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FORMULATION AND CHARACTERIZATION OF MUCOADHESIVE TABLETS OF FLUCONAZOLE

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ABSTRACT

Fluconazole is a triazole antifungal agent, and is used to treat fungal infections but because of frequent dosing and undesirable side effects it affects patient compliance. There came the need for a delivery system that can skip first pass metabolism and adhere long enough to treat the infection effectively, that was the aim for this study. Mucoadhesive drug delivery system adheres to mucous membrane and provides prolonged and sustained drug release. Method: Five formulations were formed by granulation method. The granules were then compressed and tablets were formed each of 250mg. Different evaluation parameters were determined like hardness, friability, weight variation, content uniformity, mucoadhesive strength, swelling index, dissolution and compatibility analysis. Results: The hardness (7.28.9kg), friability (0.02-0.05%), weight variation (0.1-0.4%), content uniformity (96.9-103%), were all in the pharmacopeial range. Dissolution was determined using rotating paddle apparatus with a phosphate buffer of 6.8 pH. Release kinetics showed that F1, F2, F3 showed Fickian release while F4 showed both Fickian and non Fickian release and F5 showed non Fickian release. Mucoadhesive strength was found to be the highest (46g) in formulation F5. The highest swelling index (70.34%) was shown by formulation F3 at 12h. Differential scanning calorimeter and Fourier transform infrared spectroscopy showed that there is no interaction between excipients. Conclusion: Hence, results showed that fluconazole vaginal tablets can be formed by using these ingredients and formulation F5 was the most optimum formulation.

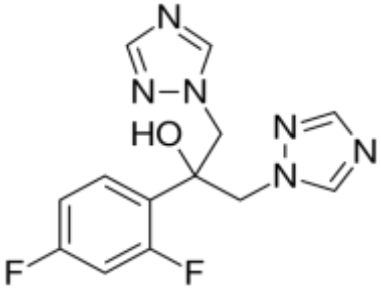
INTRODUCTION:

The field of controlled drug delivery is undergoing rapid advances. The traditional prosthetic role of polymeric materials in medical devices is being supplemented by novel applications in the pharmacological and pharmaceutical areas. Because of the relative infancy of their field, there is much confusion in the scientific literature as to what ought to be called as "controlled" drug delivery. This term, as many others, is now well entrenched in the literature, but is nevertheless often misunderstood. "Controlled" drug delivery refers specifically to the precise control of the rate by which a particular drug dosage is released from a delivery system (ideally in a constant or near constant manner over a prolonged period of time) without the need for frequent, repeated administration, either orally or parentally.

Drug release rate that is constant over some fixed prolonged period of time follows zero-order kinetics in which the rate is unaffected by the concentration. With orally ingested tablets and most parental population (other than continuous i.v. infusions), there is an initial rapid rate of release, followed by steady decrease thereafter more or less in the first order manner, in which the rate is directly proportional to the concentration, until another dose is administered to maintain appropriate therapeutically effective drug concentration levels in the blood. Controlled drug delivery means, that the rate of disposition of the active substance for absorption and the rate of availability at the actual site of action is controlled.

1.2 Need for the study: Advanced technique in biomaterials have resulted in the formulation of novel dosage form more pertinent to the oral cavity, meeting the challenges of the physiochemical properties of the drug entity itself and achieving the therapeutic aim of the drug delivery system. The buccal route has been used for many years to deliver drugs, which undergo first-pass metabolism. The buccal route has a relatively robust mucosa, has the advantage of all owing excellent accessibility, and reasonable patient compliance. Within the oral mucosal cavity, the buccal region offers attractive route of administration for local or systemic drug delivery. The mucosa has a rich blood supply and it is relatively permeable. Recently interest has been focused on the delivery of drug via mucous membrane by the use of mucoadhesive material, several mucoadhesive formulations are available under development and drug delivery via buccal mucosa is gaining importance of a novel route of drug administration. In the present study, various polymers such as HPMC K15M, Guar gum, and karaya gum were employed. These polymers are seen to be potential and comparatively economical.

Figure No 1: Structure of Fluconazole



1.2 Description: Fluconazole is an antifungal medication used for a number of fungal infections. This includes candidiasis, blastomycosis, coccidio idomycosis, cryptococcosis, histoplasmosis, dermatophytosis, and tinea versicolor. It is also used to prevent candidiasis in those who are at high risk such as following organ transplantation, low birth weight babies, and those with low blood neutrophil counts. It is given either by mouth or by injection into a vein. Its side effects include vomiting, diarrhoea, rash, and increased liver enzymes. Serious side effects may include liver problems, QT prolongation, and seizures During pregnancy it may increase the risk of miscarriage while large doses may cause birth defects. Fluconazole is in the azole antifungal family of medication. It is believed to work by affecting the fungal cellular membrane. Application of Fluconazole is commonly used to treat fungal infections such as yeast infections, oral thrush, and certain types of meningitis. It's also used to prevent fungal infections in people with weakened immune systems. its CAS Number is 86386-73-4, with Purity: 98%. Physical State of fluconazole is White crystalline powder at room temperature. Fluconazole is sparingly soluble in water, with a solubility of approximately 8 mg/mL at pH 7. However, it is more soluble in acidic environments. Fluconazole Melting Point is 138-140° C and should be Store at -20° C to 25. Molecular Weight of fluconazole is 306.27g/ml with molecular formula C13H1F2N60.

2. MATERIALS AND METHODS: The preparation of fluconazole buccal tablets involves a variety of ingredients sourced from reputable suppliers. The active pharmaceutical ingredient fluconazole is supplied by S.D Fine Chemicals Mumbai. Excipients such as Talc, Magnesium stearate, Hydroxypropyl methyl cellulose, Micro crystalline cellulose powder, Poly ethylene glycone are procured S.D Fine Chemicals Mumbai. Carbopol supplied by Hi media Laboratories Pvt. Ltd. The manufacturing process utilizes several key pieces of equipment. An Digital balance AX-200 ensues accurate measurement of ingredients. A Friabilator EF-2 from Electrolab, Mumbai, tests tablet friability. Compression of tablets is performed using a CMD (Cadmach) compression machine. The Pfizer hardness tester from Mumbai measures tablet hardness, while the LABINDIA UV 3000+ UV spectrophotometer is used for analytical purposes. The Electrolab TDT-08L dissolution apparatus evaluates the dissolution profile of the tablets. The Tap density apparatus (USP) Electro Lab, Mumbai. Finally, Vernier calipers (model CD-6"CS) are employed for precise measurement of tablet dimensions.

2.2. METHODOLOGY: The mucoadhesive buccal tablets of fluconazole were prepared by employing various polymers like carbopol, at first the API was mixed with the Carbopol in combination by direct compression method using 8 mm flat-faced punch of 10 station Rimek compression machine. For the preparation of mucoadhesive buccal tablets, all components were screened through sieve # 18 and mixed thoroughly in a mortar and pestle for 10 min. Magnesium stearate and talc were added to the above blend as flow promoters.In all the formulations the amount of fluconazole was kept constant at 4 mg. The polymers like carbopol,Hpmc,mccp and peg were used in different concentrations in combination. Total weight of the tablet was kept constant at 100 mg. The formulae of different mucoadhesive buccal tablets of fluconazole are given in. (Table.1)

EVALUATION OF TABLETS: The formulated Tablets were evaluated for the following quality control studies & In vitro dissolution studies

Pre formulation studies:

1. Angle of Repose: The angle of repose is the maximum angle between the surface of a pile of powder and the horizontal plane. It was determined using the funnel method, where a accurately weighed powder blend was placed in a funnel. The funnel height was adjusted so that the tip just touched the apex of the powder blend. The blend was allowed to flow freely through the funnel onto a surface, forming a cone. The angle of repose (q) was calculated using the formula

$$q = \tan^{-1}(h/r)$$

Where h is the height and r is the radius of the cone base. This angle is indicative of the flow properties of solids, reflecting inter-particle friction and resistance to movement.

2. Density:

Bulk Density (BD): Measure the mass of powder and its bulk volume without compaction to calculate bulk density using the formula Db = M / V0.

Tapped Density (TD): Measure the mass of powder and its volume after tapping to minimum volume using a tap density tester. Calculate tapped density using Dt = M / Vf.

3. Carr's Index: Calculate compressibility index to assess powder blend compressibility using the formula: Compressibility index (%) = [(Tapped density - Bulk density) / Tapped density] x 100.

4. Hausner's Ratio: Calculate Hausner's Ratio to evaluate powder flowability using the formula: Hausner's Ratio = Tapped density / Bulk density.

Post compression Parameters:

1. General Appearance: Evaluate tablets for shape, color, texture, and odor.

2. Average Weight/Weight Variation: 20 tablets were selected and weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to assure whether it was within permissible limits or not. Not more than two of the individual weights deviated from the average weight by more than 7.5% for 300 mg tablets and none by more than double that percentage.

Average weight = $\frac{\text{weight of 20 tablets}}{20}$

%weight variation = $\frac{\text{Average weight - Weight of each tablet}}{\times 100}$

3. Thickness: Measure tablet thickness using a Vernier caliper (n=3).

4. Hardness Test: Measure tablet hardness using a Monsanto hardness tester (n=3) to assess tablet strength.

5. Friability Test: Determine friability by weighing 20 tablets before and after tumbling in a friabilator. Calculate friability as percentage loss in weight:

%Friability = [(W1 - W2) / W1] x 100.

6. Wetting time: Five circular tissue papers were placed in a petridish of 10cm diameter. Ten millimeters of water was added to the petridish. A tablet was carefully placed on the surface of the tissue paper in the petridish at 25^0C. The time required for water to reach the upper surface of the tablets and to completely wet them was noted as the wetting time. These measurements were carried out in replicates of six. Wetting time was recorded using a stopwatch.

***7. In- Vitro* Dispersion Time:** In vitro dispersion time was measured by dropping a tablet in a beaker containing 50 ml of 0.1N HCL. Tablets from each formulation were randomly selected and in vitro dispersion time was performed.

8. Water absorption ratio(%):A piece of tissue paper folded twice was placed in a small petridish (Internal diameter=6.5 cm) containing 6ml of water. A tablet was placed on the paper and the time required for complete wetting was then measured. The water absorption ratio (R) wasw determined using the following equation.

$$\textit{Water absorption ratio}\,(R) = \frac{Wa - Wb}{Wb} * 100$$

Where, Wb is the weight of the tablet before water absorption and Wa is the weight of the tablet after absorption.

9. Assay: To determine the fluconazole content, ten tablets were weighed and powdered. A portion of the powder equivalent to 100 mg of Empagliflozin was transferred to a 100 ml volumetric flask. To this, 10 ml of methanol was added, and the mixture was shaken vigorously for 15 minutes to extract the drug. The volume was then adjusted to the mark with 0.1N HCl, and the solution was filtered. From this prepared solution, 0.1 ml was diluted in a 10 ml volumetric flask with 0.1N HCl. The Empagliflozin content was determined by measuring the absorbance at 257 nm using UV spectrophotometry. The drug content was calculated using a standard calibration curve. The mean percentage of drug content was derived from three independent determinations. The quantity of drug in the portion was calculated using the formula:

Assay = test absorbance/standard absorbance*standard concentration/sample concentration*purity of drug/100*100

10. *In-Vitro* Dissolution Studies: The dissolution of the buccal tablet was performed using USP type II XXIII dissolution apparatus (paddle method) using 900 ml of phosphate buffer pH 7.4 as the dissolution medium, which was maintained at 37°C and stirred at 50 rpm. Aliquots of 5 ml of samples were withdrawn with a bulb pipette at different time intervals of 1, 2, 3, 4, 5, 6, 7 and 8 hrs and replaced with equal volume of phosphate buffer pH 7.4 at each withdrawal, filtered it through what man filter paper No. l.

Table No 1: Formulation Composition

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
Empagliflozin	10	10	10	10	10	10	10	10	10	10
SSG	20	40	60							
Crospovidone				20	40	60				60
CCS							20	40	60	
Mannitol	60	60	60	60	60	60	60	60	60	60
Lactose	-	-	-	-	-	-	-	-	-	67
MCC pH 102	71	69	67	71	69	67	71	69	67	-
Aspartame	5	5	5	5	5	5	5	5	5	5
Peppermint flavour	1	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1	1

Table 2: Angle of Repose Limits

Flow Property	Angle of Repose (degrees)
Excellent	25–30
Good	31–35
Fair—aid not needed	36–40
Passable—may hang up	41–45
Poor—must agitate, vibrate	46–55
Very poor	56–65
Very, very poor	>66

Table 3: Compressibility Index Limits
Scale of Flow ability (USP29-NF34)

Compressibility Index (%)	**Flow Character**	**Hausner's Ratio**
≤ 10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very Poor	1.46-1.59
> 38	Very, very Poor	> 1.60

Table No .4: Weight Variation Tolerance For buccal tablets
Acceptance criteria for tablet weight variation (USP 29-NF 34)

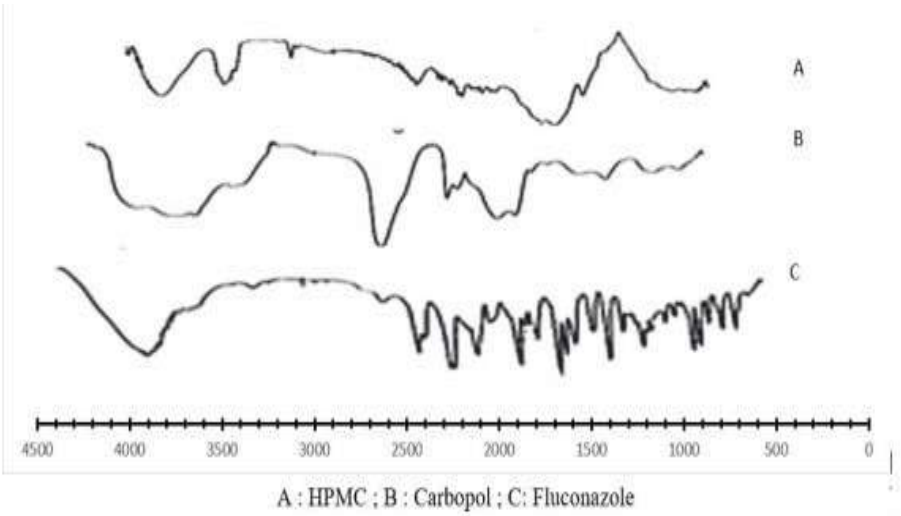
Average weight of tablet (mg)	% difference allowed
130 or Less than	± 10
130-324	± 7.5
More than 324	± 5

Table No 5: Dissolution Parameters

Parameter	Details
Dissolution apparatus	USP -Type II (paddle)
Medium	0.1N HCL
Volume	900 ml
Speed	50rpm
Temperature	37± 0.5 ºC
Sample volume withdrawn	5ml
Time points	2, 4, 6, 8, 10, 15, 20 and 30mins
Analytical method	Ultraviolet Visible Spectroscopy
Λmax	257 nm

Fig. 2: Modified balance to measure *ex vivo* bio adhesive strength

Figure 03: FTIR curve of fluconazole



A : HPMC ; B : Carbopol ; C: Fluconazole

Table no 6: Standard curve for the estimation of fluconazole:

S. no	Concentration(µg/ml)	Absorbance
1	5	0.085
2	10	0.178
3	15	0.259
4	20	0.351
5	25	0.430

Table 7: regression data of calibration curve

Sl.no	Medium	Regression data		
	Phosphate buffer	**M**	**C**	**R**
1		0.017	0.004	0.999

Where

M= slop, C =intercept, R= correlation co -efficient

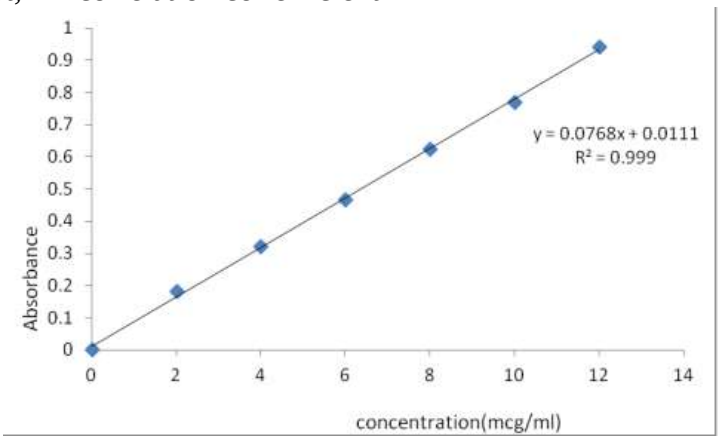


Fig 04: Calibration curve of fluconazole

Discussion: scanning of drug**:** The drug was identified by light absorption in the U.V. range of 200 to 400nm. To determine its λmax. The obtained result revealed that the maximum absorbance appeared at 249 nm which confirm the identification of fluconazole. The result shown in the fig. 4.

Pre- compressional parameters:

Table 08: micromeritics properties of buccal tablets of fluconazole:

	Angle of Repose	Bulk Density	Tapped Density	Hausners Ratio	Carr's Index
F1	24.54±0.45	0.42±0.45	0.47±0.18	1.11±0.05	10.64±0.37
F2	25.16±0.32	0.48±0.15	0.56±0.16	1.16±0.02	14.28±0.28
F3	25.10±0.25	0.51±0.O7	0.60±0.06	1.18±0.03	15.00±0.31
F4	26.22±0.30	0.53±0.09	0.63±0.13	1.19±0.08	15.87±0.49
F5	25.22±0.27	0.43±0.13	0.49±0.08	01.13±0.02	12.81±0.19

All values are expressed as mean ± SD. n=3

Physico-chemical evaluation:

Table 09: Physical appearance and surface texture of tablets:

Formulation code	Drug content	hardness	friability	Wt. Variation	Disintegration time(S)
F1	88.42	5.3 – 0.35	0.76—0.01	48.21	88
F2	85.20	5.4 – 0.40	0.72—0.04	50.26	96
F3	90.16	5.9 – 0.46	0.69—0.02	49.84	102
F4	72.18	5.9 – 0.24	0.62—0.03	56.4	81
F5	81.64	5.5 – 0.33	0.72---0.01	52.06	86

Tablet 10: Swelling Index (%) of mucoadhesive buccal tablets of fluconazole

Batch no.	**Avg. Swelling Index (%) ± SD, n=**	**Bioadhesive strength (gm)**
F1	40.15 ± 1.537	40
F2	32.65 ± 1.358	40
F3	38.01 ± 1.746	42
F4	29.93 ± 1.100	37
F5	41.16 ± 1.242	46

Table 11: *In vitro* release of buccal tablets of flocunazole

S.no	Time (hrs)	F1	F2	F3	F4	F5
1	0	0.00	0.00	0.00	0.00	0.00
2	1	35.69	21.72	6.20	9.31	20.17
3	2	50.12	31.31	15.63	20.33	26.63
4	3	64.44	40.86	31.32	28.25	31.69
5	4	78.84	39.32	39.30	39.32	51.94
6	5	83.95	48.87	48.47	45.78	64.70
7	6	87.53	72.94	66.47	56.89	74.80
8	7	89.56	82.69	76.88	69.89	81.92
9	8	94.73	90.94	81.88	77.99	87.29

Kinetics studies:

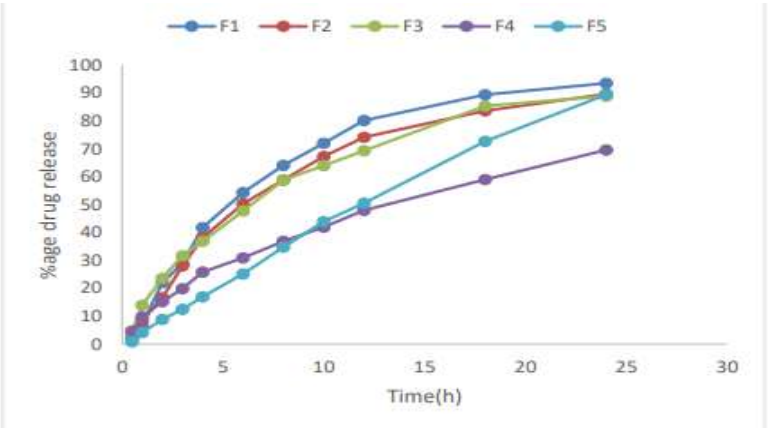


Figure No 05: release kinetic study of optimized buccal tablets fluconazole

Figure No 06: Zero order plot of optimized buccal tablets of flocunazole

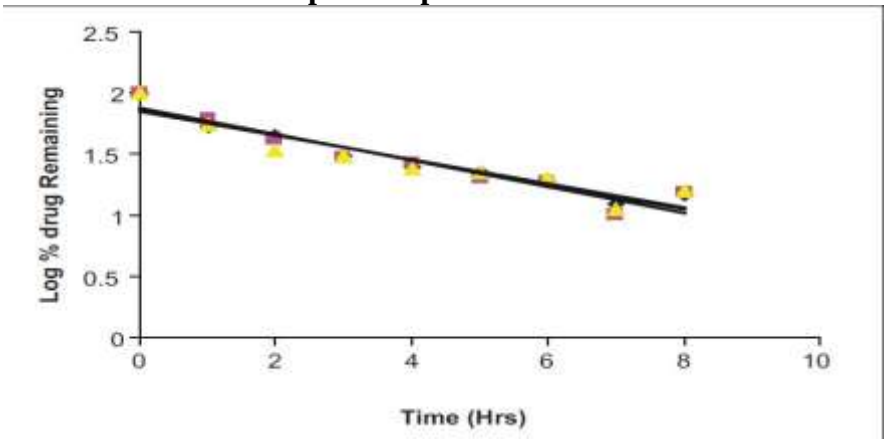


Figure No 07: first order plot of optimized buccal tablets of flocunazole

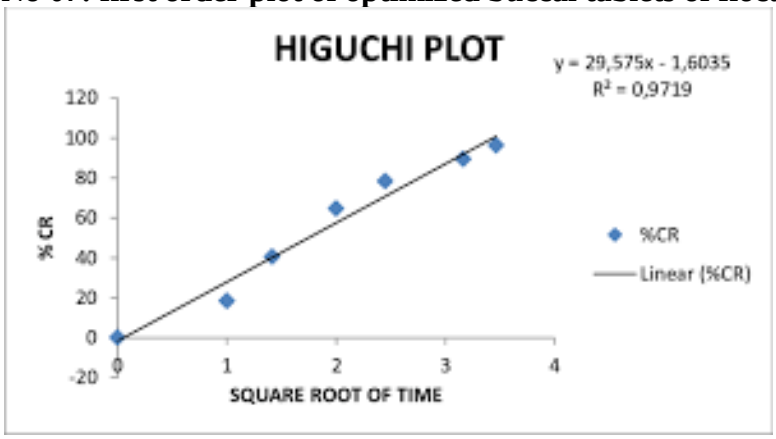


Figure No 08: Higuchi plots of optimized buccal tablets flocunazole

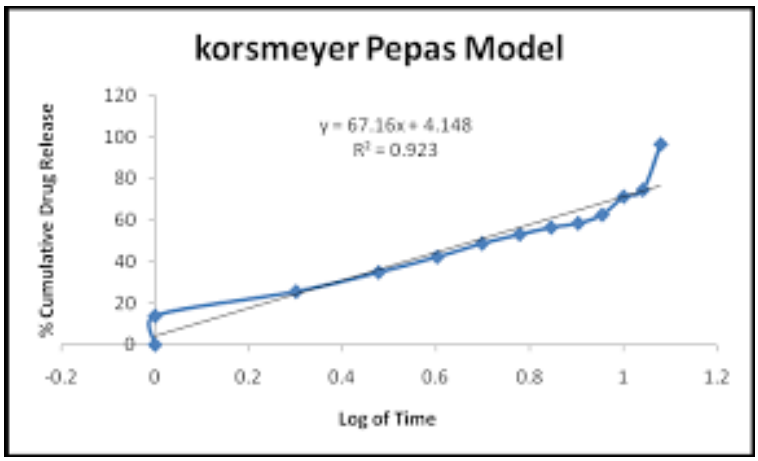


Figure No 09: korsmeyerp-peppas plot of optimization buccal tablets of fluconazole

Drug excipient compatibility studies:

Figure No 10: FTIR of pure drug:

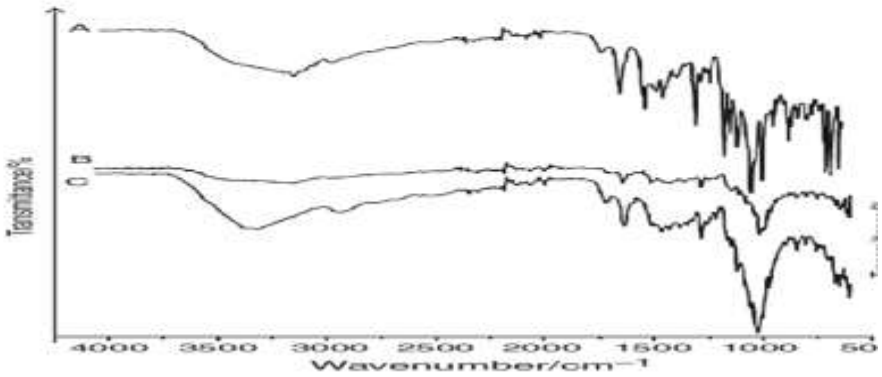


Figure No 11: FTIR of fluconazole + carbopol +HPMC

The samples were then analyzed using UV spectrophotometer at 249 nm and the cumulative amount of drug released at various time intervals was calculated

11. Release Kinetics: The release kinetics of the drug from the matrix system were analyzed by fitting the dissolution data to several release models: zero-order, first-order, and diffusion models.

A. A. Zero-Order Release:

It defines a linear relationship between the fractions of drug release Q=Ko T, Q=Fraction of drug release at time t. A plot of fraction drug release against time will be linear if the release obeys zero order release kinetics.

B. First-Order Release Kinetics: Wagner proposed that as the exposed surface area of the tablet decreases exponentially over time during the dissolution process, drug release from slow-release tablets often follows apparent first-order kinetics. The relationship is described by the equation:

log⁡ (1−Q) =−K1T\log (1 - Q) = -K_1 T log(1−Q)=−K1T. In this model, a linear plot of the logarithm of the fraction of drug remaining versus time indicates that the release kinetics conform to first-order behavior.

11. *Ex vivo* bioadhesive strength:

(UV-1700 Shimadzu Corporation, Japan) against blank18.

The test methods for determining mucoadhesion can be classified into two major categories: *in vitro/ ex vivo* methods and in vivo methods. The most common methods are based on the measurement of either tensile or shear stress. In this study, an instrument was designed to evaluate the tensile force. This instrument consists of a modified physical balance. This method was used for determination of the *ex vivo* bio adhesion strength. The balance was modified by replacement of one pan with the metal shaft 5 gm heavier in weight than pan. Fresh ox buccal mucosa obtained from local slaughterhouse was cut into pieces, washed with distilled water followed by phosphate buffer pH 7.4 containing 8.4% methanol and 0.24% tween 80. A piece of buccal mucosa was fixed in a petri dish with instant adhesive, which was filled with phosphate buffer pH 7.4 so that it just touched the mucosal surface. The tablet was stuck to the lower side of a shaft with instant adhesive. The two sides of the balance were made equal before the study, by keeping 5 gm weight on the right hand pan. A weight of 5 gm was removed from the right hand pan, which lowered the shaft along with the tablet over the mucosa. The balance was kept in this position for 3 min contact time. The weight was added slowly to the right hand pan until the tablet detached from the mucosal surface. This detachment force gave the bioadhesion strength of the buccoadhesive tablet in gm (total weight on right hand pan minus 5 gm). The Bioadhesion strength apparatus is shown in Fig. 02

3. RESULTS AND DISCUSSION

1. Calibration cuvrve for the estimation of fluconazole: The UV absorption spectrum was found to be 210 nm shown FIG.02. The same was selected as λmax for fluconazole drugs for obtaining calibration curve.

Preparation of standard curve: The absorbance of fluconazole for corresponding concentration and regress data are given in table 2 and 3. Respectively .the absorbance was plotted against concentration of fluconazole is shown

4. CONCLUSION:

Among the 5 different formulations (F1 to F5) the formulation F5 showed the controlled and effective drug release, mucoadhesive strength along with the swelling properties. This formulation also showed such physiochemical properties that were according to the pharmacopoeial standards. The final results also represents that the carbopol has very important le in increasing the mucoadhesive strength. The swelling properties of the formulation can be modified by changing the composition of HMC and CP in the formulation. HPMC has showed a very important role in controlling the swelling property of the formulation and drug release. However, there is a lot more space of the research on the different suitable combinations of the polymers to achieve the desired goals. More importantly, by formulation mucoadhesive fluconazole vaginal tablets, the first pass effect can be avoided resulting in enhanced bioavailability of the fluconazole into the system by absorption through the mucosal membrane. It can also help in increasing patient compliance by the extended drug release.

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