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FORMULATION ANDINVITRO & INVIVO EVAUATION OF ITRACONAZOLE MUCCOADHESIVE SUSTAINED RELEASE TABLETS

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ABSTRACT

Our aim of this research work was to prepare and evaluate various evaluation parameters which are suitable for sustained release mucoadhessive tablets of Iitraconazole and to develop and characterize sustained release mucoadhessive tablets of Iitraconazole AsIitraconazole have losw solubility in aqueous phases and permeability will be high so in order to improve its solubility in HCL and water it is formulated as solid dispersion by using solvent evaporation method technique solid discussion was formulated using solvent evaporation method. In particular the buccal route appears to offer a series of advantages, such as good accessibility, robustness of the epithelium, facile removal of the dosage form in case of need, relatively low enzymatic activity, and possibility of elimination of the administered dosage from the buccal area by natural clearance mechanisms, satisfactory patient acceptance and compliance.

KEYWORDS: Iitraconazole, mucoadhessive, solvent evaporation, robustness of the epithelium.

INTRODUCTION

The oral cavity is an inviting site for drug delivery due to ease of administration, avoidance of possible drug degradation in the gastrointestinal tract, and first-pass metabolism. Within the oral mucosal cavity, drug delivery is classified into three categories: (i) sublingual delivery, which is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth (ii) buccal delivery, drug administration mainly through the mucosal membranes lining the cheeks (buccal mucosa), and (iii) local delivery, which is drug delivery into the oral cavity. Buccal region of oral cavity is an effective target for administration of the drug of choice. Buccal delivery involves the administration of the desired drug through the buccal mucosal membrane lining of the oral cavity. Unlike oral drug delivery, which presents a opposing background for drugs, especially proteins and polypeptides, due to acid hydrolysis and the hepatic first-pass effect, the mucosal lining of buccal tissues provides a much milder environment for drug absorption. Different routes, such as nasal, ocular, pulmonary, rectal, and vaginal drug administration, have provided magnificent opportunities for the delivery of a variety of compounds.

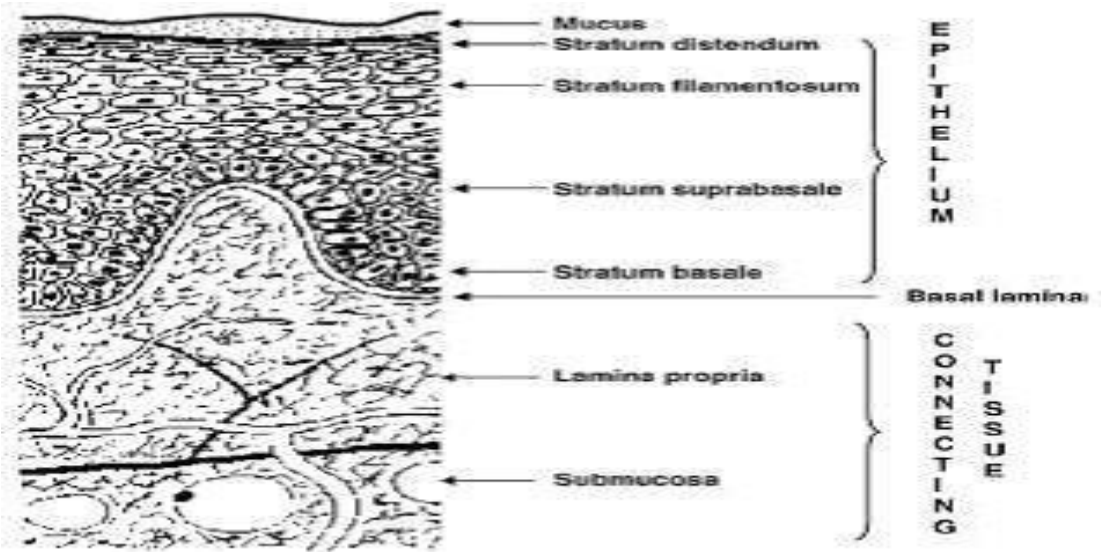


Figure 1: Cross-section of buccal mucosa.

MATERIALS AND METHODOLOGY

Itraconazole was a gift sample from Zydus Cadila, Ahmedabad, India. Carbopol 934 P from Zydus Cadila, Ahmedabad, India. Hydroxy propyl methyl cellulose K15 M, Hydroxy propyl cellulosebuyed from AET laboratories, Hyderabad, India. Ethyl cellulose, Spray dried lactose From Dr Reddy's laboratories, Hyderabad, India. Microcrystalline cellulose, Sodium taurocholate Aspartame, Magnehsium stearate from Dr Reddy's laboratories, Hyderabad, India.

Methodology

Preparation of buccal tablets

The Buccal tablets were prepared by direct compression method. Before going to direct compression all the ingredients were screened through sieve no.100, except lubricant all the ingredients were thoroughly blended in a glass mortar with pestle for 15 min. After sufficient mixing lubricant was added and again mixed for additional 2-3 min. Preparation involves two steps, first the mixture is compressed using 8 mm flat faced punch on 16 stages rotary tablet compress machine. Then upper punch is raised and the backing layer of ethyl cellulose is placed on above compact then two layers are compressed again to get bilayered buccal tablet. Composition of the prepared bio adhesive buccal tablet formulations of Iitraconazole were given in Table.

Table 1: Formulation table.

Ingredient	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	
Carbapol	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 Sacharine	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

Evaluation of Mucoadhessive tablets

a. Thickness

The thickness of buccal tablets was determined using digital micrometre. Ten individual tablets from each batch were used and the results averaged.

b. Weight variation test

Weight variation was performed for 20 tablets from each batch using an electronic balance and average values were calculated.

c. Hardness

Hardness was conducted for 3 tablets from each batch using Monsanto hardness tester and average values were calculated.

d. Assay

Ten tablets were weighed and grounded in a mortar with pestle to get fine powder; powder equivalent to the mass of one tablet was dissolved in methanol by sonication for 30 min and filtered through filter paper. The drug content

was analysed spectrophotometrically at 263 nm using an UV spectrophotometer.

e. Disintegration test

The test was performed for buccal tablets which are not having backing; six tablets were taken randomly from each batch and placed in USP disintegration apparatus baskets. Apparatus was run for 4 hr and the basket was lift from the fluid, observe whether all of the tablets have disintegrated (USP NF, 2004).

f. Measurement of bio adhesion strength

Bio adhesive strength of the tablets was measured on a modified physical balance (Gupta et al, 1993). The apparatus consisted of a modified double beam physical balance in which a lighter pan had replaced the right pan and the left pan had been replaced by a glass slide (4 cm length and 2.5 cm width) with plastic hang suspended by Teflon rings and copper wire. The left-hand side of the balance was exactly 5 g heavier than the right side .The height of the total set up was adjusted to accommodate a glass container of 6.6cm height. All parts of modified physical balance were shown in Figure 6. In order to find out the bio adhesion strength first buccal tablet (n=3) was stacked to the glass slide with the help of knob, which was situated at the base of physical balance. Now five grams weight from the right pan was then removed. This lowered the glass slide along with the tablet over the membrane with a weight of 5.0 g. This was kept undisturbed for 5 min. Then the weights on the right-hand side were slowly added in increments of 0.1 g till the tablet just separated from the membrane surface. The excess weight on the right pan, i.e. total weight minus 5g was taken as a measure of the bio adhesive strength.

g. Determination of the *ex vivo* residence time

The *ex vivo* residence time was determined using a locally modified USP disintegration apparatus, based on the apparatus applied by Nakamura et al., The disintegration medium was composed of 800 mL pH 6.6 phosphate buffer maintained at 37◦C. The porcine buccal tissue was glued to the surface of a glass slab, vertically attached to the apparatus. The buccal tablet was hydrated from one surface using 0.5 mL of pH 6.6 phosphate buffer and then the hydrated surface was brought into contact with the mucosal membrane. The glass slab was vertically fixed to the apparatus and allowed to run in such a way that the tablet was completely immersed in the buffer solution at the lowest point and was out at the highest point. The time necessary for complete erosion or detachment of the tablet from the mucosal surface was recorded. The experiments were performed in triplicate (n=3) and mean of triplicate was determined.

h. Swelling Studies

Buccal tablets were weighed individually (designated as W1) and placed separately in Petri dishes containing 15 mL of phosphate buffer (pH 6.6) solution. At regular intervals (1, 2, 3, 4, 5, 6, 7 and 8 hr), the buccal tablets were removed from the Petri dishes and excess surface water was removed carefully using the filter paper. The swollen tablets were then reweighed (W2**)** (Ritthidej et al., 2002). This experiment was performed in triplicate. The swelling index (water uptake) calculated according to the following Eq**.** (Agarwal et al., 1999)

Swelling index= (W2-W1)/W1

i. Surface pH Study

The bio adhesive tablet was allowed to swell by keeping it in contact with 1 mL of distilled water for 2 hr at room temperature. The pH was measured by bringing the pH-meter electrode, in contact with the surface of the tablet and allowing it to equilibrate for 1 min (Battenberg et al., 1991).

j. *In vitro* drug release of buccal tablets

The United States Pharmacopeia (USP) XXIII rotating paddle method was used to study the drug release from the buccal tablets. The dissolution medium consisted of 200 mL of phosphate buffer pH 6.6. The release was performed at 37oC ± 0.5oC, with a rotation speed of 50 rpm (Vishnu et al., 2007). The backing layer of buccal tablet was attached to the glass slide with instant adhesive (cyanoacrylate adhesive). The slide was placed in to the bottom of the dissolution vessel. Samples (5 mL) were withdrawn at predetermined time intervals and replaced with fresh medium. Dissolution for the conventional marketed product was conducted without Glassslide. The samples were filtered through filter paper and analysed after appropriate dilution by UV spectrophotometer at 263 nm.

k. *Ex vivo* permeation of buccal tablets

Ex vivo permeation study of buccal tablets through the porcine buccal mucosa was performed using Franz-type diffusion cell at 37°C ± 0.2°C and 50rpm. This temperature and rpm was maintained by using magnetic stirrer. Porcine buccal mucosa was obtained from a local slaughterhouse and used within 2 hr of slaughter. The tissue was stored in Krebs buffer at 4°C upon collection. The epithelium was separated from underlying connective tissues with surgical scissors and clamped between donor and receiver chambers of the Franz-type diffusion cell. After the buccal membrane was equilibrated for 30 min with Krebs buffer solution between both the chambers, the receiver chamber was filled with fresh pH 7.4 buffer solution (Afifi, Mahmoud and El-Samaligy, 2006). The buccal tablet was placed in donor chamber and 1mL of buffer solution (pH 6.6) was added (Mira Be´cirevi´c-La´can and Mario Jug, 2004). Aliquots (5 mL) were collected at predetermined time intervals and filtered through a filter paper, and the amount of drug permeated through the buccal mucosa was then determined by measuring the absorbance at 262 nm using a UV spectrophotometer. The medium of the same volume (5 mL), which was prewarmed at 37°C, was then replaced into the receiver chamber. The experiments were performed in triplicate (n = 3) and mean value was used to calculate the flux, permeability coefficient. Due to the low permeability of drug from the

formulation, permeation enhancer (Sodium taurocholate) was added in the concentrion of 10 mM to the optimized formulation to increase the permeability.

The enhancement ratio for flux was determined by dividing the cumulative amount permeated of Itraconazole in the presence of sodium taurocholate (Qenh) by the amount of Itraconazole alone (Q control).

Enhancement ratioflux= Qenh/Qcon

***l. In vivo* mucoadhessive performance of tablets**

A clearance was obtained from the institutional human ethical committee and then informed consent was obtained from all the volunteers before conducting the study. This study was conducted according to the guidelines given by the committee under the supervision of the principal investigator. *In vivo* studies were performed by applying tablets on five healthy volunteer (aged 23-28 years) gums to assess the residence time, the organoleptic characteristics, the fragment loss, the salivary level variation, and the possible production of irritation or pain. Volunteers were given optimized Iitraconazole buccal tablets along with an instruction sheet and were instructed to press the buccal tablet against the buccal mucosa for about 1 min. For the purpose of photography proof, in one volunteer buccal tablet was applied to the inner side of the lower lip and photographs were taken immediately after application, after 2, 4, 6, and 8hr. *In vivo* behaviour of the bio adhesive buccal tablet was shown in the Figure 8. Volunteers were then asked to record the time of application and time of dislodgement of tablet. After completion of the study, a question sheet was given to volunteers to get the parameters such as irritancy, comfort, taste, dry mouth, salivation and dislodgement of the system during the study, and heaviness of the system at the place of applied. Food was prohibited from 0.5 hr before the study until its conclusion, after 0.5hr of application water was provided as needed (LuanaPeriolia et al., 2004).

RESULTS AND DISCUSSION

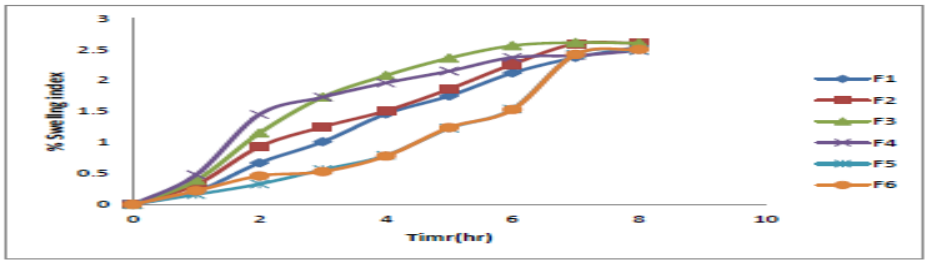
Table 2: Results of the Physical parameters.

Formulation Code	Thickness (mm)	Weight Variation(mg)	Friability (%)	Hardness (Kg/cm2)	%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	5.3±0.13	99.69
F4	2.64±0.010	155.2±0.70	0.07	6.6±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	5.1±0.05	100.39
F7	2.70±0.010	159.9±0.25	0.42	5.5±0.05	99.57
F8	2.64±0.030	157.3±0.60	0.08	6.7±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	5.6±0.10	101.03

Appropriate swelling property of a buccal device is essential for uniform and prolonged release of drug and proper mucoadhesion (Pappas and Bury, 1985). In all formulations F1-F12 shows swelling index of 2.43-2.62; the optimized formulation (F7) shows 2.5.

Table 3: Swelling Studies of buccal tablets.

Time(hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	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



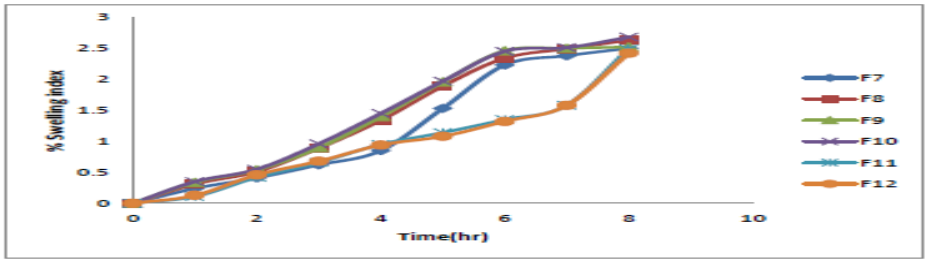


Table 4: In-vitro drug release profile for formulations F1-F3.

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	-	-	-

Table 5: In-vitro drug release profile for 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

Table 6: In-vitro drug release profile for 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

Table 7: In-vitro drug release profile for 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

***In vitro* drug release of buccal tablets**

An ideal controlled release system should be able to release the drug immediately to attain the therapeutic level at a faster rate and maintain this drug level for a prolonged period of time (Lopez et al., 1998)**.** *In vitro* drug release studies revealed that the release of

Itraconazole from different formulations varies with characteristics and composition of matrix forming polymers as shown in graphs. The release rate of Itraconazole decreased with combination of HPMC K15M, HPMC K4 M and Carbapol. Carbapol is more hydrophilic, it can swell rapidly, and therefore decrease of Carbapol content delays the drug release (Dortunc et al., 1998). Drug release rate was increased with increasing amount of hydrophilic polymer. The maximum cumulative percent release of Iitraconazole F9 found to release 98.72.

Measurement of bio adhesion strength

Formulation 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	7.06	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	7.4	2.05	0.52

CONCLUSION

The physico-chemical properties of all the formulations prepared with different polymers like HPMC K15M, HPMC K4M, Carbapol and Combination of polymers were shown to be within the limits. Maximum bioadhesion strength and *ex vivo* residence time values were found for formulation (F9) prepared with HPMC K4M and Carbapol (1:1) it is 7hr 45min. The drug release rate of formulations prepared with HPMC K4M and Carbapol combination (Max.98.7%).

Release kinetics of optimized formulation shows it follows first order release, Higuchi odel and Non fickian Diffusion mechanism. Development of bio adhesive buccal drug delivery of Iitraconazole tablets is one of the alternative routes of administration to avoid first pass effect and provide prolongs release. A combination of Carbapol 934 and hydroxyl propyl cellulose at the ratio of 1:1 is with complementary physical properties. From the results, it was concluded that the *in vitro* drug release, bioadhesion strength, *ex vivo* residence time of the optimized formulation is suitable for buccal delivery. The release pattern followed non-fickian diffusion with First order release. FTIR studies concluded that there was no interaction between drug and excipients.

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