



# DEVELOPMENT AND EVALUATION OF MUCOADHESIVE BUCCAL TABLETS OF ITRACONAZOLE

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## ABSTRACT

The main objective of developing stable mucoadhesive formulations of itraconazole using natural and synthetic mucoadhesive and rate retarding polymers is to treat fungal infections, particularly oral candidiasis, and to investigate the effect of different polymers on drug release profiles for prolonged release. The rheological parameters of the powder bed, such as bulk density, compressibility index, and angle of repose, were assessed. Mucoadhesive buccal tablets were compressed on a Chamunda, Pilot Press II D-B with 8 mm flat faced punches, and every batch was evaluated for weight variation, hardness, thickness, percent swelling index, mucoadhesive strength, and in vitro drug release using a USP TDT-081 dissolution testing apparatus, method II with a paddle at 50 rpm and a kinetic study. In addition, the prepared mucoadhesive formulations were evaluated for a number of quality control tests, antifungal efficacy and stability studies, which were conducted at 40°C/75%RH in a stability chamber for a period of six months.

**KEYWORD:** Itraconazole, Buccal tablet, Chitosan, Xanthan gum, Mucoadhesive properties.

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## INTRODUCTION

Mucoadhesive drug delivery systems are drug delivery techniques that rely on the bioadhesion of certain water soluble polymers that become adhesive following hydration. These techniques can be used to deliver a medicine for an extended length of time to a particular location of the body. Since the early 1980s, transmucosal therapeutic agent delivery has drawn a lot of interest due to the presystemic metabolism of several therapeutic agents or their instability in the acidic environment associated with oral administration. (Salamat et al., 2005) Thrush, commonly referred to as yeast infection or candidiasis, is a common illness that affects the mucous membranes of the mouth. Adult mouth or throat candidiasis is a fungal infection (mycosis) of any of the *Candida* species, with *Candida albicans* being the most prevalent. Baby mouth candidiasis is known as oral thrush. As a result, "candidiasis" is a general word that covers a wide range of diseases, from small ones like vaginitis and oral thrush to more serious ones like systemic and possibly lethal disorders. While superficial *Candida* infections of the skin and mucous membranes, which cause localised inflammation and discomfort, are common in many human populations, the second category of *Candida*

infections, also known as candidemia, typically affects people with severely weakened immune systems, such as cancer, transplant, and AIDS patients. (Sangeorzan et al., 1994) Itraconazole is drug used for the management of topical and systemic fungal infections such as oral candidiasis (Jug and Bećirević-Laćan., 2004). Itraconazole has a limited oral bioavailability and a lengthy plasma half-life of roughly 24 hours. As a result, the oral approach is not much more effective. In order to release itraconazole while adhesion is occurring, the formulation is made into a bioadhesive tablet that reversibly sticks to the oral mucosa. Buccal mucoadhesive delivery methods were made possible by the introduction of direct compression tablets. (Munasur et al. 2006)

## MATERIALS AND METHODS

### Material

Itraconazole was provided as gift sample from Leben Laboratories Pvt. Ltd., Akola, Maharashtra, Chitosan, Mannitol, Xanthan gum and Gaur Gum were obtained from Mylochem Ltd., Mumbai, while HPMCK15M was obtained from Trio Pharma Chem Paldi, Ahmedabad, Talc and Magnesium stearate were obtained from SD Finechem Limited, Mumbai.

### Methods

**A) Micromeritics Studies** (Martin, 1993; Martin, 2001; Sinko, 2011; Maheshwari et al., 2018)

**Angle of Repose:** It was determined by fixed funnel method. Accurately weighed quantity (5gm) of drug was taken in a funnel; the height of the funnel is adjusted such that the tip of the funnel just touches the apex of heap of the blend. Then the drug is allowed to flow the funnel freely on to the surface. The diameter is then measured and angle of repose was calculated by following equation.

$$\tan \theta = h/r$$

Table 1: Angle of Repose Parameter		
Sr. No.	Angle of repose ( $\theta$ )	Nature of Flow
1	< 20	Excellent
2	20 - 30	Good
3	30 - 40	Passable
4	> 40	Very poor

**Bulk Density:** It was determined by pouring a weighed quantity (5gm) of drug/excipients powder blend in to a graduated cylinder. The cylinder was dropped at 2 sec interval on hard wood surface three times from the height of 1 inch. It was then calculated by the equation given below.

$$\text{Bulk Density} = \text{Weight of the Powder} / \text{Bulk Volume}$$

**Tapped Density:** It was determined by pouring a drug/excipients powder blend (5gm) in a measuring cylinder. The cylinder was dropped at 2 sec interval on hard surface 100 times from the height of 1 inch. Then the final volume occupied by the drug was measured.

$$\text{Tapped Density} = \text{Weight of the Powder} / \text{Final Volume}$$

**Compressibility Index:** The compressibility index (Carr's index) is a measure of a powder to be compressed.

$$\text{Carr's Index} = [(\text{Tapped Density} - \text{Bulk Density} / \text{Tapped Density})] \times 100$$

Table 2: Carr's Index Parameter		
Sr. No.	Carr's Compressibility Index (%)	Relative Flowability
1	5 - 11	Excellent
2	12 - 16	Good
3	18 - 21	Fair
4	23 - 28	Slightly Poor
5	28 - 35	Poor
6	35 - 38	Very Poor
7	> 40	Extremely Poor

**Hausner Ratio:** The Hausner Ratio of powder was calculated according to equation given below,

$$\text{Hausner Ratio} = D_t / D_f$$

Where,  $D_t$  = Tapped Density

$D_f$  = Bulk Density

Table 3: Hausner Ratio Parameter		
Sr. No.	Hausner Ratio	Type of Flow
1	1.0 - 1.12	Excellent
2	1.12 - 1.18	Good
3	1.19 - 1.25	Fair
4	1.26 - 1.34	Passable
5	1.35 - 1.45	Poor
6	1.46 - 1.59	Very Poor
7	> 1.60	Very Very Poor

## B) Preparation of Mucoadhesive Buccal Tablets

(Jin et al., 2017; Dattatraya et al., 2016; Mohammed, F.A. and Khedr, H., 2003)

Mucoadhesive Buccal Tablets of Itraconazole each were containing 50 mg of drug prepared as per formula given in Table 4. Accurately weight quantity of Itraconazole equivalent to 50 mg drug was weighted and other excipients such as xanthan gum, chitosan, guar gum, and HPMC K4M were weighed accurately and thoroughly mixed, following addition of magnesium stearate as lubricant and talc as glidant. The powder blend of Itraconazole and excipients was then subjected to compression into tablet with suitable set of dies and punches using 10 Station Rotary Tablet Compression Machine (Chamunda, Ahmadabad). The ITZ and excipients powder blend was studied for the pre-compression parameters such as angle of repose, density, flowability, compressibility index and hausner's ratio etc.

<b>Ingredients (mg)</b>	<b>Formulation</b>								
	<b>ITB1</b>	<b>ITB2</b>	<b>ITB3</b>	<b>ITB4</b>	<b>ITB5</b>	<b>ITB6</b>	<b>ITB7</b>	<b>ITB8</b>	<b>ITB9</b>
Itraconazole	50	50	50	50	50	50	50	50	
Chitosan	30	60	30	30	60	30	30	60	30
HPMC K15M	30	30	60	-	-	-	-	-	-
Xanthan Gum	-	-	-	30	30	60	-	-	-
Guar Gum	-	-	-	-	-	-	30	30	60
Mannitol	84	54	54	84	54	54	84	54	54
Magnesium Stearate	2	2	2	2	2	2	2	2	2
Talc	4	4	4	4	4	4	4	4	4
Total Weight of Tablet	200	200	200	200	200	200	200	200	200

### C) Physical Characterization of Tablets

**Visual Inspection:** Upper and lower punches were inspected by naked eye for presence of sticking or picking.

**Diameter and Thickness:** (Lachman et al., 2009; Saeedi et al., 2018)

Tablet thickness is an important characteristic in reproducing appearance and also in counting by using the filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. 10 tablets were randomly picked from each batch and their thickness and diameter were measured at 3 different positions using a calibrated dial Vernier caliper. It is expressed in mm.

**Tablet Hardness:** (I.P., USP, Sweety et. al., 2016)

The resistance of tablet during shipping to breakage, under condition of storage, transportation and handling before use depends on its hardness. For each formulation, the hardness of 3 tablets was determined using the Pfizer hardness tester. The tablet was held along its oblong axis in between two jaws of taster. At this point, reading should be zero kg/cm<sup>2</sup>. Then constant force was applied until the tablet fractured. The value at this point was noted in kg/cm<sup>2</sup>.

**Friability:** (I.P., USP, Sweety et. al., 2016)

Friability is the measure of tablet strength. Roche friability Apparatus (Electrolab, India) was used for testing the friability. For each formulation, the friability of 20 tablets was determined. This test subjects a number of tablets to the combined effect of shock abrasion by utilizing the plastic chamber which revolves at the speed of 25 rpm, dropping the tablet to a distance of 6 inches in each revolution. A sample of pre weight 20 tablets was placed in friabilator which was then operated for 100 revolutions i.e. 4 min. tablets were then dedusted and reweight. A loss of less than 1% in weight is generally considered acceptable Friability (%) was calculated as follows,

$$\% \text{ Friability} = (\text{Initial weight} - \text{Final weight}) / \text{Initial weight} \times 100$$

**Weight Variation Test:** (I.P., USP, Sweety et. al., 2016)

The weight variation test was done by taking 20 tablets and weight accurately. The average weight of tablet was calculated.

Table 5: Weight Variation Test Parameter		
Sr. No.	Average Weight of Tablet	Deviation (%)
1	80 mg or less	10
2	More than 80 mg but less than 250 mg	7.5
3	250 mg or more	5

**Drug Content:** (I.P., USP, Sweety et. al., 2016)

The drug content determination was done by taking 20 tablets & triturate. Take equivalent weight of powder (50 mg) was dissolved in 5 ml methanol and volume was made up to 50 ml with pH 6.8 phosphate buffer. The solution was filtered through Whatman filter paper no. 41. After appropriate dilutions with pH 6.8 phosphate buffer and analyzed spectrophotometrically at 262 nm (Shimadzu 1800, Japan). Drug content was calculated from the calibration curve of Carvedilol in pH 6.8 phosphate buffer.

**Surface pH:** (Mittal and Pawar, 2018; Patil et al., 2018)

The surface pH of the buccal tablet was determined in order to investigate the possibility of any side effects *in vivo*, as an acidic or alkaline pH may irritate the buccal mucosa, we sought to keep the surface pH as close to neutral as possible. For the determination of the surface pH of the buccal tablets, a combined glass electrode is used. The bioadhesive buccal tablet was allowed to swell by keeping it in contact with 5 ml distilled water in a petri dish for 2 hr at room temperature. The pH was identified by bringing the electrode into contact with the tablet surface and allowing the surface to equilibrating for 1 min.

**Swelling Index:** (Balaji et al 2014, Koradia, H. and Chaudhari, K., 2018)

Buccal tablets were weighed individually; initial weight was considered as  $W_1$  and placed separately in petri dishes containing 10 mL of phosphate buffer (pH 6.8) solution. At time intervals of 2h, 4h, 6h, 8h, 10h and 12h, the buccal tablets were removed from the petri dishes using coverslips and excess surface water was removed carefully using the Whatman filter Paper. The swollen tablets were then reweighed ( $W_2$ ). This experiment was performed in triplicate. The degree of swelling (water uptake) was calculated according to the following formula.

$$\text{Degree of swelling} = [(W_2 - W_1)/W_1] \times 100$$

Swelling index increases with increasing polymer concentration and thereby retarding the release of drug from the mucoadhesive buccal tablet.

**Matrix Erosion Test:** Tablets initial weight was noted down (W1). Swollen tablets were dried at 60°C for 24 hrs in an oven and kept in desecator for 48 hrs and reweighed (W3). % matrix erosion were calculated using following formula,

$$\% \text{ Matrix erosion} = [(W1-W3) \div W3] \times 100$$

**Tablet Wetting Time and Water Absorption Ratio:** (Panchal et al., 2012)

A piece of double folded tissue paper was placed in a petridish containing 6 ml of water. One tablet was placed on this paper and the time for complete wetting of tablet was recorded. The wetted tablet was weighed and the water absorption ratio, R, was determined according to the following equation:

$$R = 100 (W_a - W_b) / W_b$$

Where,  $W_b$  - Weight of tablet before water absorption

$W_a$  - Weight of tablet after water absorption

**Measurement of Bioadhesive Strength:**

(Pritchard et al., 1996; Gupta et al., 1992; Garg et al., 2002; Patel et al., 2007)

An in-vitro assembly has been developed to measure and compare the bioadhesive strengths of Mucoadhesive Tablets proposed by Sanjay Garg et.al. The strength of the bond between the formulation and the membrane excised from goat buccal mucosa was determined using tensile experiment on a specially fabricated assembly.

**Ex vivo Mucoadhesion Time** (Shankar et al., 2009; Singh and Ahuja, 2002; Kadam., 2004)

The ex vivo mucoadhesion time was determined using a locally modified USP disintegration apparatus. The medium was composed of 200 ml of phosphate buffer (pH 6.8) maintained at  $37 \pm 1^\circ\text{C}$ . The goat buccal mucosa was tied to the surface of a glass slab, vertically attached to the disintegration apparatus. The buccal tablet was hydrated using phosphate buffer (pH 6.8) and the hydrated surface was brought in contact with the mucosal membrane by applying a light force with fingertip for 30 seconds. The glass slide allowed moving up and down and hence that, the tablet was completely immersed in the buffer solution at the lowest point and was out at the highest point. After 2 min, a slow stirring rate was applied to simulate the buccal cavity environment, and tablet adhesion was monitored for 12 h. The time for detach from the goat buccal mucosa was recorded as the mucoadhesion time. The experiments were performed in triplicate (n=3) and mean values were used to calculate the ex vivo mucoadhesion time.

**Detachment Force Measurement** (Madhusudan et al., 1998; Sudarshan et al., 2015)

This is the method used to measure in vitro mucoadhesive capacity of different polymers. It is a modified method developed by Martti Marvola to assess the tendency of Mucoadhesive materials to adhere to the esophagus. The assembly consists of single organ bath, a stand, for keeping beaker and a reservoir for addition of water into beaker, Aerator.

The force in Newton in calculated by the equation,

$$F = 0.00981 W/2$$

Where;

W- The amount of water.

The following characteristics were studied:-

1. The effect of the contact time for
2. Which the product remains in the intestine and the force needed to detach it.
3. The strength of different mucoadhesive polymers and the effect of amount of polymer in the formulation on the force needed to detach it.

#### D) In-Vitro Dissolution Study

The release rate of Itraconazole from Bioadhesive tablets was determined using USP dissolution testing apparatus II (Paddle type). The dissolution test was performed using 900 ml buffer pH 6.8, at  $37 \pm 0.5^\circ\text{C}$  and 50 rpm. A sample (5ml) of the solution was withdrawn from the dissolution apparatus hourly for 12 h, and the samples were replaced with fresh dissolution medium. The solution was appropriately diluted and the absorbance of these solutions was measured at 262 nm.

#### E) Kinetic Study

(Suvakanta et al., 2010; Lokhandwala et al., 2013; Paarakh et al, 2018)

The matrix systems were reported to follow the Peppas release rate and the diffusion mechanism for the release of the drug. To analyze the mechanism for the release and release rate kinetics of the dosage form, the data obtained was fitted in to, Zero order, First order, Higuchi matrix, Peppas and Hixson Crowell model. In this by comparing the r-values obtained, the best-fit model was selected.

**Zero Order Kinetics:** Drug dissolution from Pharmaceutical dosage forms that do not disaggregate and release the drug slowly, assuming that the area does not change and no equilibrium conditions are obtained can be represented by the following equation:

$$Q_t = Q_0 + K_0 t$$

**First Order Kinetics:** To study the first order release kinetics the release rate data were fitted to the following equation.

$$\log C_t = \log C_0 + K_t / 2.303$$

**Higuchi Model:** Higuchi developed several theoretical models to study the release of water soluble and low soluble drugs incorporated in semi-solid and/or solid matrixes. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media. The Higuchi equation is

$$Q_t = K_H \times t^{1/2}$$

**Korsmeyer - Peppas Model:** To study this model, the release rate data is fitted to the following equation.

$$M_t / M = K. t^n$$

#### F) Accelerated Stability Studies of Optimized Formulation

(Grimm, 1998; Bagul, et al 2009; Chime et al., 2013)

Short-term accelerated stability testing was carried out according to ICH guidelines considering  $40 \pm 2^\circ\text{C}/75 \pm 5\%$  relative humidity (RH) in a stability chamber for a period of 6 month. The mucoadhesive buccal tablets of itraconazole of optimized formulation ITB3 was subjected to stability chamber at a minimum of three-time points, including the initial, intermediate and final time points (e. g., 0, 3, and 6 month). At the end of 3<sup>rd</sup> and 6<sup>th</sup> month of

the tablets exposed to stability chamber, the mucoadhesive buccal tablets were again analyzed for their physical appearance, assay (%) and *in vitro* drug release profile.

### G) In - Vitro Antifungal Studies of Optimized Formulation

(Swamy et al., 1974; Sawyer, et al 1975; Scorzoni et al., 2007)

The activity of selected formulations containing itraconazole was determined. For this, formulation ITB3 was selected amongst the various formulation as optimized one. An agar diffusion technique was applied using *C. albicans* ATTC 10231 organism. The tablet was placed on the agar surface. The zone of inhibition diameter was measured after 24 h incubation at 35°C. Also, the placebo tablets were subjected to the same conditions to detect any activity of the used polymers.

## RESULT AND DISCUSSION

**Micromeretics Studies:** The results of micromeretic properties all formulations ITB1 to ITB9 of mucoadhesive buccal tablets of Itraconazole are shown in Table 6, which were evaluated for various parameters such as Bulk Density, Tapped Density, % Compressibility Index, Hausner's Ratio and Angle of Repose. The % Compressibility Index was in the range of 10.91-18.21 for all the formulations ITB1 to ITB9 indicating good flow property. The values of angle of repose for formulations ranged from 23.40-29.47, indicating the good flow properties of all the formulation's powder blend.

The flow property of study such as the Bulk Density, Tapped Density, Carr's Index, Hausner's Ratio and Angle of Repose for all the formulations were found to be good and all parameter obtained within range as per official standard.

Formulation	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Angle of Repose	Carr's Index	Hausner's Ratio
ITB1	0.39±0.032	0.68±0.029	26.09±0.83	14.23±0.65	1.13±0.021
ITB2	0.41±0.054	0.61±0.036	28.65±0.48	16.23±0.51	1.16±0.036
ITB3	0.35±0.025	0.78±0.028	23.40±0.62	10.91±1.09	1.17±0.077
ITB4	0.34±0.033	0.57±0.030	27.63±0.52	15.62±0.62	1.18±0.062
ITB5	0.39±0.041	0.63±0.034	29.47±0.76	17.37±1.23	1.21±0.024
ITB6	0.38±0.028	0.71±0.040	25.01±0.39	18.21±0.87	1.17±0.043
ITB7	0.42±0.052	0.67±0.031	26.81±0.46	13.39±0.27	1.19±0.052
ITB8	0.40±0.035	0.69±0.027	28.97±0.80	12.98±0.57	1.15±0.029
ITB9	0.36±0.029	0.72±0.038	27.36±0.44	13.75±0.46	1.14±0.037

(Standard Deviation, n=3)

### Physical Characterization of Tablets

**Visual Inspection:** There is no sticking or picking on the compressed tablets. The punches were crisp, and the tablet logos were visible.

**Evaluation of Mucoadhesive Buccal Tablets of Itraconazole:** The mucoadhesive buccal tablets of Itraconazole were formulated using direct compression method. All the



formulations evaluated for the important parameters such as Diameter, Thickness, Hardness, Friability, Weight Variation, Drug Content, Surface pH etc. as indicated in Table 7 and 8 respectively.

Formulation	Diameter (mm)	Thickness (mm)	Hardness (kg/cm <sup>2</sup> )
<b>ITB1</b>	7.9±0.05	4.1±0.03	4.3±0.05
<b>ITB2</b>	8.1±0.04	4.0±0.04	4.1±0.04
<b>ITB3</b>	8.0±0.03	4.0±0.02	4.5±0.01
<b>ITB4</b>	8.3±0.05	3.6±0.01	4.0±0.02
<b>ITB5</b>	8.1±0.03	3.4±0.03	3.8±0.02
<b>ITB6</b>	8.2±0.04	3.4±0.02	4.2±0.05
<b>ITB7</b>	8.1±0.03	3.3±0.02	3.6±0.03
<b>ITB8</b>	8.1±0.03	3.1±0.01	3.7±0.04
<b>ITB9</b>	8.1±0.03	3.2±0.02	4.3±0.06

Formulation	Friability (%)	Weight Variation (mg)	Drug Content (%)	Surface pH
<b>ITB1</b>	0.53±0.005	203±1.00	96.37±0.02	6.95±0.006
<b>ITB2</b>	0.69±0.006	199±0.33	101.24±0.06	7.14±0.03
<b>ITB3</b>	0.59±0.004	201±0.57	100±0.04	7.20±0.05
<b>ITB4</b>	0.63±0.003	200±0.25	98.67±0.03	6.48±0.008
<b>ITB5</b>	0.72±0.003	206±1.15	99.45±0.01	6.83±0.02
<b>ITB6</b>	0.49±0.004	204±0.93	102.31±0.07	6.25±0.01
<b>ITB7</b>	0.75±0.005	198±0.22	99.21±0.04	6.85±0.05
<b>ITB8</b>	0.66±0.006	200±0.31	97.98±0.04	7.10±0.08
<b>ITB9</b>	0.52±0.004	197±0.19	98.51±0.02	6.68±0.009

(Standard Deviation, n=3)

#### **Swelling Index and Matrix Erosion Study of Mucoadhesive Buccal Tablets:**

All the tablet formulations containing varying concentration of mucoadhesive and rate retardant polymers were stable throughout the period of swelling, without any disintegration being observed. The swelling index of all formulations was found to be more or less superimposable, due to the low invariance amongst their chosen polymer compositions. The swelling index profile of all formulation prepared as per the experimental design, is shown in Table 9 and Figure 1.

Table 9: Swelling and Matrix Erosion Study of Mucoadhesive Buccal Tablets of Itraconazole							
Formulation	% Swelling Index After Time (hr)						Matrix Erosion (%)
	2 hr	4 hr	6 hr	8 hr	10 hr	12 hr	
ITB1	17	26	38	52	57	69	26±0.02
ITB2	18	27	40	56	62	71	28±0.01
ITB3	19	39	51	68	83	100	30±0.05
ITB4	20	45	64	75	89	101	29±0.03
ITB5	11	16	22	31	37	50	31±0.06
ITB6	17	40	59	77	90	104	26±0.04
ITB7	18	36	53	72	91	103	29±0.02
ITB8	20	35	56	78	95	107	28±0.05
ITB9	21	43	64	82	101	110	32±0.07

(Standard Deviation, n=3)

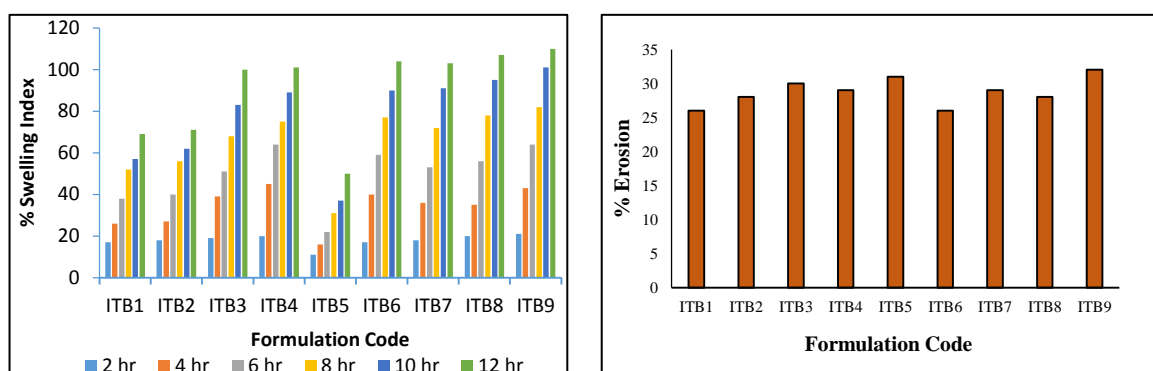


Figure 1: % Swelling Index and Matrix Erosion of Mucoadhesive Buccal Tablets

### Study of Bioadhesive Strength, Ex vivo Mucoadhesion Time and Detachment Force Measurement of Mucoadhesive Buccal Tablets of Itraconazole:

The result bioadhesive properties of tablet were shown in Table 10. As the concentration of polymer in the formulation increase, the mucoadhesive strength of tablets was increases. The strength of tablet was dependent on the property of mucoadhesive polymers, which adheres to the mucosal surface and also on the concentration of polymer used. The polymers in the maximum concentration were necessary to achieve maximum duration of bioadhesion. The decrease in the polymer concentration resulted in decrease in bioadhesive time. Chitosan is the most widely used mucoadhesive polymer in the pharmaceutical industry, in various dosage forms such as transdermal bioadhesive patches, tablets, capsules, fast disintegrating films, and mucoadhesive films. Thus, chitosan was used chosen in this study for imparting

mucoadhesive property to the tablets. The data obtained indicated that mucoadhesion time was significantly increased by increases in the concentration of chitosan.

Table 10: Study of Bioadhesive Properties of Mucoadhesive Buccal Tablets of Itraconazole				
Formulation	Bioadhesive Strength (gms)	Ex vivo Mucoadhesion Time (hr)	Water Required (ml)	Force of Adhesion (N)
ITB1	10.52±0.312	12.2±0.03	189.5	0.929
ITB2	9.45±0.092	12.3±0.01	203	0.995
ITB3	13.20±0.168	12.5±0.2	230	1.128
ITB4	12.43±0.543	11.3±0.02	212.5	1.042
ITB5	9.50±0.741	11.6±0.01	171	0.838
ITB6	9.82±0.221	12.2±0.01	183.5	0.900
ITB7	11.19±0.323	11.7±0.1	200	0.981
ITB8	10.65±0.441	12.2±0.01	209	1.025
ITB9	10.28±0.234	11.1±0.23	197	0.899

(Standard Deviation, n=3)

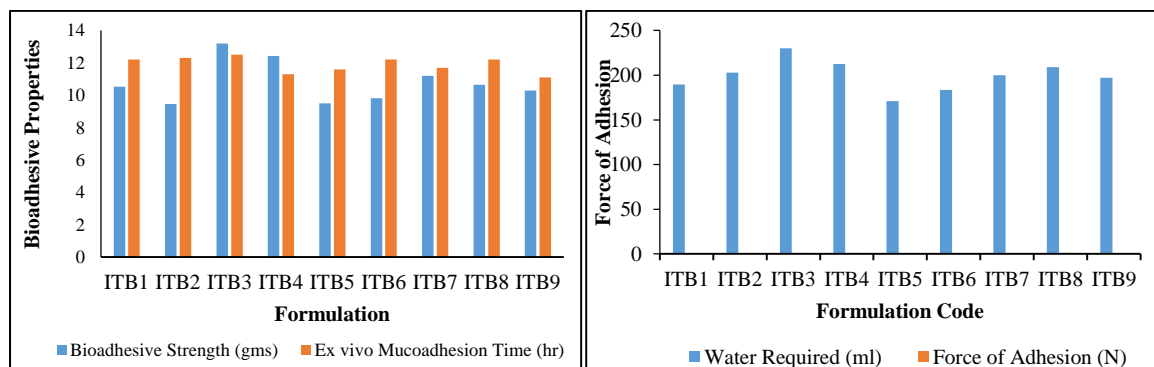


Figure 2: Detachment Force Measurement of Mucoadhesive Buccal Tablets of Itraconazole

**In Vitro Dissolution Study of Mucoadhesive Buccal Tablets of Itraconazole:** The tablets belonging to the all nine formulations (ITB1 - ITB9) were examined, showed a sustain release pattern of drug release up to 12 hrs as given in Table 11. The results showed that as the concentration of polymer present within the formulation increased, the amount of drug released was retarded, showed that formulation ITB1, ITB5, ITB6 and ITB7 showed the drug release upto 90 % in 12 hrs. Which contains rate retardant polymer HPMC, guar gum and Xanthan gum. The overall rate of drug release upto 12 hrs. using mucoadhesive HPMC and rate retardant polymer. The formulation ITB2, ITB3, ITB8 and ITB9 showed maximum drug released 93, 96, 91 and 91% drug release respectively up to 12 hrs. The comparison of the mechanism of drug release from swellable matrices could be determined by several physicochemical phenomenon. In the case of HPMC K15M, guar gum and xanthan gum which is also a hydrophilic swellable polymer, a retarded drug release pattern was observed. As a result, drug release was found to be decreased as the concentration of hydrophilic

polymer was increased. Chitosan and HPMC had a combined effect on ITZ drug release from the mucoadhesive tablets. The release data revealed a significant and inverse relationship between chitosan and HPMC concentrations, and drug release from the tablets. Thus proved the sustained-release property of both chitosan and HPMC.

<b>Time (Hrs)</b>	<b>Formulation Code</b>								
	<b>ITB1</b>	<b>ITB2</b>	<b>ITB3</b>	<b>ITB4</b>	<b>ITB5</b>	<b>ITB6</b>	<b>ITB7</b>	<b>ITB8</b>	<b>ITB9</b>
1	8	9	7	12	5	8	7	8	12
2	17	18	17	18	12	15	14	16	24
3	29	30	29	25	24	21	25	26	35
4	44	42	40	35	36	28	37	40	50
5	56	55	53	42	50	34	52	52	61
6	65	64	62	50	61	46	61	63	70
7	74	72	71	59	71	56	70	70	75
8	80	76	78	65	75	64	74	75	80
9	85	82	83	72	81	70	80	80	86
10	89	88	88	79	86	76	85	85	90
11	90	92	91	83	88	84	87	86	91
12	90	93	96	86	90	90	89	91	91

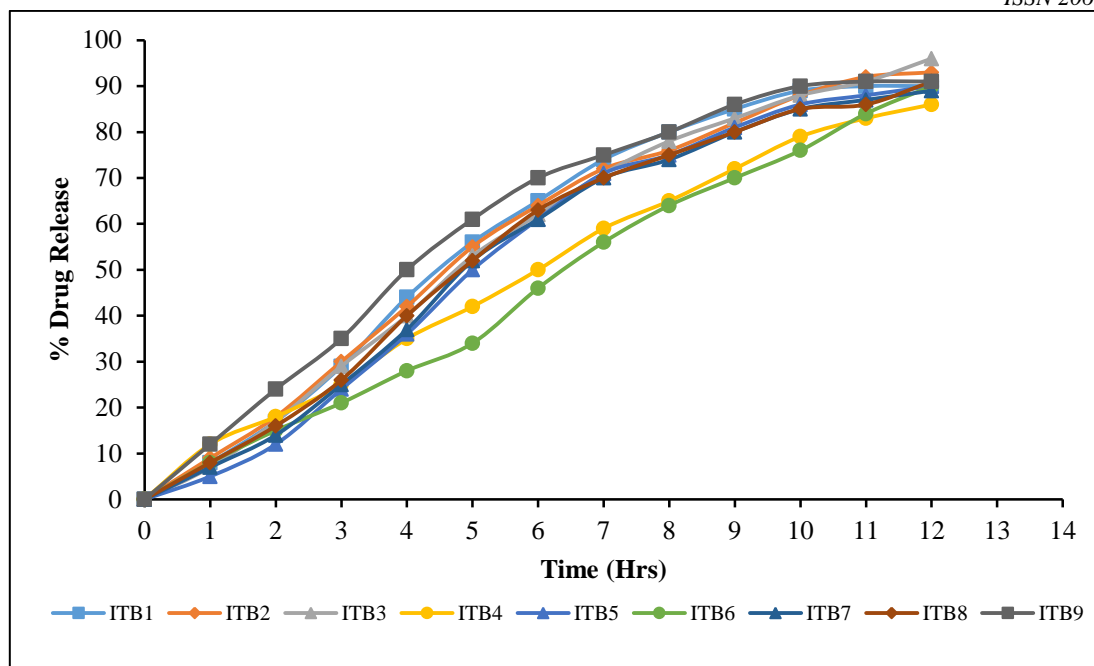


Figure 3: Drug Release Study of Mucoadhesive Buccal Tablets of Itraconazole

**Drug Release Kinetics of Optimized Formulation:** In case of most of the formulations the  $R^2$  values were higher for Zero order model than for First order model indicating that the drug release from the formulation followed Zero order kinetics. Higuchi model, indicating that the drug release mechanism from the tablets was diffusion controlled. Obtained values of  $n$  lies between 0.5 - 1.0 indicating Non-Fickian release kinetics, which is indicative of drug release mechanisms involving, diffusion mechanisms. Therefore, the release of drug from the prepared tablets is controlled by swelling of the polymers, followed by drug diffusion through the swelled polymer.

Table 12: Drug Release Kinetics of Optimized Formulation ITB3				
Formulation Code	Zero Order	First Order	Higuchi	Korsmeyer - Peppas
ITB3	$R^2$	$R^2$	$R^2$	$R^2$
	0.9702	0.9489	0.945	0.8513

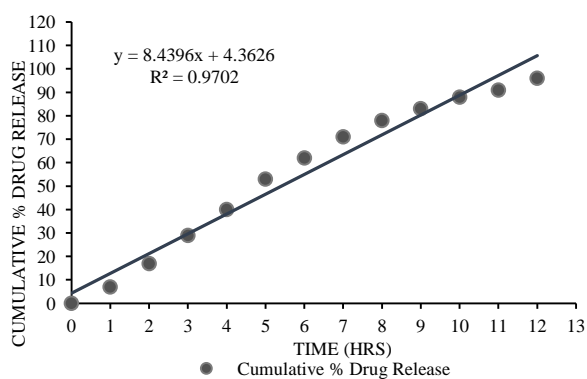
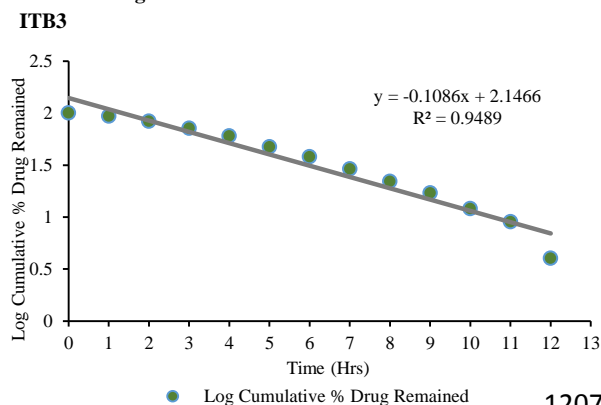


Figure 4: Zero Order Kinetic Plot for Formulation ITB3



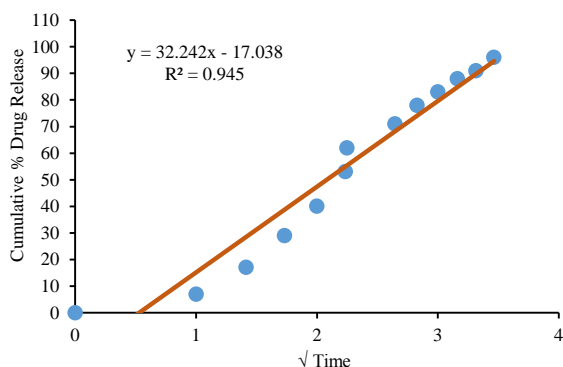


Figure 6: Higuchi Kinetic Plot for Formulation ITB3

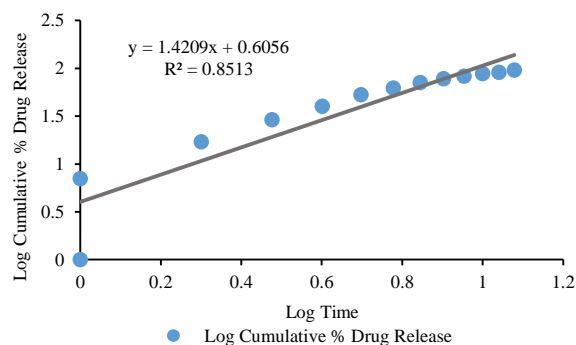


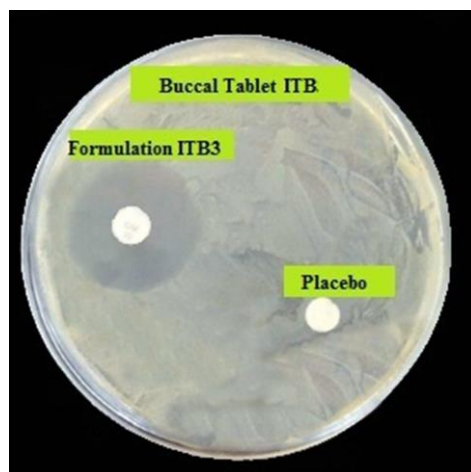
Figure 7: Korsmeyer - Peppas Kinetic Plot for Formulation ITB3

**Stability Study of Optimized Formulation:** All the Mucoadhesive Buccal Tablets of Itraconazole were screened for accelerated stability studies and showed slight physical changes during the study period. The drug content was observed (n=3) for all the Mucoadhesive Buccal Tablets (Table 13) which was quite stable at accelerated storage conditions. The stability of Mucoadhesive Buccal Tablets were proved by determining the percentage content under the above said accelerated storage condition. Values of all parameter slightly changes indicated that all the Mucoadhesive Buccal Tablets were stable without any alteration on the physical characters.

<b>Table 13: Accelerated Stability Study of Optimized Formulation ITB3</b>			
<b>Evaluation Parameter</b>	<b>Before Stability Storage</b>	<b>After 3 Months Storage</b>	<b>After 6 Months Storage</b>
<b>Hardness (Kg/cm<sup>2</sup>)</b>	4.5±0.1	4.4±0.1	4.4±0.2
<b>Friability (%)</b>	0.59±0.004	0.61±0.013	0.65±0.018
<b>Weight Variation</b>	201±0.057	200±0.063	200±0.084
<b>Drug Content (%)</b>	100±0.04	99±0.07	98±0.06
<b>Surface pH</b>	7.20±0.05	7.20±0.07	7.15±0.03
<b>Swelling Index (%)</b>	100	98	97
<b>Matrix Erosion (%)</b>	30±0.05	29±0.06	29±0.09
<b>Bioadhesive Strength (gms)</b>	13.20±0.168	12.92±0.172	12.70±0.213
<b>Ex vivo Mucoadhesion Time (hr)</b>	12.5±0.2	12±0.4	11.3±0.3
<b>Water Required</b>	230	220	215
<b>Force of Adhesion</b>	1.1258	1.120	1.095
<b>In vitro Drug Release (%)</b>	96	95.50	94.28

**Antifungal Study of Optimized Formulation:** The antifungal activity of the optimized formulation ITB3 of mucoadhesive buccal tablet of itraconazole was determined using agar-cup diffusion method. Table 14 and Figure 8 show the zone of inhibition diameter obtained. The optimized formulation ITB3 tested, showed activity against *C. albicans*. Also, the placebo tablet was subjected to the same conditions to detect any activity of the used polymers. The control placebo tablet showed no zone of inhibition.

Sr. No.	Zone of Inhibition (mm)	Mean
1	27	28
2	29	
3	28	



**Figure 8: Inhibition Zone of Mucoadhesive Buccal Tablet of ITZ**

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