method. The selection of polymers were done from HPMC K 100M, Chitosan and Glycerine as plastisizer. Lactic acid was used as solvent for filmcasting. 3^2 factorial design was applied using X1 (Chitosan) polymer and X2 (HPMC K100M) at -1 to +1 level, for selection of optimized batch. All the parameters were found satisfactory in Chitosan with HPMC K100M batch (F4) was the most satisfactory batch as compared to other batches. The drug content, mucoadhesive strength, drug release, surface pH of developed formulation were found to be satisfactory and also showing that there were no significant changes in drug content, surface pH and drug release after performing short term stability for 1 month.

KEYWORDS: Itraconazole, Chitosan, HPMC K100M, lactic acid.

INTRODUCTION

Buccal drug delivery is the novel drug delivery systems. The buccal region of the oral cavity is an attractive site for the choice of drug administration. Buccal delivery involves the administration of drug through the buccal mucosal lining of the oral cavity. The drug can be administered via many different routes to produce a systemic Pharmacological effect. It is the localized delivery of drug to tissues of the oral cavity for the treatment of bacterial and fungal infection as well as periodontal disease. This delivery system specifically refers to delivery of

drugs through the buccal mucosa to affect local/systemic effects. The oral cavity is an attractive site for drug delivery due to ease of administration and avoidance of possible degradation in of drugs by G.I tract, local G.I. toxicity and inactivation by hepatic first-pass metabolism. The Buccal route is preferred for that drugs which having poor bioavailability because of high first pass metabolism. Buccal films are highly flexible and more readily tolerated for patient than tablets. Moreover, the buccal films are able to protect the wound surface, thus reducing pain and treating oral diseases more effectively.

Oral mucosal sites

- The oral mucosal cavity, delivery of drugs is classified in three categories.
- **1. Sublingual delivery**: (floor of the mouth to the systemic circulation).
- **2. Buccal delivery**: The administration of drug via the buccal mucosa the lining of the cheek to the systemic circulation.
- **3. Local delivery**: Treatment of oral cavity in ulcers, fungal conditions and periodontal disease.

MATERIAL AND METHOD

Sr. no.	Name of materials	Manufacture
1	Itraconazole	Granules india limited, Visakhapatnam, INDIA
2	Chitosan	Balaji drugs, INDIA
3	HPMC	S.D Fine chemicals Ltd., Mumbai, INDIA
4	Glycerine	S.D Fine chemicals Ltd.,Mumbai, INDIA
5	Poly ethylene glycol 400	Pulse Pharma, Himmatnagar, INDIA
6	Ethanol	Pulse Pharma, Himmatnagar, INDIA
7	Methylene Dichloride	Pulse Pharma, Himmatnagar, INDIA
8	Lactic acid	Ozone international , Mumbai, INDIA

EXPERIMENTAL WORK

Preformulation Study

Characterization of drug (Itraconazole)

Organoleptic Properties: Colour, odour and appearance of Itraconazole was physically evaluated and results recorded.

Melting point Determination: Melting point was determined by Taking small amount of drug in capillary tube closed at the one end and was placed in melting point apparatus and the drug was melt that point melting point was recorded.

Solubility Study*:* Solubility study of drug was performed using different solvents such as

water, pH 6.8, methanol, dimethyl sulfoxide, 0.1 N HCl, and ethanol.

Drug: Excipients Compatibility Study: Compatibility study is one of the important steps in development of delivery system i.e. in Preformulation stage, which helps us to evaluate the stability problems which may be faced during formulation development. Therefore in the present work, a study was carried out using FT-IR spectrophotometer to confirm the absence of any possible chemical interaction between the drug and polymer. The spectrum of physical mixtures was compared with the original spectra to determine any possible molecular interactions between the drug and polymer. FTIR analysis measures the selective absorption of light by the vibration modes of specific chemical bonds in the sample.

Standard Calibration Curve

Preparation of stock solution: Standard stock solutiom was prepared by accurately weighed quantity of 100 mg by using electronic balance. Itraconazole reference standard was transferred into 100 ml volumetric flask and dissolved and diluted up to the mark with methanol to give a stock solution having strength 1000µg/ml. label it stock -1.

Selection of wavelength for analysis of Itraconazole: Accurately measured 1ml of stock I solution was transferred into 10ml volumetric flask and diluted to 10ml to give concentration of 10µg/ml and it was used for initial spectral scan in the UV range of 400- 200nm to detect maximum wavelength and further dilutions for linearity were prepared from the stock solution.

Preparation of serial dilutions subsequently: The serial dilutions from the stock I in the range of 4, 8, 10, 12, 14µg/ml were prepared. i.e., methanol. Same procedure was followed for the preparation of standard curve in pH 6.8 + 0.5% SLS by using appropriate blank solution. The standard calibration curve ranges of 4-14 µg/ml respectively. The absorbance values observed are given in table.

Construction of calibration curve: The absorbance of prepared different concentrations was measured at λmax 262 nm. The absorbance of the prepared solutions was measured at their respective λmax. Standard calibration curves were prepared by plotting absorbance vs. concentration. Linear regression equation (y = mx + c) and coefficient of correlation (R^2) were determined for calibration curves of each drug. Reproducibility of the calibration curves was confirmed by repeating the study for three times. The data obtained was summarized in

table.

Dose Calculation of Itraconazole for Film Preparation

Required amount of drug was calculated for each batch based on the size of petridish in which film will be casted. Based on the petridish size (Diameter) it was calculated as per below.

Diameter of Petridish (D) = 8.0 cm

Radius of Petridish (r) = D/2 = 8.0/2 = 4.0 cm Area of Petridish (A) = $\pi r^2 = 3.14 \times (4.0)^2$ A = 50.24 cm^2.

Formulation of Buccal Film of Itraconazole

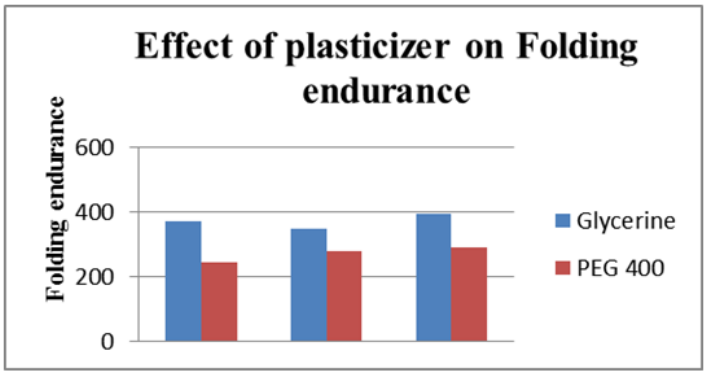
Table 1: Formulation of Itraconazole Buccal Films Trial Batches A1-A12.

INGREDIENTS	A1	A2	A3	A4	A5	A6	A7	A8	A9	A10	A11	A12
DRUG (mg)	502.4	502.4	502.4	502.4	502.4	502.4	502.4	502.4	502.4	502.4	502.4	502.4
HPMC K100M (mg)	400	500	600	-	-	-	400	500	600	-	-	-
HPMC K4M (mg)	-	-	-	400	500	600	-	-	-	400	500	600
Chitosan (mg)	100	200	300	100	200	300	100	200	300	100	200	300
PEG 400 (ml)	3	3	3	3	3	3	-	-	-	-	-	-
Solvent (Ethanol: MDC)	2:1	2:1	2:1	2:1	2:1	2:1	-	-	-	-	-	-
Glycerin (ml)	-	-	-	-	-	-	1.5	1.5	1.5	1.5	1.5	1.5
1% Lactic acid in water (ml)	-	-	-	-	-	-	30	30	30	30	30	30

Evaluation of Trial Batches of Itraconazole Buccal Films

DISCUSSION

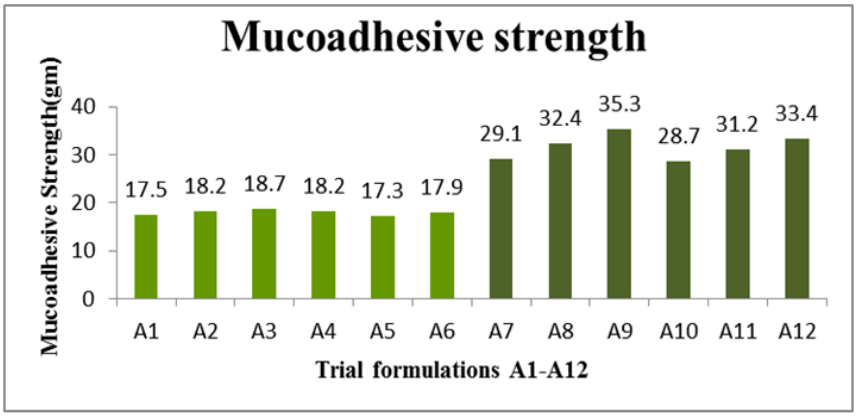
A1-A6 Batches containg (MDC: Ethanol) showed opaque with powdery surface. Were lactic acid containing batches A7-A12 had good appearace with good plascity, flexibility and good film forming capacity.



Discussion: By this graph it can be discussed that glycerin is showing maximum folding indurance than PEG 400.

Swelling (%) was checked in batch A1-A12. The results were observed between 16.12-25.28.

Mucoadhesive strength: was checked in all batches. Batches A7-A12 showed high mucoadshesive property compare to A1-A6 batches. A1-A6 batches containes Ethanol:MDC. Wher A7-A12 batches conatines 1% lactic acid. Solvent type showed effect on mucoadhesion in graph. The films casted from LA showed higher elasticity and mucoadhesion than other batches.



Optimization Of Formulation Using 3^2 Full Factorial Designs. Selection of dependent and independent variables: On the basis of preliminary trial results, 2 independent variables at 3 levels were selected. For optimization 3^2 designs was employed to study the effect of independent variables (i) concentration of Chitosan (X1) and (ii) Concentration of HPMC K100M (X2) on dependent variables, Mucoadhesion time(Y1), Folding endurance(Y2) and % Drug release (Y3) All the batches were prepared according to the experimental design.

Independent variable (concentration)		Dependent variable		
X1	**X2**	**Y1**	**Y2**	**Y3**
Chitosan (polymer)	HPMC K100M (polymer)	Mucoadhesion strength (gm)	Folding endurance	% Drug release

Full Factorial Design		
Batch No.	**X_1 chitosan (mg)**	**X_2 HPMC K 100M (mg)**
1	-1	-1
2	-1	0
3	-1	1
4	0	-1
5	0	0
6	0	1
7	1	-1
8	1	0
9	1	1

Coded value	Actual value	
	X1 CHITOSAN	**X2 HPMC K100M**
-1	150 mg	450 mg
0	200 mg	500 mg
1	250 mg	550 mg

Method of preparation for 3^2 factorial formulations: Buccal films containing Itraconazole were prepared by solvent casting method. However, initial screening with formulations containing single polymers showed unsatisfactory results.

Solvent casting Method

- Polymeric solution of chitosan was prepared by dissolving chitosan in 1% lactic acid solution with constant stirring and clear gels are formed.
- Than HPMC K100M was added to this gel solution and kept a side to remove air bubbles.
- Add drug into this polymer solution under continuous stirring.
- Add plasticizer in to above solution (glycerine).
- Cast the solution into perti dish & Drying at room temperature for 48 hours & cut 1×1 cm^2 and evaluate it.

Table 2: formulation of factorial batches f1-f9.

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug (mg)	502.4	502.4	502.4	502.4	502.4	502.4	502.4	502.4	502.4
Chitosan (mg)	150	150	150	200	200	200	250	250	250
HPMC K100M (mg)	450	500	550	450	500	550	450	500	550
Glycerine (ml)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
1% Lactic acid in water(ml)	30	30	30	30	30	30	30	30	30

EVALUATION OF ITRACONAZOLE BUCCAL FILMS

Weight Variation/Film Weight: The five film of 1x1 cm^2 was cut and weighed on electronic balance for weight variation test. The test was done to check the uniformity of weight and thus check the batch to batch variation.

Thickness: Three films of each formulation were taken and film thickness was measured using Vernier calliper or micrometerscrew at three different places and the mean value was calculated.

Surface pH of films: The films were allowed to place in petridish with 5 ml buffer (pH 6.8) for 10 min to swell. After complete swelling, the surface pH was measured by pH meter. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allow to equilibrate for 1 min. The average 3 values were reported.

Folding endurance: Three films of each formulation of size (1 × 1 cm^2) were cut by using sharp blade. Folding endurance is determined by repeated folding of the film at the same place till the film breaks. The number of times the film is folded without breaking is computed as the folding endurance value.

Swelling ratio (%): After calculating the primary weight of film (W1), the swelling properties of films was determined by placing films in PBS (pH 6.8) at 37 °C. At specific interval time 1 hour of films were removed from PBS solution and excess PBS was removed with filter paper until the films degraded. The swollen films were weighed (W 2) and swelling ratio was calculated using following equation;

Swelling (%) = (w2−w1)/ w1×10……(1)

Drug content: Three Films were cut into 1 × 1 cm^2 pieces and placed in a solution of 100 ml pH 6.8 phosphate buffer. Dissolve the films completely and filtered through whatman filter paper. The solution was checked using UV spectrometry method at 264 nm wavelength. The average of drug contents of three films was taken a final reading.

In vitro drug release study: In vitro drug release from films was determined at 37˚C at 50 rpm using 350 ml of phosphate buffer 6.8 pH + 0.5 % w/v SLS as a dissolution medium (n=3) in USP XXIV type-II apparatus. Samples (5.0 ml) were withdrawn from dissolution medium at predetermined intervals at 10 mins. Equal volume of fresh medium of identical temperature was replaced in dissolution vessel. Samples were, followed suitable dilution and

analyzed spectrophotometer at λmax 264 nm. Amount of dissolved drug was calculated from standard curve drawn between absorbance of known concentrations of drug.

Drug Release Kinetic Study

Several theories/kinetic models describe drug dissolution from immediate and modified release dosage form. In order to analyze the release mechanism, several release models were tested such as.

Zero order release Kinetic

To study the zero order release kinetics the release data was fitted into the following equation.

Qt= Qo+ Kot……..(2)

First order Release Kinetic

To study the first order release kinetics the release rate data are fitted into the following equation.

1n Qt = 1n Qo+K1t……...(3)

Where, k1 = first order release constant

The graph is plotted log % CDR remaining versus time.

Higuchi Release Model

To study the Higuchi release rate data are fitted in the following equation.

Qt = KH vt……(4)

Korsmeyer and Peppas Kinetics

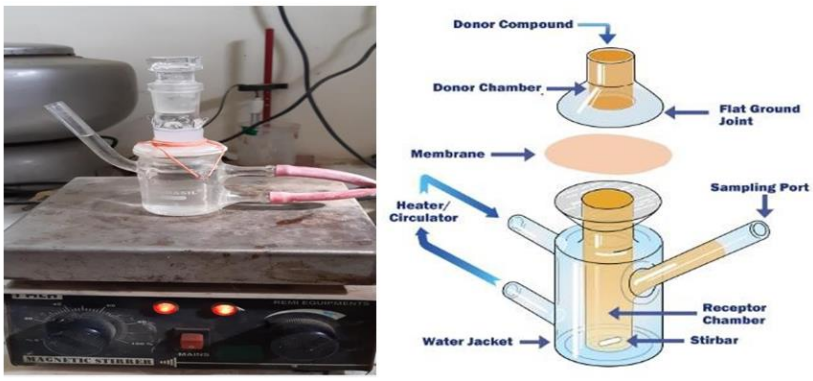
To study Korsmeyer and Peppas release kinetics the release rate data are fitted into following equation.

Qt/Q∞ = KKtn…….(5)

IN VITRO DRUG PERMEATION STUDY

Diffusion cell: Permeation studies was carried out on Franz diffusion cells. The Franz diffusion cell contains the donor and receptor two compartments. The receptor compartment was 5mm and volume of 15 ml. The receptor compartment is attached with collecting tube which allows easy collection of samples while the process of diffusion. The donor and the receptor compartment are hold together with the help of a clap and the diffusion cell was placed on the magnetic stirrer while diffusion studies carried. The total area of the receptor

compartment that is exposed to the Buccal film for diffusion is 1 × 1cm^2.



The in vitro buccal permeation of films was studied through the sheep buccal mucosa using Franz-diffusion cell. The skin placed in the cell had been allowed to rest in contact with PBS for an hour before the formulation (1ml) was added. Freshly obtained buccal mucosa was mounted between the donor and receptor compartments so that the smooth surface of the mucosa faced the donor compartment. The receiver compartment of the diffusion cell was filled with 15.0 ml of PBS pH 6.8 and the setup was placed over a magnetic stirrer with maintained temperature at 37 ^{0}C. Sample of 1 ml were withdrawn at predetermined time of intervals from the receptor compartment and buffer was immediately replaced to maintain sink condition. The amount of Itraconazole in the diffusion was estimated by UV spectrophotometer at 264 nm.

Ex vivo mucoadhesion time: A locally modified USP disintegration apparatus was used to determine the ex vivo mucoadhesion time. The mucosal membrane of fresh sheep buccal mucosa was removing the fat and loose tissues. The membrane was washed with the distilled water and then wash with 6.8 phosphate buffer at 37 °C. Sheep mucosa, 2 cm long, was glued to the surface of a glass slide. The film was wetted with 6.8 phosphate buffer and attached to sheep mucosa by applying light pressure with fingertip for 20 sec. The glass slide was vertically fixed with to the apparatus and allowed to move up and down so that the film was completely immersed in the buffer solution at the lowest point and was out at the highest point. The beaker was filled with 200 mL of 6.8 phosphate buffer and kept at 37°C. The required time for the film detach from the buccal mucosa. It was recorded as the mucoadhesion time.

In vitro mucoadhesion strength: The mucoadhesive strength of films was measured in triplicate on a modified physical balance. A piece of sheep buccal mucosa was tied to the

mouth of a glass vial filled completely with 6.8 phosphate buffer. The glass vial was tightly fitted in the centre of a beaker filled with 6.8 phosphate buffer at 37±1 °C. Films was stuck at lower side of rubber stoppers with glue and the mass (g) required to detach the films from the mucosal surface was taken as the mucoadhesive strength (shear stress).

Mechanical property: Tensile Strength and % Elongation were calculated using following equations; Tensile strength (kg/mm^2) =Force at brek / Area of Film % Elongation = (L-Lo/L) x 100 Where, L 0 = initial length, L = increase in the length.

The tensile strength of the buccal films was determined by a modified method, A Film of dimension 1×1 cm^2 was held at one end, in a clamp hung from modified balance. Another clamp was attached to the other end of the film the weight was slowly increased. During measurement, the film were pulled upwards by adding weights in pan till the film breaks. Increase in the force (weight) was measured when films broke.

Stability study: The stability study is performed according to ICH guidelines It is packed in the aluminium foil and stored in stability chamber for stability studies at 2-8˚C (45% RH),25-30˚C (60%RH), 45-50˚C (75%RH) for 30 days. The films were characterized by drug content and other parameters during stability studies.

RESULT AND DISCUSSION

Preformulation Study Results: Characteristic properties of Drug (Itraconazole): The sample of Itraconazole was identified and characterized as per requirements of COA (certificate of analysis) issued by the manufacturer.

Melting point analysis: The observed experimental melting point by capillary method complies with the reported melting point as 165-169 ^{0}C.

Drug Excipients Compatibility Study

FTIR study: The FTIR spectrum of pure reference Itraconazole and drug shows the characteristic peaks at 2823.21-3127.16cm-1 due to –C-H- vibrations. peak at 2823.79 cm^{-1} shows the stretching of aromatic rings, range between 3127.16- 3384.62 cm^{-1} was because of N-H stretching of amide groups peak at 3381.21 cm^{-1}. Peaks occurs at 711.96- 899.01 cm^{-1} arises due to the groups occupying different positions on benzene ring; among these inspecific band between 824-852 cm^{-1} shows the para substitution. –C-O stretching was characterized at 1228.32-1052.97 cm^{-1}, -C-N- stretch of alkyl group was observed at 1043-

1185 cm^{-1}, peak at 1701.22 cm-1 was due to stretching of –C=O- and spectrum from 561-762cm-1 indicating C-Cl stretching respectively.

FTIR interpretation data

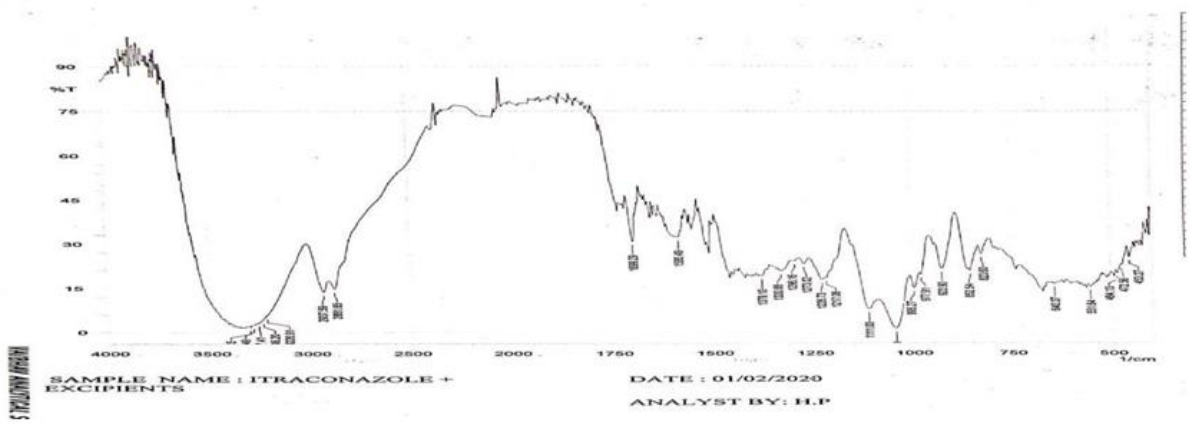


Figure 1: FTIR of Buccul Film Formulation.

Functional Group	Pure Drug Peak Itraconazole	Final Formulation Peak	Observation
N-H	3381.21	3309.85	**No Interaction Observed**
C-H	2877.79	2881.65	
C=C	1583.56	1585.49	
C=O	1701.22	1699.29	

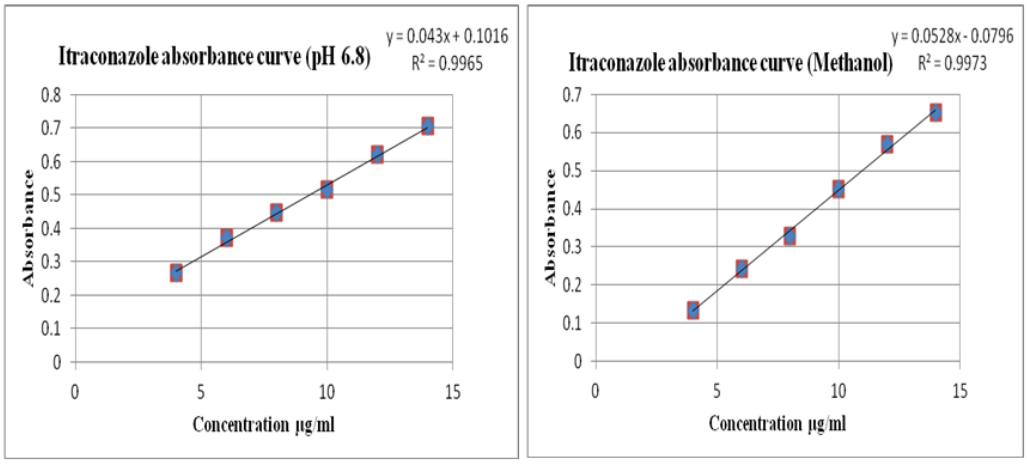
Discussion for IR: The mixture of IR showed that polymers used were not having any interaction with the drug as the peak values of drug were already present so, no interpretation of drug was there with polymers HPMC K100M, Chitosan, lactic acid, glycerine so they were compatible with Itraconazole drug.

Calibration Curve: The standard calibration curve was prepared in methanol and pH 6.8. The scanning of the drug was done in the range (200-400 nm). Before that the λmax was found in methanol at 262.5 nm, the Absorbance range was found to be 0.134-0.652. The regression coefficient (R^2 value) was 0.997 which showed linearity between 4-14 µg/ml concentrations in pH 6.8 at 264 nm. The Absorbance range was found to be 0.268-0.706. The regression coefficient (R^2 value) was 0.9965 which showed linearity between 4-14 µg/ml concentrations. All further analysis was done on that particular wavelength.

Standard Calibration Curve of Itraconazole

Concentration (mg/ml)	Absorbance (nm) ± S.D (n= 3)	
	I. Methanol	II. pH 6.8
4	0.134	0.268

6	0.241	0.371
8	0.327	0.448
10	0.451	0.515
12	0.568	0.621
14	0.652	0.706
R2	0.997	0.9965



Results of Itraconazole Buccal Films of Factorial Batches: Based on trial batches results, factorial design was applied to check the significant factors in the formulation. F1-F9 batches are evaluated and results were given below.

Figure 2: Final Formulation Film of Itraconazole.

Table 3: Evaluation Parameters of Factorial Batches.

Formulation Code	Film Forming Capacity	Texture	Peel Ability	Weight variation (mg)	Thickness (mm)	Folding endurance
F1	++	Smooth	++	22.93± 1.9	0.15±0.03	>300
F2	++	Smooth	++	23.17± 1.5	0.17±0.02	>300
F3	++	Smooth	+	25.82± 1.1	0.16±0.02	>300
F4	+++	Smooth	+++	23.97± 1.6	0.15±0.01	>300
F5	+++	Smooth	+++	24.37± 1.8	0.16±0.04	>300
F6	+++	Smooth	+++	25.65± 1.0	0.15±0.02	>300
F7	+++	Smooth	+++	23.89± 1.7	0.17±0.03	>300

F8	+++	Smooth	++	24.98± 1.2	0.18±0.01	>300
F9	+++	Smooth	++	26.52± 1.5	0.18±0.02	>300

(++ good, +++ very good)

Appearance: Good, smooth and easy to hold.

Peeling ability: All formulation peel ability is good.

Weight variation test: Drug loaded films were tested for uniformity of weight and the results of weight uniformity are in table.

Surface pH determination: All formulation pH was close to the neutral pH so this thing indicates that no irritation is there in mouth.

Thickness of films: The concentration of polymer decides that it is dependable factor for thickness of buccal film. The value of thickness ranges from 0.15mm ± 0.02 to 0.18 mm ± 0.02.

Table 4: Evaluation Parameters of Factorial Batches.

Formulation Code	Surface pH	% Swelling Index	Mucoadhesive Strength (gm)	Mucoadhesion Time (min)
F1	6.92±0.05	23.1 ± 0.15	24.36± 0.10	56±0.05
F2	6.85±0.10	21.3 ± 0.12	26.42± 0.09	65 ±0.12
F3	6.89±0.15	20.7 ± 0.20	28.23± 0.10	70 ±0.28
F4	6.95±0.12	23.6 ± 0.10	26.18 ± 0.15	62 ±0.13
F5	6.88±0.10	22.3 ± 0.21	28.75± 0.12	74 ±0.12
F6	7.02±0.16	21.2 ± 0.18	31.86± 0.07	112±0.16
F7	6.92±0.18	22.9 ± 0.23	28.05± 0.10	90 ±0.08
F8	6.82±0.20	20.2 ± 0.25	30.15± 0.12	105 ±0.13
F9	6.86±0.08	18.8 ± 0.21	33.28± 0.09	120±0.04

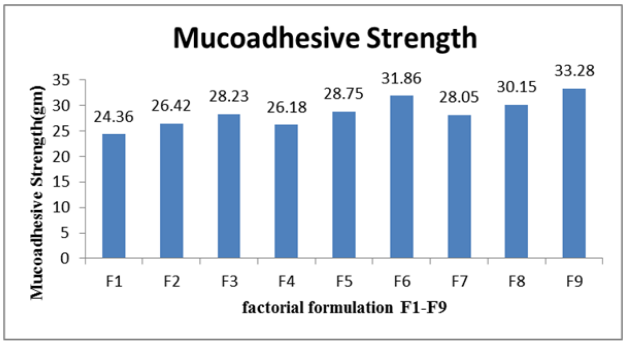


Table 5: Evaluation Parameters of Factorial Batches.

Formulation Code	% Drug Release (1hr)	% Drug content	Tensile strength (kg/mm2)	% Elongation
F1	91.58 ±0.05	98.44±0.01	0.148 ±0.02	31.26 ±0.01
F2	90.63±0.03	94.60±0.04	0.153 ±0.08	35.70 ±0.07
F3	89.90±0.06	96.61±0.02	0.156±0.05	38.66 ±0.07
F4	91.87±0.02	99.30±0.07	0.151±0.03	33.63 ±0.02

F5	89.52±0.04	98.75±0.01	0.154±0.07	36.47 ±0.04
F6	87.08±0.07	96.45±0.03	0.158±0.07	41.22 ±0.02
F7	86.67±0.05	99.10±0.07	0.157 ±0.03	37.46 ±0.05
F8	85.26±0.08	97.32±0.05	0.160±0.04	41.40 ±0.03
F9	83.35±0.04	95.73±0.09	0.162 ±0.08	46.61 ±0.08

Tensile strength: Increase in polymer concentration is dependent factor for changes in all other variables Here viscosity is proportional to concentration of polymer which effects the thickness and brittleness of the film, which indicate that a polymer concentration increase, the tensile strength also increases. The above factors directly indicates that concentration of polymer eflects the effect on tensile strength and % elongation. Here its show the result of tensile strength 0.148-0.162 and % elongation 31-46 %.

Table 6: In Vitro Cumulative Drug Release of Itraconazole Buccal Films.

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
10	33.96± 0.091	30.65± 0.034	29.64± 0.015	33.35± 0.010	27.6± 0.072	28.81± 0.018	26.84± 0.012	26.83± 0.025	28.85± 0.008
20	45.62± 0.068	43.81± 0.078	48.66± 0.044	47.65± 0.036	42.95± 0.048	46.42± 0.032	49.16± 0.091	39.65± 0.041	43.28± 0.010
30	58.89± 0.066	58.04± 0.052	56.28± 0.045	59.71± 0.085	54.83± 0.004	56.69± 0.058	57.42± 0.066	52.63± 0.025	56.51± 0.015
40	72.78± 0.045	71.32± 0.041	68.91± 0.030	74.35± 0.012	67.18± 0.014	63.24± 0.062	65.09± 0.045	65.91± 0.039	64.32± 0.066
50	83.13± 0.043	78.93± 0.012	80.09± 0.078	82.98± 0.042	78.92± 0.026	79.71± 0.018	75.64± 0.043	76.93± 0.061	72.80± 0.041
60	91.58± 0.003	90.63± 0.05	89.9± 0.010	91.87± 0.003	89.52± 0.006	87.08± 0.015	86.67± 0.023	85.26± 0.028	83.35± 0.009

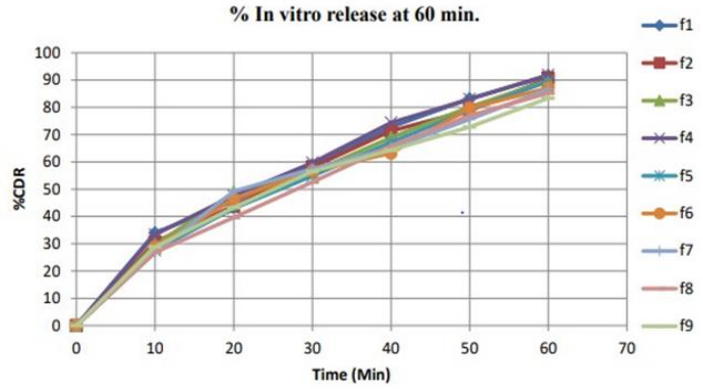


Figure 3: In-vitro drug release of itraconazole buccal films formulations.

Discussion: These in vitro drug release studies were carried out using pH 6.8 +0.5% SLS as the a dissolution medium. The obtained drug release data for all formulations is tabulated in

Table 19. The comparison of % Cumulative drug release of factorial designed formulation is done in which batch F4 is showing 91.87 % of release. Increase in the concentration of polymer showed decrease in the % drug release.

Table 7: Modeling and Mechanism Drug Release Study.

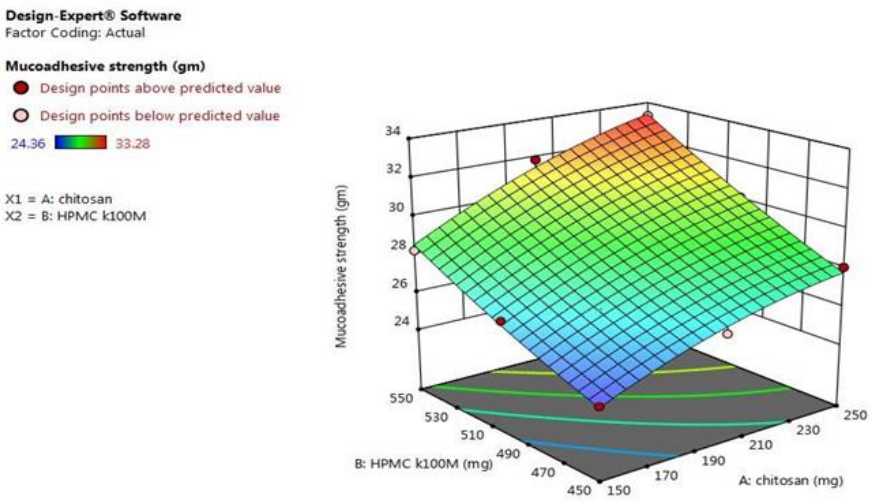
Formulation	Zero order kinetics	First order kinetics	Higuchi matrix	Korsmeyer–Peppas model
	R2	R2	R2	R2
F1	0.951	0.9659	0.9915	0.9237
F2	0.9585	0.9593	0.9891	0.915
F3	0.9518	0.9634	0.9904	0.9222
F4	0.9467	0.9691	0.994	0.9301
F5	0.9711	0.9582	0.9831	0.8983
F6	0.951	0.9672	0.9872	0.9178
F7	0.9393	0.97	0.9885	0.9274
F8	0.9715	0.9818	0.9813	0.8946
F9	0.9447	0.9845	0.9946	0.9327

- The obtained results of in vitro release studies were attempted to fit into various mathematical models.

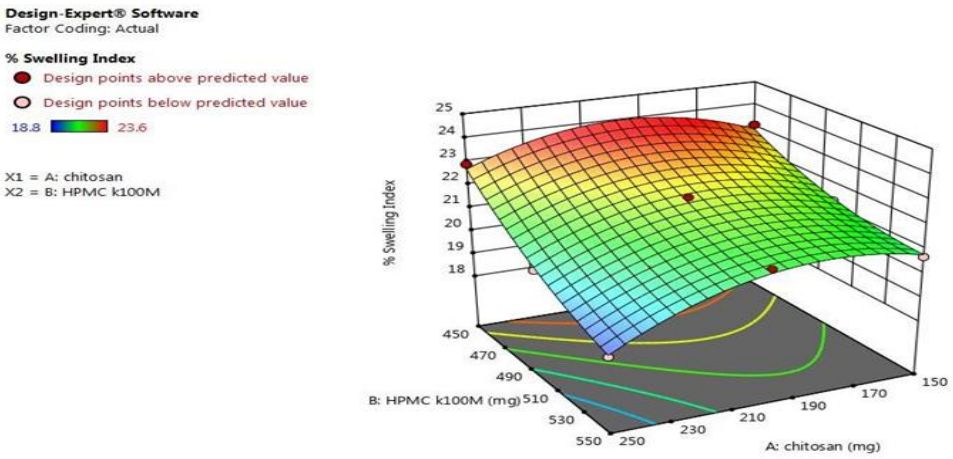
Order Ranked For Investigated Formulation

Higuchi model > First Order > Zero Order > Krosmeyer Peppas Model, Effect of formulation variables on Mucoadhesive strength, swelling index, and drug release

- The R^2 value for mucoadhesive strength was found 0.9912 which was indicating the adequate fitting of quadratic model. From the polynomial equation, coefficients with either positive or negative signs -1 to +1 are obtained which indicate the effect on variables. The p value of the X_1 (0.0013) < 0.05 and X_2 (0.0008) < 0.05. Increase in Bioadhesion force of buccal films is mainly because of increase in X_1 concentration. High level of factor X_2 gave high value of bioadhesion force at all the levels of factor X_1 which indicates that X_1 had significant effect.



- The R^2 value for swelling index was found 0.9811which was indicating the adequate fitting of quadratic model. From the polynomial equation for swelling index it was found that as p value for X_1 is (0.0331) < 0.05 and for X_2 p value is (0.0019) <0.05 indicates that both had significant effect on swelling index.



- Formulation F4 showed highest drug release. This optimized formulation (F4) was subjected to various mathematical models to understand the release pattern. The R^2 value for drug release was found 0.9747 which was indicating the adequate fitting of quadratic model. From the polynomial equation it was found that as p value of X_1 is 0.0030 < 0.05 and for X_2, the p value is 0.0140 < 0.05 indicates that both had significant effect on drug release.

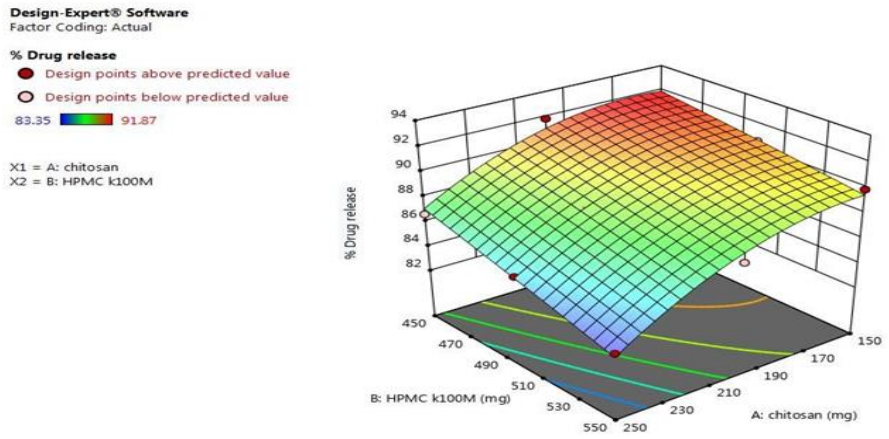
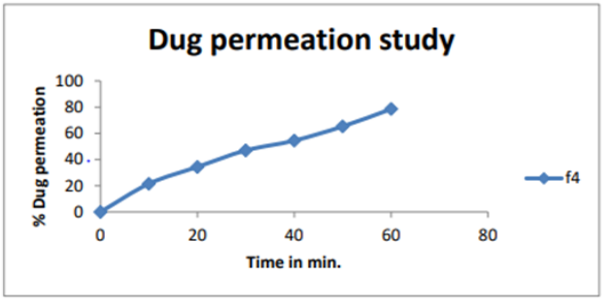


Table 8: In vitro Permeation Study of Formulation F4.

Cumulative % of drug release permeated in buccal mucosa ± SD						
Formulation	**Time (min)**					
	10	20	30	40	50	60
F4	11.48 ±1.65	20.35 ±2.08	33.09±1.15	41.12 ±1.98	52.25±1.76	65.53 ±1.80



Discussion- based on the results of factorial formulations, the F4 formulation was selected for in vitro drug permeation studies. The drug permeation shows 65.53 % of Itraconazole could permeate through the buccal membrane in 1 hr.

Stability Study: Stability study of the final optimized batch F4 was carried out at 40°C/75% RH and the results are tabulated below. The Results show that there is no significant change in the formulation. Batch was found to be stable for 1 month.

Table 9: Stability Data of Optimized Formulation F4.

Stability conditions	**Observation**					
	Sampling time	**Appearance**	**Mucoadhesive Strength (g)**	**Surface pH**	**% In vitro drug release**	**% Drug content**
Storage (40 ± 2˚C and 75 ± 5% RH)	Initial	Good	26.25 ± 0.10	7.17±0.03	91.83± 0.10	99.36 ±0.03
	After 15 days	Good	26.05 ±0.09	7.10± 0.02	90.62 ± 0.21	98.85 ± 0.07
	After 30 days	Good	25.92 ± 0.12	7.0±0.03	89.25 ± 0.13	98.52 ±0.09

CONCLUSION

In present investigation, Buccal films of Itraconazole was formulated by using solvent casting method. The selection of polymers was done from HPMC K100M, Chitosan, glycerine was used as plastisizer. 1% lactic acid used as solvent for film casting. This formulation could be designed for oral candidiasis. The film is locally target in oral buccal mucosa. This drug is used as various type of antifungal infection. The amount of polymer concentration had increased thickness of film. Swelling index increased with time and with increase in hydrophilic polymer. The concentration of polymer increased also increased tensile strength. The in vitro drug release of Itraconazole was carried out in phosphate buffer pH 6.8+ 0.5% SLS. The % drug release from the formulation F4 (450 mg of HPMC K100M and 200mg chitosan) was 91.87 %.

The results showed that mucoadhesive buccal film containing HPMC K100M and chitosan buccal film having good mucoadhesive strength. Based on trial batches results, 3^2 full factorial design was applied by taking HPMC K100M, chitosan as independent factors. Factorial batches F1-F9 prepared and evaluated for various parameters like thickness, weight variation, folding endurance, tensile strength, % elongation, surface pH, in vitro drug release, kinetic order. All the results were found satisfactory. Optimized formulation batch were further subjected to stability study which showed no significant changes in mechanical properties drug content, % drug release, surface pH, mucoadhesive strength after storage at accelerated condition. The formulation F4 showed ther maximum drug content. It was observed that optimized formulation followed higuchi matrix order drug release which showed that the drug release was in controlled manner. So, Itraconazole buccal film is a good dosage form for oral candidiasis.

REFRENCES

1. Chinna Reddy P, Chaitanya KSC and Madhusudan Rao Y, "A review on bioadhesive buccal drug delivery systems: current status of formulation and evaluation methods." Daru., 2011; 19(6): 385-403.
2. Hao J and Heng PW, "Buccal delivery systems." Drug dev and industrial pharm., 2003; 29(8): 821-832.
3. Rencber SK, sinem yaprak & Yilmaz, Fethiye & Eraç, Bayri & Nenni, Merve & Gurer-Orhan, Hande & Hosgor Limoncu, Mine & Güneri, Pelin & Ertan, Gökhan., "Formulation and evaluation of fluconazole loaded oral strips for local treatment of oral candidiasis." J

of D D Sci and Tec., 2019; 49(2019): 615-621.

4. Rajesh Mujoriya, "A review on study of buccal drug deliverysystem.,"." Innovsys Des Eng,. 2011; (3): 1-14.
5. Galey W LH, Nacht S, "The in vitro permeability of skin and buccal mucosa to selected drugs and tritiated water." J Invest Dermat., 1976; 67: 713-717.
6. Rathbone MJ, Drummond BK and Tucker IG, "The oral cavity as a site for systemic drug delivery." Advanced Drug Delivery Reviews, 1994; 13(1): 1-22.
7. Hooda R, Tripathi M and Kapoor PK, "A Review on Oral Mucosal Drug Delivery System." The Pharma Innovation, 2012; 1(1): 14-20.
8. Shrutika M. Gawas AD, Ganesh Deshmukh, S. Rathod, "Current approaches in buccal drug delivery system." Pharm And Bio Eva., 2016; 3(2): 165-177.
9. Parth S. Patel, Ashish M. Parmar,et al, "Buccal Drug Delivery System: A Review." int j of drug dev and res., 2013; 1-13.
10. Nishan N. Bobade SCA, Vikrant P. Wankhade., "A Review on Buccal Drug Delivery System." Int J Pharm Pharma sci,. 2013; 3(1): 35-40.
11. Vaishali A. Chaudhari SMS, B. S. Sathe, G. P. Vadnere., "Mucoadhesive Buccal Drug Delivery System: A Review." Int j pharma sci., 2014; 5(2): 142-162.
12. Singh R SDaGR, "Review on Mucoadhesive Drug Delivery System with Special Emphasis on Buccal Route: An Important Tool in Designing of Novel Controlled Drug Delivery System for the Effective Delivery of Pharmaceuticals." J of Dev Drugs, 6(1): 2.
13. Pahuja P, Kashyap H and Pawar P, "Design and evaluation of HP-beta-CD based voriconazole formulations for ocular drug delivery." Current drug delivery, 2014; 11(2): 223-232.
14. N BN, "A Review on buccal drug delivery system." Int J Pharm, and Pharm Sci Res., 2013; 3(1): 21.
15. J Z, "An In Vivo Dog Model for Studying Recovery Kinetics of the Buccal Mucosa Permeation Barrier after Exposure to Permeation Enhancers Apparent Evidence of Effective Enhancement without Tissue Damage." Int J Pharm., 1994; 15-22.
16. Jain STaN, "Buccal Control Drug Delivery System: A Review." Int J Pharma Sci., 2017; 916-927.
17. Adhikari SN, Nayak BS, Nayak AK and Mohanty B, "Formulation and evaluation of buccal films for delivery of atenolol." AAPS Pharm Sci Tech., 2010; 11(3): 1038-1044.
18. Raghavendra Rao, "Overview on Buccal Drug Delivery Systems." J Pharm Sci & Res., 2013; 5(4): 80-88.

19. "Drug information: https://www.medicines.org.uk/emc/product/3293/smpc."
20. "Drug information, 2019." https://en.wikipedia.org/wiki/Itraconazole.
21. "Drug information, 2019." https://pubchemncbinlmnihgov/compound/Itraconazole.
22. "Drug infornation 2019." https://wwwwebmdcom/drugs/2/drug-128-2179/itraconazole-oral/itraconazole-oral/details.
23. "Drug information, May 2020, https://www.drugbank.ca/drugs/DB01167.
24. Rowe R, Sheskey P, Owen S, Handbook of Pharmaceutical excipients, 6th edition, 2009; 346-349.
25. "Introduction to excipients: dichloromethane." https://enwikipediaorg/wiki/Dichloromethane, May 2020.
26. Shalin K. Parikh ADP, Dr. J. B. Dave, Dr. C. N. Patel and Dr. D. J. Sen, "Development and validation of Uv Spectrophotometric method for estimation of Itraconazole bulk drug and Pharmaceutical Formulation." Int J of Drug Dev & Res., 2011; 3(2): 324-327.
27. Madgulkar A, Kadam S and Pokharkar V, "Studies on formulation development of mucoadhesive sustained release itraconazole tablet using response surface methodology." AAPS Pharm Sci Tech., 2008; 9(3): 998-1005.
28. Dobaria NB, Badhan AC and Mashru RC, "A novel itraconazole bioadhesive film for vaginal delivery: design, optimization, and physicodynamic characterization." AAPS Pharm Sci Tech., 2009; 10(3): 951-959.
29. Abdul Sayeed FSaMHM, "Design and Invitro Evaluation of Buccoadhesive Tablet Of Itraconazole." Int J Of Resh In PharmAnd Chemy., 2014; 381-395.
30. Munira Momin SJ, Chaitrali Kute and Aarti Jaybhaye, K. kar, "Formulation Development and Pharmacotechnical Evaluation of Mucoadhesive Drug Delivery System for Oral Candidiasis." Int j of pharma sci., 2018; 1-13.
31. Eid A, "Preparation And Release Charcteristics Of Itraconazole Poymeric Films For Topical Application." Int J of Pharm and Pharma Sci., 2013; 4: 167-170, 1-5.
32. Rompicherla NC, Shripriya, Jose J and Shetty V, "Design and Characterization Of Mucoadhesive Buccal Film Containing Antifungal Agent For Oral Candidiasis." Int J of Pharm and Phytopharma Rese (eIJPPR). 2013; 245-249.
33. Singh S, Jain S, Muthu MS, Tiwari S and Tilak R, "Preparation and evaluation of buccal bioadhesive films containing clotrimazole." AAPS Pharm Sci Tech., 2008; 9(2): 660-667.
34. Mangilal TC, Kethirabalan Naveen, J. Kumar, Maddula Ravi, "Formulation and evaluation of voriconazole Buccal Films By Using Selected Polymers" Indo Am J P Sci., 2018; 4072.

35. Adhikari S, Nayak BS, Nayak AK and Mohanty B, "Formulation and evaluation of buccal films for delivery of atenolol." AAPS Pharm Sci Tech., 2010; 11(3): 1038-1044.
36. Jagdale S, Mohanty P, Chabukswar A and Kuchekar B, "Development of Buccal Films for Delivery of Darifenacin from Beta-Cyclodextrin Complexes." Revista de Ciencias Farmaceuticas Basica e Aplicada., 2014; 35: 29-39.
37. Shivhare U SP, Varvandkar S,, "Formulation andevaluation of buccal film containing aceclofenac." J app Sci., 2014; 6(1): 65-76.
38. Patel VM, Prajapati BG and Patel MM, "Design and characterization of chitosan-containing mucoadhesive buccal films of propranolol hydrochloride." Acta Pharmaceutica: 2007; 57(1): 61-72.
39. Mujib I et all, "mucoadesive buccal films of glibenclamide: development and evaluation." Int j pharma investigation, 2011; 1: 42.
40. Sarita Krishan Chand SK, "Design, development and evaluation of Itraconazole loaded transfersomal gel." Int J of Farm., 2016; 2(4): 198-207.
41. Kumar A and Dua JS, "Formulation and Evaluation Of Itraconazole Niosomal Gel." Asian J of Pharma Res and Dev., 2018; 6: 76-80.
42. Al-Dhubiab BE, Nair AB, Kumria R, Attimarad M and Harsha S, "Formulation and evaluation of nano based drug delivery system for the buccal delivery of acyclovir." Colloids and surfaces B, Bio interfaces, 2015; 136: 878-884.
43. Preis M, Woertz C, Schneider K, Kukawka J, Broscheit J, Roewer N, et al., "Design and evaluation of bilayered buccal film preparations for local administration of lidocaine hydrochloride." European j of Pharmaceutics and bioPharmaceutics: official j of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik eV., 2014; 86(3): 552-561.
44. Yildiz Pekoz A, Sedef Erdal M, Okyar A, Ocak M, Tekeli F, Kaptan E, et al., "Preparation and in-vivo evaluation of dimenhydrinate buccal mucoadhesive films with enhanced bioavailability." Drug development and industrial Pharmacy, 2016; 42(6): 916- 925.
45. Zhang C, Liu Y, Li W, Gao P, Xiang D, Ren X, et al., "Mucoadhesive buccal film containing ornidazole and dexamethasone for oral ulcers: in vitro and in vivo studies." Pharma dev and tech., 2019; 24(1): 118-126.
46. Naz K, Shahnaz G, Ahmed N, Qureshi NA, Sarwar HS, Imran M, et al., "Formulation and In Vitro Characterization of Thiolated Buccoadhesive Film of Fluconazole." AAPS Pharm Sci Tech., 2017; 18(4): 1043-1055.
47. Trastullo R, Abruzzo A, Saladini B, Gallucci MC, Cerchiara T, Luppi B, et al., "Design

and evaluation of buccal films as paediatric dosage form for transmucosal delivery of ondansetron." European journal of Pharmaceutics and bioPharmaceutics: official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik eV., 2016; 105: 115-121.

48. Khalifa RA SAaAM, "Design and Evaluation of Fast Dissolving Oral Films of Granisetron Hydrochloride." Am J Pharm Tech Res., 2012; 2(6): 591-609.
49. Zhang C , Li W, "Mucoadhesive buccal film containing ornidazole and dexamethasone for oral ulcers: in vitro and in vivo studies." Pharm Dev Tec., 2019; 24(1): 118-126.
50. Gajdziok J, Holesova S, Stembirek J, Pazdziora E, Landova H, Dolezel P, et al., "Carmellose Mucoadhesive Oral Films Containing Vermiculite / Chlorhexidine Nano composites as Innovative Biomaterials for Treatment of Oral Infections." Bio Med Res Int., 2015; 2-16.
51. Alka Tomar KS, Nitesh S Chauhan, Ashu Mittal, Umakant Bajaj, "Formulation and Evaluation of Fast Dissolving OralFilm of Dicyclomine as potential route of Buccal Delivery." Int J Drug Dev & Res., 2012; 4(2): 408-417.