EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 8
Issue: 8
418-430
Year: 2021

FORMULATION AND EVALUATION OF ITRACONAZOLE MUCOADHESIVE TABLETS

Addanki Anusha*, Asma Begum, D. lingamurthi and G. Sowjanya and B. Jhansi

Assistant Professor, Malla Reddy Institute of Pharmaceutical sciences, Maissamaguda, Hyderabad, Telangana, 500014.

***Corresponding Author: Addanki Anusha**
Assistant Professor, Malla Reddy Institute of Pharmaceutical sciences, Maissamaguda, Hyderabad, Telangana, 500014.

Article Received on 12/06/2021 **Article Revised on 02/07/2021** **Article Accepted on 22/07/2021**

ABSTRACT
Bioadhesive buccal delivery of drugs is most beneficial especially for drugs that experience first pass effect. Administration of the medication via the buccal route will overcome problems such as drug degradation in the harsh gastrointestinal environment, parenteral administration inconvenience. Production of Itraconazole tablets for the delivery of bioadhesive buccal drugs is one of the alternative routes of administration to prevent first-pass effect and provide sustained release. Itraconazole experiences first-pass liver metabolism. This is the reason Itraconazole has lower bioavailability. This molecule meets general considerations about the distribution of buccal drugs. Therefore, it is selected as a drug candidate for the delivery of bioadhesive buccal drugs. A mixture of carbopol 934 and 1:1 ratio hydroxyl propyl cellulose is with complementary physical properties. From the tests, it was concluded that drug release in vitro, resistance to bioadhesion, ex vivo residence time of optimized formulation is suitable for buccal delivery. The pattern of release preceded non-fickian diffusion with release of first volume.

KEYWORDS: Itraconazole, Mucoadhesive, Buccal, Carbopol.

INTRODUCTION
Mucoadhesive drug delivery methods make use of the bioadhesion of certain polymers, which become adhesive when hydrated and can thus be utilised to target a medicine to a specific area of the body for longer period of time. Bioadhesion is an interfacial phenomenon in which two materials are held together by interfacial forces, at least one of which is biological. Adhesion between a polymer and a biological membrane is an example of an artificial material adhering to a biological substrate. The word "mucoadhesion" is used to describe the attachment of a polymer to the mucin layer of a mucosal tissue.[1] Various mucoadhesive polymers can be utilised to achieve the necessary mucoadhesive strength in mucoadhesive dosage forms. As a result, polymers are macromolecules that can adhere to mucosal surfaces, whether they are natural or synthetic. The utilisation of various mucoadhesive polymers has piqued attention in the field of pharmaceutical technology for the past three decades. These days, the usage of mucoadhesive polymers has been recognised as an important method for extending the residence time and improving the localised effect of drug delivery systems on a biological system's different mucus membranes.[2,3] The mucosal layer lines a number of regions of the body including the gastro-intestinal tract, the urogenital tract, the airways, the ear, the nose and the eyes. these represent the potential sites for attachment of any bioadhesive systems and hence, the mucoadhesive drug delivery system includes the Ocular, nasal, buccal, oral and vaginal drug delivery system.[4] The term "mucoadhesive" refers to an artificial substance that can interact with mucus membranes and stick to them or hold them together for a lengthy period of time. In general, two steps have been recognised during the adhesion process, include stages like contact stage and consolidation stage.[5,6] Mucoadhesive system offers many advantages such as it provides a relatively rapid onset of action, can be easily used in case of unconscious and less co-operative patients.[7] One of the major limitations in the development of oral mucosal delivery is the lack of a good model for in vitro screening to identify drugs suitable for such administration. Various polymers are used in the formulation of mucoadhesive drug delivery system.[8] Now a days this mucoadhesive drug preparation have been used significantly.[9,10]

1. MATERIALS AND METHODS
All the chemicals and materials used in the present investigation were Analytical Reagent (AR) & Laboratory Reagent (LR) grade available in the laboratory and supplied by the manufacturer. The details are given below.

Table 1: List of Materials Used.

S. No.	Material	Manufacturer
1	Itraconazole	Zydus Cadila, Ahmedabad, India.
2	Carbopol 934 P	Zydus Cadila, Ahmedabad, India.
3	Hydroxy propyl methyl cellulose K15 M	AET laboratories, Hyderabad, India.
4	Hydroxy propyl methyl cellulose K4M	AET laboratories, Hyderabad, India.
5	Hydroxy propyl cellulose	AET laboratories, Hyderabad, India.
6	Ethyl cellulose	Vilin Biomed Ltd, Roorkee, India.
7	Mannitol	Vilin Biomed Ltd, Roorkee, India.
8	Spray dried lactose	Dr Reddy's laboratories, Hyderabad, India.
9	Microcrystalline cellulose	Viilin Biomed Ltd, Roorkee, India.
10	Sodium saccharine	Moly Chem, Mumbai, India.
11	Aspartame	Dr Reddy's laboratories, Hyderabad, India.
12	Magnesium stearate	Vilin Biomed Ltd, Roorkee, India.

1.1 Experimental Methods

1.1.1 Preparation of phosphate buffer pH 6.6: Weigh accurately and dissolve 10.716 g of Disodium hydrogen phosphate heptahydrate and 8.26 g of Sodium dihydrogen phosphate monohydrate in distilled water to produce 1000 ml.

1.1.2 Preparation of phosphate buffer pH 7.4: Weigh accurately and dissolve 20.214 g of Disodium hydrogen phosphate heptahydrate and 3.394 g of Sodium dihydrogen phosphate monohydrate in distilled water to produce 1000 ml.

1.1.3 Preparation of standard graph of Itraconozole in phosphate buffer pH 6.6: 100 mg of Itraconazole was dissolved in a volumetric flask containing 100 mL of phosphate buffer pH 6.6 (1000mcg/ml) stock solution. 1 mL of that primary stock was moved to another volumetric flask containing up to 100 mL of phosphate buffer pH 6.6 (100mcg/ml); 0.2, 0.4, 0.6, 0.8, 1 and 1.2 of that secondary stock was taken separately and produced up to 10 mL of phosphate buffer pH 6.6 to produce 2, 4, 6, 8, 10 and 12 mcg / mL respectively; Using a UV spectrophotometer the absorbance was measured at 262 nm.

1.1.4 Preparation of standard graph of Itraconozole in phosphate buffer pH 7.4: 100 mg of Itraconazole was dissolved in a volumetric flask containing 100 mL of phosphate buffer pH 7.4 (1000mcg/ml) stock solution; 1 ml of that primary stock was moved to another volumetric flask containing up to 100 mL of phosphate buffer pH 7.4 (100mcg/ml); 0.2, 0.4, 0.6, 0.8, 1 and 1.2 of that secondary stock was taken separately and produced up to 10 mL of phosphate buffer pH 7.4 to produce 2, 4, 6, 8, 10 and 12 mcg / mL respectively. Using a UV spectrophotometer, the absorbance was measured at 262 nm.

1.1.5 Preparation of standard graph of Itraconozole in methanol: 100 mg of Itraconazole was dissolved in a volumetric flask containing 100 mL of methanol, from that primary stock 1 mL was transferred to another volumetric flask containing up to 100 mL of methanol, from that secondary stock 0.2, 0.4, 0.6, 0.8, 1 and 1.2 mL was taken separately to produce 2, 4, 6, 8, 10 and 12 mcg/ml of methanol, respectively. Using a UV spectrophotometer, the absorbance was measured at 262 nm.

1.1.6 The analysis of solubility: Phase equilibrium approach determined the solubility of Itraconazole in phosphate buffer solution pH 6.6 and pH 7.4. In 50ml Conical Flasks containing 20 mL of phosphate buffers (pH 6.6 and pH 7.4), an excess of medication was taken in. Conical flasks were capped with aluminium foil and continuously agitated with rotary shaker at room temperature for 24 hrs.

1.1.7 FTIR Studies: In the present study, the potassium bromide disc (pellet) method was employed. Fourier Transform Infrared (FTIR) spectra of the Drug and polymer were obtained on Alpha Brooker FTIR (Tokyo, Japan). The spectra were scanned over the wave number range of 4000- 400cm-1.

2. Formulation Development: Bilayered buccal tablets were prepared using a direct compression process, all ingredients were screened via sieve no.100 before going to direct compression, except lubricant lubricant all ingredients were thoroughly blended in a glass mortar with pestle for 15 min. After applying adequate mixing lubricant and mixing it again for 2-3 min more. Preparation involves two stages.

First, the mixture is compressed on a 16-stage rotary tablet compressing machine using 8 mm flat-faced punch. Then the upper punch is raised and the ethyl cellulose backing layer is put on top compact, then two layers are compressed again to obtain bilayered buccal tablet.

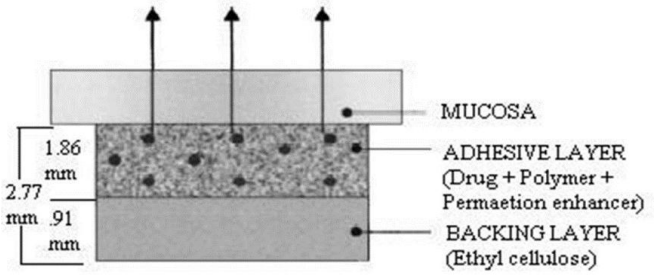

Figure 1: Schematic diagram of bioadhesive buccal tablet.

Table 2: Formulation table with composition.

Ingredients	Formulation Code											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Itraconazole	100	100	100	100	100	100	100	100	100	100	100	100
HPMC K15	50	-	-	20	30	25	-	-	-	20	30	25
Carbopol	-	50	-	30	20	25	20	30	25	-	-	-
HPMC K4M	-	-	50	-	-	-	30	20	25	30	20	25
Mannitol	20	20	20	20	20	20	20	20	20	20	20	20
Menthol	2	2	2	2	2	2	2	2	2	2	2	2
Sodium Saccharine	5	5	5	5	5	5	5	5	5	5	5	5
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Mg. Stearate	1	1	1	1	1	1	1	1	1	1	1	1
Total weight(mg)	180	180	180	180	180	180	180	180	180	180	180	180

3. An examination of the buccal tablets

3.1 Endurance: Digital micrometre was used to determine the thickness of the buccal tablets. Ten individual tablets were used from each batch, and the tests were summed.

3.2 Check for Weight Variation: For 20 tablets from each sample, weight variation was performed using an electronic balance, and average values were determined.

3.3 Hardness: Hardness was performed using Monsanto hardness tester for 3 tablets from each sample, and average values were determined.

3.4 Assay: Ten tablets were weighed and grounded in a mortar and pestle to obtain fine powder; powder equal to one tablet mass was dissolved for 30 minutes in methanol by sonication, and filtered via filter paper. Using a UV spectrophotometer, the drug content was measured spectrophotometrically at 262 nm.

3.5 Disintegration test: The test was conducted for non-backing buccal tablets; six tablets were randomly taken from each batch and placed in baskets of USP disintegration apparatus. The appliance was working for 4 hours and the bucket was removed from the fluid to see if all the tablets had disintegrated.

3.6 Bio adhesion strength assessment: The bioadhesive strength of the tablets was calculated on a modified physical balance. The system consisted of a modified double beam physical balance in which a lighter panel replaced the right panel and the left panel was replaced by a glass slide (4 cm long and 2.5 cm wide) with a plastic hanging suspended from Teflon rings and copper wire. The balance's left side was precisely 5 g heavier than the right side. The overall set-up height was changed to fit a 6.6 cm height glass jar. First buccal tablet (n=3) was attached to the glass slide with the aid of knob, which was located at the physical balance base, in order to find out the bioadhesion power. Then remove five grams of weight from the right pan. This lowered the glass slide over the membrane along with the tablet at a weight of 5.0 g. It remained unchanged for 5 min. Weights were gradually applied in increments of 0.1 g at right-hand side until the tablet just separated from the surface of the membrane. The excess weight was taken as a measure of the bioadhesive strength on the right plate, i.e. total weight minus 5g.

3.7 Determining the ex vivo time of residence: The ex vivo residence time was calculated using a locally adapted USP disintegration system, the disintegration medium consisted of 800 mL pH 6.6 phosphate buffer maintained at 37C. The porcine buccal tissue was glued to the surface of a glass slab, fastened vertically to the frame. Using 0.5 mL of pH 6.6 phosphate buffer, the buccal tablet was hydrated from one surface and then the hydrated surface was placed in contact with the mucosal membrane. The glass slab was attached vertically to the device and allowed to operate in such a way that at the lowest point the tablet was fully submerged in the buffer solution and at the highest point was out. The time required to completely detach the tablet from the mucosal surface was reported. The experiments were conducted in triplicate (n=3), and the triplicate mean was determined.

3.8 Studies on Swelling: Buccal tablets were individually weighed (designated as W1) and placed separately in Petri dishes containing a 15 mL phosphate

buffer solution (pH 6.6). The buccal tablets were removed from the Petri dishes at regular intervals (1, 2, 3, 4, 5, 6, 7 and 8 hr), and excess surface water was carefully collected using the filter paper. Then swollen tablets (W2) are reweighed. The triplicate experiment was conducted. The index of swelling (water uptake) measured according to the equation. **Swelling index= $(W_2-W_1)/W_1$.**

3.9 Surface pH Study: The bioadhesive tablet had been allowed to swell by holding it in contact at room temperature with 1 mL of distilled water for 2 hours. The pH was determined by bringing the electrode of the pH-meter into contact with the tablet surface and allowing it to stabilize for 1 min.

3.10 In vitro drug release studies: The revolving paddle system of the United States Pharmacopeia (USP) XXIII was used for testing drug release from the buccal tablets. The dissolution medium consisted of a phosphate buffer pH 6.6 of 200 ml. The study was carried out at 37°C ± 0.5°C, with 50 rpm of rotational speed. The buccal tablet backing layer was placed on the glass slide with instant adhesive (cyanoacrylate adhesive). The slide was mounted in the dissolution vessel's bottom. Samples (5ml) were collected at fixed periods of time and replaced with fresh media. The dissolution was carried out without glass slide for the traditional marketed drug. The samples were filtered onto filter paper and analysed at 262 nm after sufficient UV spectrophotometer dilution.

3.11 Permeation ex vivo of the buccal tablets: Using Franz diffusion cell at 37°C ± 0.2°C and 50 rpm, ex vivo permeation analysis of buccal tablets through the porcine buccal mucosa was performed. From a nearby slaughterhouse porcine buccal mucosa was received and was used within 2 hours of slaughter. After selection the tissue was placed in Krebs buffer at 4°C. The epithelium was removed from the underlying connective tissues with surgical scissors, and clamped between the Franz-type diffusion cell donor and receiver chambers. The receiver chamber was filled with fresh pH 7.4 buffer solution after balancing the buccal membrane for 30 min with Krebs buffer solution between the two chambers. The buccal tablet was put in donor chamber and added 1mL of buffer solution (pH 6.6). Aliquots (5 mL) were collected at predetermined time intervals and filtered via a filter paper, and the amount of drug permeated by the buccal mucosa was then calculated using a UV spectrophotometer to calculate the absorbance at 262 nm. The medium of the same amount (5 mL) was then substituted into the receiver chamber, which was prewarmed at 37°C.

Due to the low formulation permeability of the medication, permeation enhancer (Sodium taurocholate) was applied to the optimized formulation to improve the permeability. The flux enhancement ratio was determined by dividing the cumulative amount permeated with Itraconazole by the amount of Itraconazole alone (Q control) in the presence of sodium taurocholate (Qenh).

Enhancement ratio$_{flux}$= Q_{enh}/Q_{con}

3.12 Kinetic Studies

A. Zero Order Release Equation: The equation for zero order release is **Qt = Qo+ Kot**

Where, Qo= Initial amount of drug, Qt= Cumulative amount of drug release at time "t" Ko= Zero order release constant, t = Time in hours

It describes the systems where the drug release rate is independent of its concentration of the dissolved substance. A graph is plotted between the time taken on x-axis and the cumulative percentage of drug release on y-axis and it gives a straight line.

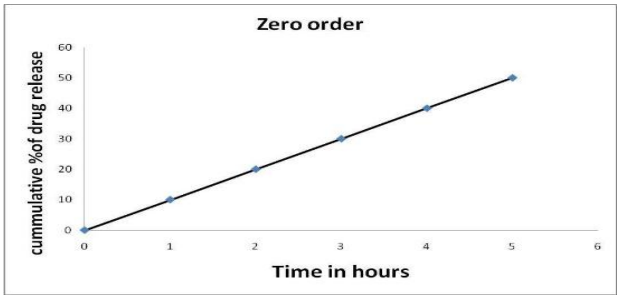

Figure 2: Zero Order Kinetics Graph.

- **First Order Release Equation:** The first order release equation is

Log Q_t = Log Q_0 + Kt /2.303

Where, Q_o = Initial amount of drug, Qt = Cumulative amount of drug release at time "t", K = First order release constant, t = Time in hours

Here, the drug release rate depends on its concentration. A graph is plotted between the time taken on x-axis and the log cumulative percentage of drug remaining to be released on y-axis and it gives a straight line.

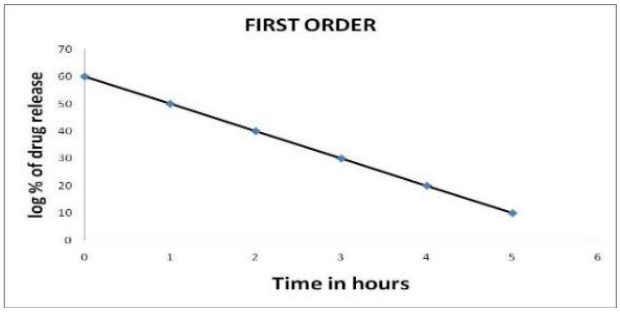

Figure 3: First Order Kinetics Graph.

4. RESULTS AND DISCUSSION

The details of results and discussion of analytical method, formulation methods and evaluation techniques were given in the following sections.

4.1 ANALYTICAL METHOD

Suitable analytical methods were developed for the drug using UV spectrophotometer in phosphate buffer pH 6.6. The wavelength maxima of absorption was found to be 262 nm. Itraconazole obeyed the Beer's-Lambert's Law in the concentration range of 2-12µg/ml (Figure 4) at this wavelength. This is well correlated with the reported value (262 nm). And all the further estimations were done at 262 nm.

Standard graph of Itraconazole was plotted as per the procedure in experimental methods. The standard graph of Itraconazole showed good linearity with R^2 of 0.993, 0.997 and 0.996 in different medium i.e., phosphate buffer pH 6.6, 7.4 and methanol which indicates that it obeys "Beer- Lamberts" law.

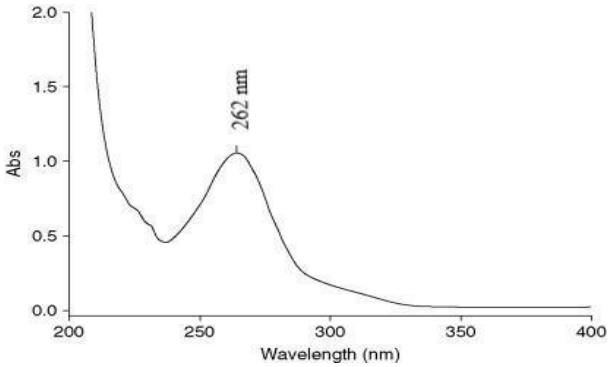

Figure 4: UV spectrum of Itraconozole in phosphate buffer pH 6.6.

Table 3: Data for standard plot of Itraconozole in phosphate buffer pH 6.6.

S. No.	Concentration (µg/ml)	Absorbance (nm)
1	2	0.240
2	4	0.377
3	6	0.505
4	8	0.656
5	10	0.789
6	12	0.945

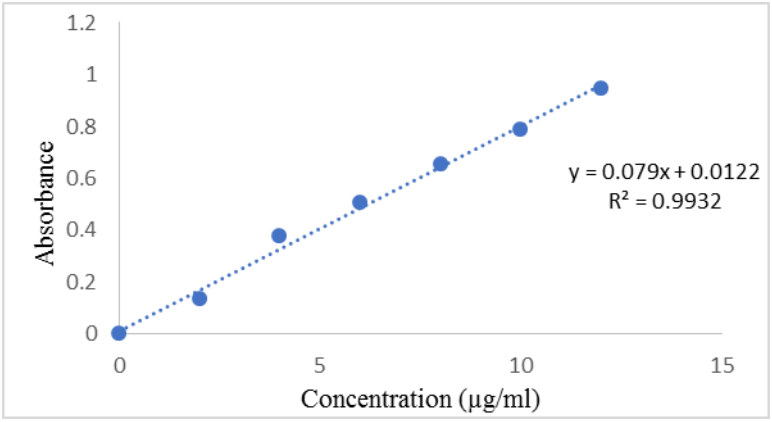

Figure 5: Itraconazole standard plot in Phosphate buffer pH 6.6.

Table 4: Data for standard plot of Itraconozole in phosphate buffer pH 7.4.

S.No.	Concentration (µg/ml)	Absorbance (nm)
1	2	0.198
2	4	0.354
3	6	0.487
4	8	0.645
5	10	0.796
6	12	0.925

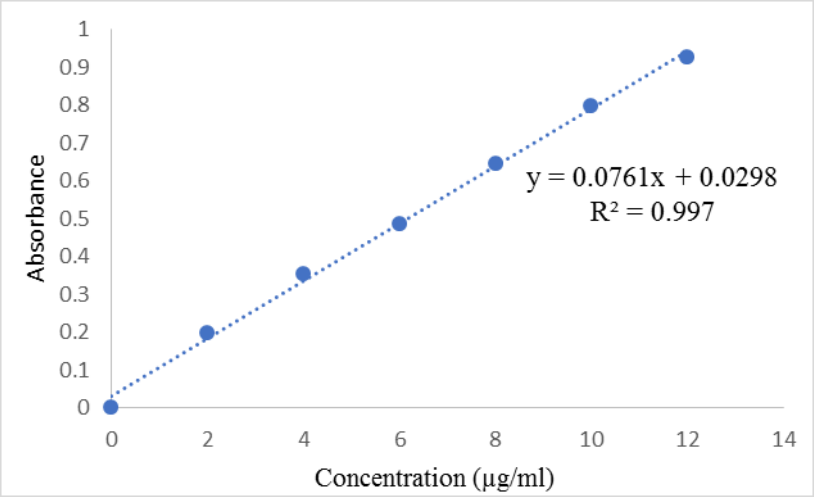

Figure 6: Itraconazole Standard plot in Phosphate Buffer pH 7.4

Table 5: Data for standard plot of Itraconozole in Methanol.

S.No.	Concentration (µg/ml)	Absorbance (nm)
1	2	0.164
2	4	0.307
3	6	0.473
4	8	0.597
5	10	0.726
6	12	0.934

Figure 6: Itraconazole Standard plot in Phosphate Buffer pH 7.4.

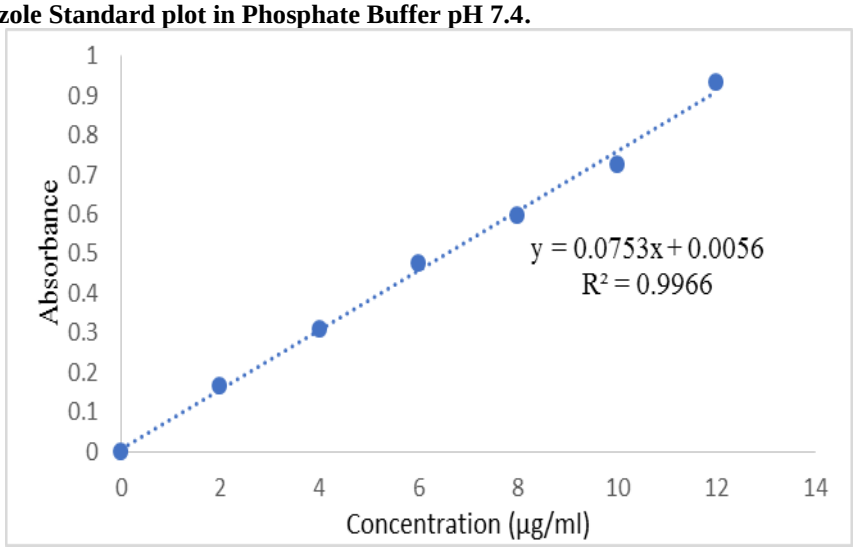

Figure 7: Itraconazole Standard plot in Methanol.

4.2 PREFORMULATION

4.2.1 API CHARACTERIZATION

4.2.1.1 Organoleptic properties

Table 6: Results of Organoleptic Properties.

S. NO	PARAMETER	OBSERVATION
1.	Colour	Off white-White
2.	Odour	Cherry
3.	Appearance	Crystalline solid

4.2.1.2 FTIR analysis spectra of Itraconozole pure drug

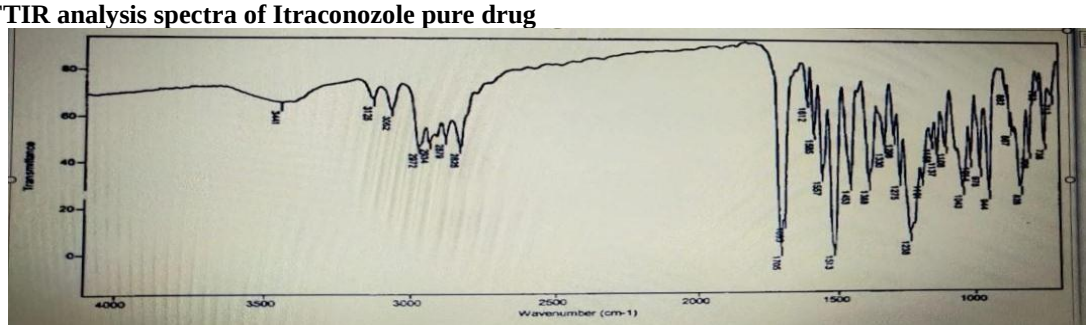

Figure 8: FTIR spectra of Itraconazole pure drug.

The FTIR spectrum showed the characteristic peaks of itraconazole which occurred at 3128, 3062, 2972, 2828, 1513, 1453 cm−1. The absorption bands between 2800 and 3200 cm-1 was attributed to the alkane, aromatic CH and amine groups. The wave numbers observed at 1609 and 1425 may be assigned to the C=N and C-N bonds, respectively and the sharp peak occurred at 1699 is due to C=O of the drug. The IR region from 1400 to 600 cm-[1]. Which is termed the fingerprint region, usually contains large number of unassigned vibrations.

4.2.1.3 Solubility Analysis: The solubility analysis was performed in phosphate buffers of pH 6.6 and pH 7.4 as these are mean pH values of oral cavity and blood respectively. Itraconazole solubility was found to be 10±2,85 mg / mL, 5.9±3.23 mg / mL respectively, at pH 6.6 and pH 7.4.

4.3 Post Compression Parameters

Table 7: Data for Post-Compression Studies.

Formulation Code	Thickness (mm)	Weight Variation(mg)	Friability (%)	Hardness (Kg/cm^2)	%Drug content
F1	2.43±0.010	142.6±0.20	0.09	4.3±0.13	99.74
F2	2.26±0.020	146±0.24	0.17	4.8±0.33	101.17
F3	2.73±0.035	151.9±0.15	0.08	4.3±0.13	99.69
F4	2.64±0.010	155.2±0.70	0.07	4.6±0.10	99.04
F5	2.64±0.040	149±0.50	0.24	4.6±0.10	99.58
F6	2.71±0.030	156.3±0.20	0.31	4.1±0.05	100.39
F7	2.70±0.010	159.9±0.25	0.42	4.5±0.05	99.57
F8	2.64±0.030	157.3±0.60	0.08	4.7±0.05	99.07
F9	2.71±0.042	147.9±0.50	0.08	3.9±0.09	99.40
F10	2.38±0.057	152.9±0.48	0.42	4.9±0.15	99.37
F11	2.56±0.023	154.4±0.20	0.08	4.7±0.21	99.38
F12	2.55±0.010	153.1±0.47	0.46	3.6±0.10	101.03

The weight variation and friability values were found to be within the limits specified in the Indian Pharmacopoeia for traditional oral tablets (IP, 1996). Within 4 hours, no tablet was disintegrated. The tablet thickness ranged from 2.26 mm to 2.75 mm and reached the theoretical value (2.75 mm). Tablet hardness increased as the carbopol concentration grew and ranged from 3.8 Kg / cm2 to 4.9 Kg / cm2. The assay values were also 98.0 percent -102 percent within the limits.

4.4 Swelling Studies of buccal tablets

Table 8: Swelling Studies of buccal tablets.

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
s0	0	0	0	0	0	0	0	0	0	0	0	0
1	0.21	0.32	0.39	0.48	0.16	0.22	0.24	0.31	0.34	0.35	0.11	0.13
2	0.67	0.93	1.15	1.45	0.33	0.46	0.41	0.51	0.54	0.55	0.42	0.46
3	1.01	1.25	1.73	1.73	0.56	0.53	0.62	0.89	0.90	0.96	0.66	0.68
4	1.46	1.51	2.08	1.96	0.79	0.78	0.85	1.34	1.40	1.45	0.95	0.94
5	1.75	1.86	2.36	2.15	1.23	1.24	1.53	1.89	1.96	1.97	1.14	1.08
6	2.12	2.26	2.56	2.37	1.54	1.53	2.23	2.34	2.46	2.45	1.35	1.32
7	2.37	2.59	2.61	2.40	2.42	2.42	2.38	2.49	2.50	2.51	1.58	1.58
8	2.54	2.6	2.6	2.48	2.49	2.50	2.5	2.63	2.52	2.68	2.49	2.42

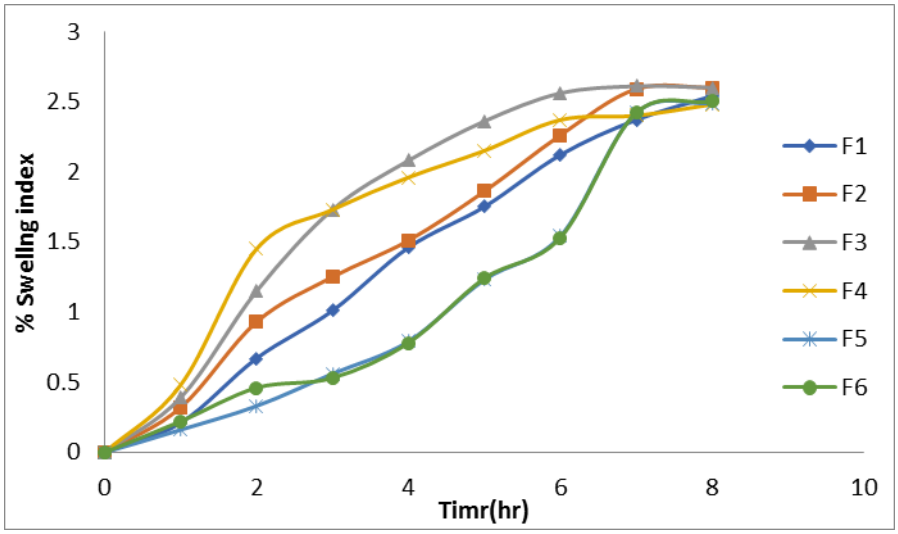

Figure 9: Swelling studies graphs of F1-F6.

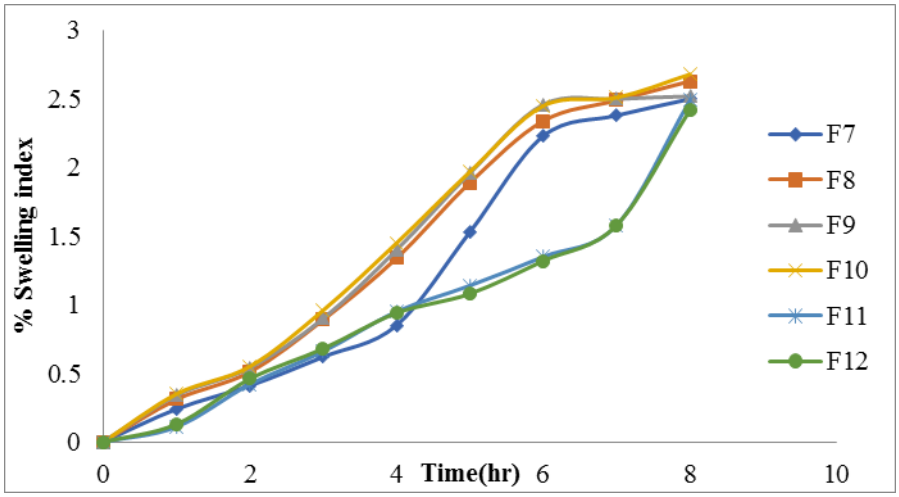

Figure 10: Swelling studies graphs of F7-F12.

Appropriate swelling property of a buccal system is important for uniform and sustained drug release and proper muco-adhesiveness. For both F1-F12 formulations the swelling index of 2.43-2.62 is shown; the optimized formulation (F7) shows 2.5. The swelling index is directly proportional to the content of carbopol, and inversely proportional to polymers of cellulose. High levels of carbopol water intake at a faster rate may have resulted in higher rate and degree of swelling due to its fluffy nature. Maximum swelling occurred in the 5th and 6th hours after which polymer began to erode in the swelling medium. Swelling index values were given in the table below for all formulations.

4.5 IN-VITRO DRUG RELEASE STUDY

Table 9: Data for in-vitro drug release formulations F1-F3.

Time (hr)	F1	F2	F3
0	0	0	0
1	46.8	40.24	38.49
2	81.92	68.52	62.76
4	98.9	82.9	84.60
6	-	99.78	97.84
8	-	-	-

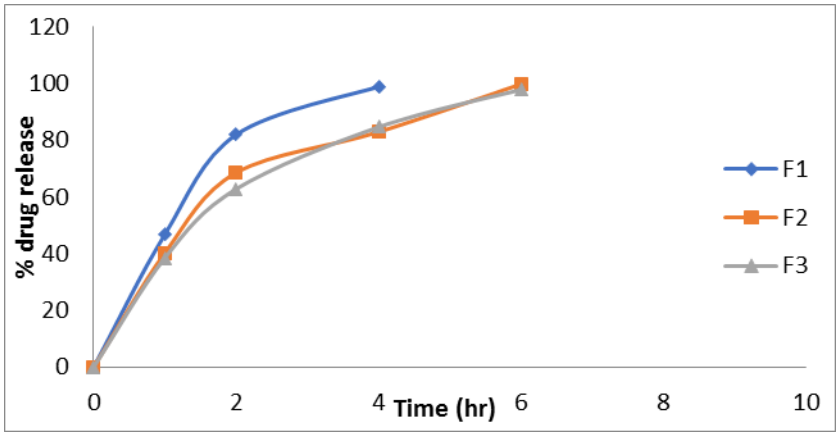

Figure. 11: In-vitro Drug Release Profile of Formulations F1, F2, F3.

Table 10: Data for in-vitro drug release formulations F4-F6.

Time (hr)	F4	F5	F6
0	0	0	0
1	36.4	41.2	34.23
2	74.21	78.6	68.92
4	86.76	90.4	84.54
6	97.9	-	92.08
8	-	-	94.8

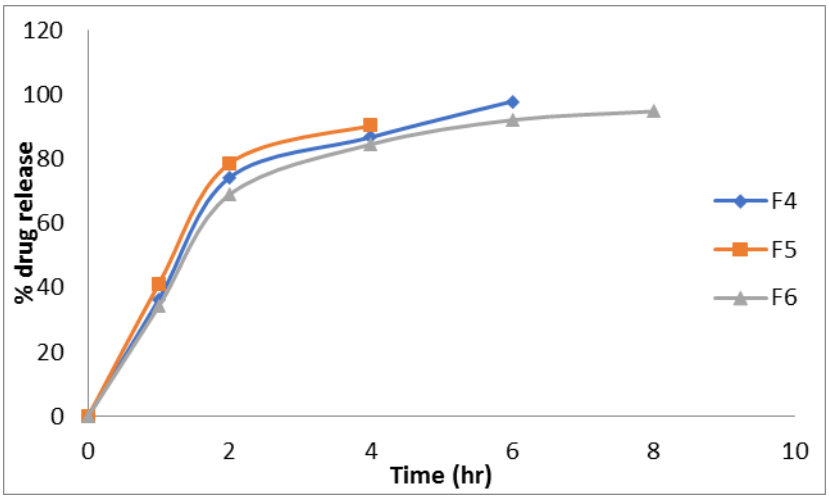

Figure 12: In-vitro Drug Release Profile of Formulations F4, F5, F6

Table 11: Data for in-vitro drug release formulations F7-F9.

Time (hr)	F7	F8	F9
0	0	0	0
1	24.56	28.21	26.5
2	51.2	53.4	54.5
4	76.8	78.9	76.28
6	86.4	90.72	88.7
8	94.3	96.5	98.72

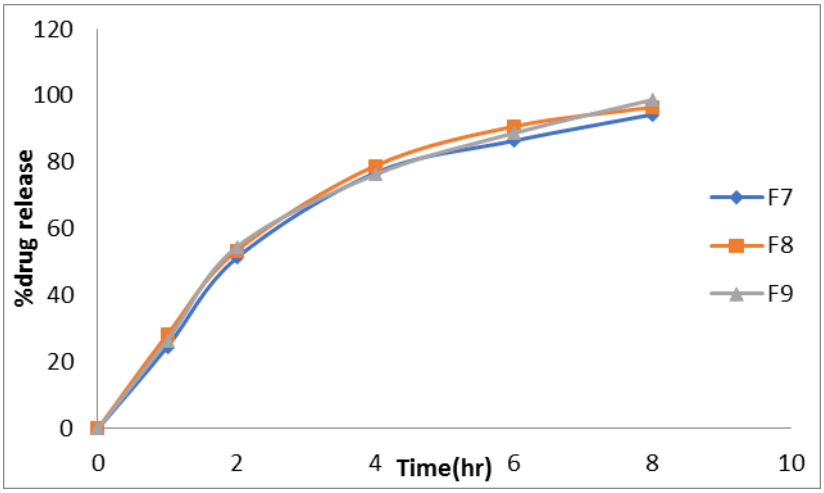

Figure 13: In-vitro Drug Release Profile of Formulations F7, F8, F9.

Table 12: Data for in-vitro drug release formulations F10-F12.

Time (hr)	F10	F11	F12
0	0	0	0
1	31.09	34.78	30.05
2	58.16	62.04	61.9
4	83.7	85.52	84.7
6	94.06	96.34	92.7
8	-	-	-

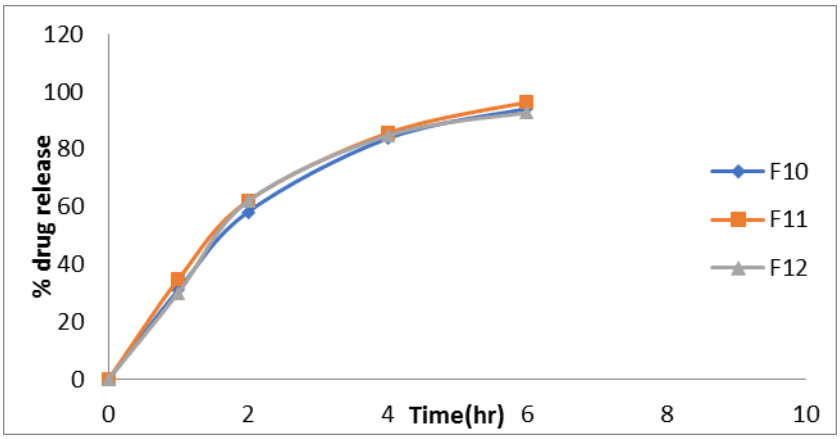

Figure 14: In-vitro Drug Release Profile of Formulations F10, F11, F12.

An optimal controlled release device would be able to release the medication rapidly to hit the level of treatment at a quicker pace and sustain the level of this medication for an prolonged period of time. Studies of in vitro drug release showed that the release of Itraconazole from different formulations varies with the characteristics and composition of polymers forming matrix, as shown in graphs. Itraconazole 's release rate decreased when paired with HPMC K15 M, HPMC K4 M, and Carbopol. Carbopol is more hydrophilic, can swell easily, and hence decrease in carbopol content delays the release of drugs. Drug release rate increased with hydrophilic polymer growing. Itraconazole F9 release of full cumulative percent found to release 98.72.

4.6 Period of life Ex vivo: Of all formulations the ex vivo residence time ranged from 3-11 hr. The optimized formulation (F9) showed 6.10±0.25 hr. The difference may be due to the combination of various polymer quantities that influence the mucoadhesion. In addition, the mucoadhesion time was found to be increased with bilayered tablets containing higher proportion of carbopol and HMPC K4 M combination. This is due to the high carbopol's mucoadhesive nature and the interpenetration of polymeric chains in the mucus membrane.

4.7 Bioadhesion strength assessment

Table 13: Data for assessment of bioadhesion strength.

Code	*Ex vivo* residence time	Moisture absorbance	Surface pH	Bioadhesive strength	
				Peak detachment force (N)	Work of adhesion (mJ)
F1	4Hrs 20 min	32.63	6.76	1.90	0.57
F2	5 Hrs 55 min	41.56	6.76	2.40	0.42
F3	4Hrs 59 min	21.45	5.95	1.55	0.51
F4	5 Hrs 36 min	11.51	7.5	1.84	0.29
F5	5 Hrs 10 min	19.61	6.86	2.29	0.55
F6	5 Hrs 15 min	22.85	7.3	2.30	0.47
F7	6Hrs 10 min	14.11	6.8	2.35	0.62
F8	6 Hrs 15 min	17.30	6.77	2.60	0.65
F9	**7Hrs 45 min**	**19.21**	**7.07**	**2.78**	**0.95**
F10	5Hrs 42 min	32.53	6.96	2.29	0.47
F11	5 Hrs 15 min	25.66	6.86	2.34	0.64
F12	5Hrs 45 min	32.45	6.9	2.05	0.52

This assessment test was performed for all formulations; Bioadhesive strength depends on the molecular weight and swelling behavior of the polymers, contact time with mucus. Bioadhesive properties were found to be influenced by the type and proportion of the bioadhesive polymers used. As the carbopol concentration increased the bioadhesive strength was also increased, the rea was also assessed. The optimized tablet (F9) exhibited 2.7peak detachment force and 0.9 bioadhesion strength adhesion function.

4.8 FLUX Determination for Formulation Optimisation

Table 14: Data for flux determination.

Time (hr)	Drug solution		Optimised formulation F9	
	Cum amount of drug (mg)	Cum % Drug release	Cum amount Drug (mg)	Cum % drug release
0	0	0	0	0
1	3.48	13.6	4.2	13.9
2	6.9	23.04	7.25	28.9
4	11.2	37.3	15.18	50.6
6	20.4	68.0	22.8	76.36
8	26.8	91.2	29.5	98.6
FLUX	**5.6**	-	**5.7**	-

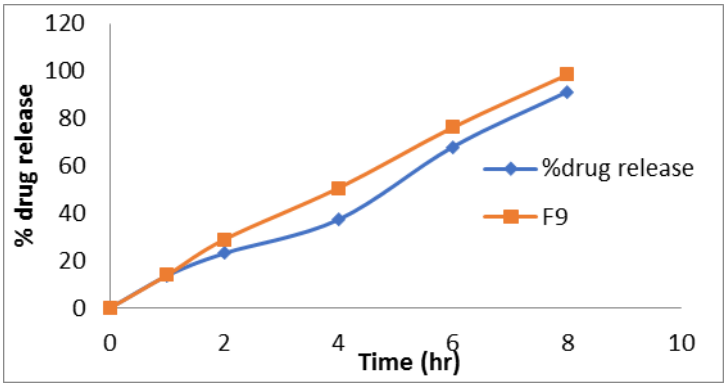

Figure 15: Flux determination.

4.9 Kinetics for In-Vitro Release

Table 15: Data for kinetic drug release pattern.

Code	Mathematical models (Kinetics)				
F9	**Zero order**	**First order**	**Higuchi**	**Peppas model**	
	r^2	**r^2**	**r^2**	**N**	**r^2**
	0.891	**0.933**	**0.982**	**0.61**	**0.947**

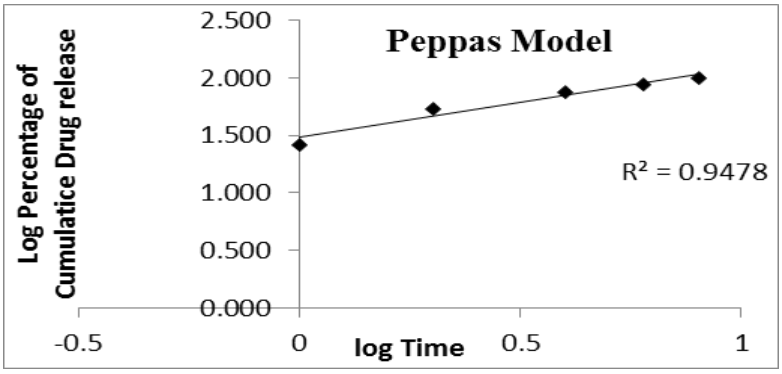

Figure 16: Peppas model graph.

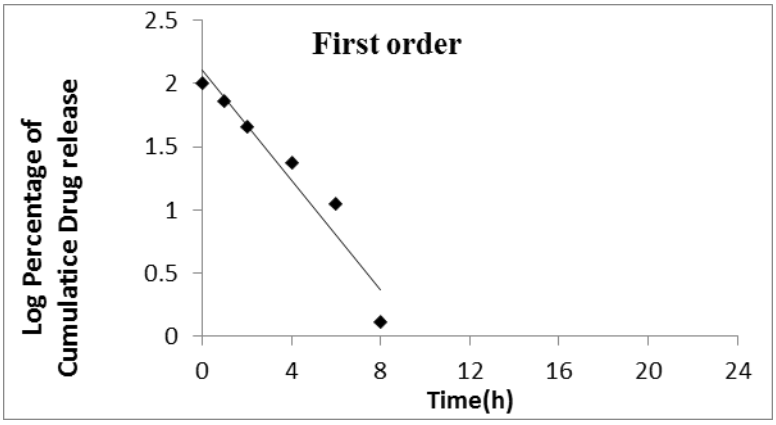

Figure 17: First order graph.

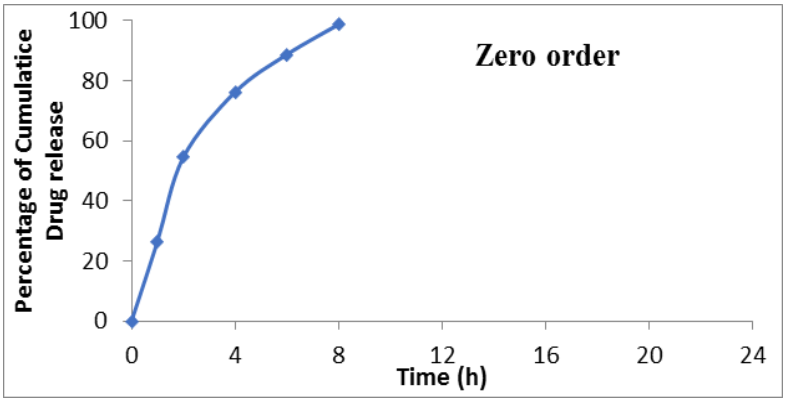

Figure 18: Zero order graph.

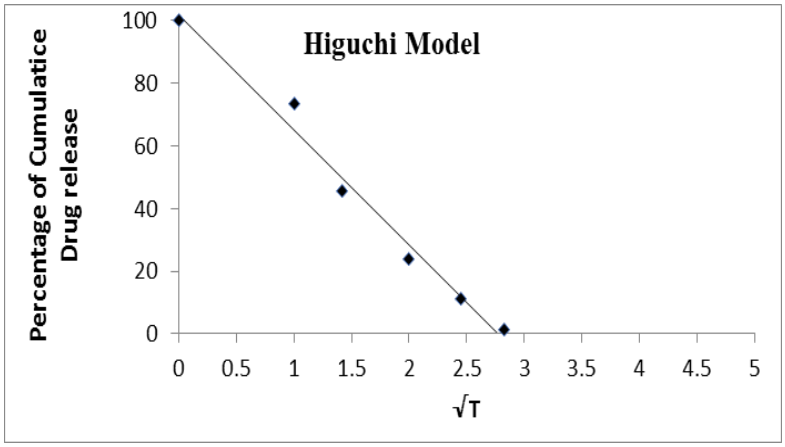

Figure 19: Higuchi model graph.

In vitro drug release data of optimized formulation by linear regression analysis according to zero order and first order kinetic equations, Higuchi's and Korsmeyer – Peppas models were subjected to fitness test goodness to determine the mechanism of drug release. Table and plots shown in Figures outline the findings of linear regression analysis including regression coefficients. From the above results, it can be seen that all the formulations showed kinetics of first order release ('r' values in the range from 0.61 to 0.987). From data from Higuchi and Peppas it is obvious that the drug is released through non-fickian diffusion mechanism (n<0.5). It is clear from the kinetic data of factorial formulations that the F9 formulation has demonstrated drug release by First Order kinetics. The values of 'r' for the equation of Peppas equation 0.942 of formulation F9 0.982 'n' in Higuchi. This data shows that drug release follows Higuchi pattern, a non-Fickian diffusion mechanism.

SUMMARY AND CONCLUSION

In the present work, mucoadhesive tablets were formulated and evaluated. All the batches F1-F12 were subjected to pre compression and post compression parameters.

Based on the above study following conclusions can be drawn

- It has been shown that the physico-chemical properties of all the formulations prepared with various polymers such as HPMC K15 M, HPMC K4 M, Carbopol and Polymer Combination are within the limits.
- For formulation(F9) prepared with HPMC K4 M and Carbopol (1:1) it was found to have maximum bioadhesion power and ex vivo residence time values 7hr 45min.
- Drug release rate of formulations prepared with combination HPMC K4 M and Carbopol (Max.98.7%)
- Release kinetics of optimized formulation shows that it meets First Order release, Higuchi model and Non Fickian Diffusion process.

ACKNOWLEDGMENT

The authors are thankful and would like to express special gratitude to Malla Reddy institute of pharmaceutical sciences for providing necessary facilities to successfully complete the research work.

REFERENCES

1. Gandhi S., Pandya P., Umbarkar R., Tambawala T., Shah M. Mucoadhesive Drug Delivery System- An Unusual Maneuver for Site Specific Drug Delivery System, Int J of Pharm Sci., 2011; 2: 132- 152.
2. Senthil KM Mucoadhesive Buccal Drug Delivery System - An Overview. Int J Pharm & Tech, 2012; 4: 3951-3969.
3. Jiménez-Castellanos MR, Zia H, Rhodes CT. Mucoadhe-sive drug delivery systems. *Drug Dev Ind Pharm*, 1993; 19: 143–94. [Google Scholar].
4. Chen G, Bunt C, Wen J. Mucoadhesive polymers-based film as a carrier system for sublingual delivery of glutathione. Journal of Pharmacy and Pharmacology, 2015; 67(1): 26-34.
5. Mylangam CK, Beeravelli S, Medikonda J, Pidaparthi JS, Kolapalli VRM, Badam gum: A natural polymer in mucoadhesive drug delivery. Design, optimization, and biopharmaceutical evaluation of badam gum-based metoprolol succinate buccoadhesive tablets, Drug Delivery, 2016; 23(1): 195-206. doi:10.3109/10717544.2014.908979.
6. Khanna R, Agarwal S P, Alka A, Mucoadhesive buccal drug delivery: a potential alternative to conventional therapy. Indian Journal of Pharmaceutical Sciences, 1998; 60(l): 1–11.
7. Salamat-Miller N, Chittchang M, Johnston TP, The use of mucoadhesive polymers in buccal drug delivery, Advanced Drug Delivery Reviews, 2005; 57(11): 1666-1691. doi:10.1016/j.addr.2005.07.003.
8. Vyas SP, Khar RK, Controlled Drug Delivery—Concepts and Advances, 1st ed., Vallabh Prakashan, New Delhi, 2002.
9. Edsman K, Hägerström H, Pharmaceutical applications of mucoadhesion for the non-oral routes, Journal of Pharmacy and Pharmacology, 2005; 57(1): 3-22. doi:10.1211/0022357055227.
10. Berginc K, Suljaković S, Škalko-Basnet N, Kristl A, Mucoadhesive liposomes as new formulation for vaginal delivery of curcumin, European Journal of Pharmaceutics and Biopharmaceutics, 2014; 87(1): 40-46. doi:10.1016/j.ejpb.2014.02.006.