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FORMULATION AND EVALUATION OF MUCOADHESIVE FLUCONAZOLE VAGINAL TABLETS

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ABSTRACT

Objective: 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 provide 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 (7.2-8.9kg), 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.

Keywords: Fluconazole, Mucoadhesive, Controlled release, Vaginal tablets.

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INTRODUCTION

One of the common fungal infections among women is vaginal candidiasis and almost 75% of women suffer from this infection at least once in their lifetime. Out of which, Candida albicans is responsible for 80% of them. Majority of the patients get treated with just topical application of limidazoles or Nystatin **[1]**. Fluconazole belongs to a subclass of triazole antifungals. Fluconazole was discovered in 1982 and approved for use in 1990 by US FDA, for the treatment of infections caused by candida and cryptococcosis **[2]**. Available formulations of fluconazole include tablets, suspensions or capsules orally and in solution to be used as an intravenous injection. Oral treatment of fluconazole is mostly enough for treating the infection but the undesirable side effects affect patient compliance. Formulations available for vaginal delivery include tablets, solutions **[3]**. Gels, suspensions and foam. Creams and gels are better at providing lubrication but can be easily removed by water and are messy to be deal with. Solutions and suspensions have a disadvantage of uneven distribution in the vagina **[4]**. Topical gels incorporated with the active agent have been made. The release of the fluconazole made in lipogels and gel microemulsion, has been studied in vitro, as well as the penetration, by applying the gel topically. One of the major problems was the easy and fast removal of the topical agent from the skin which didn't let the drug penetrate into the skin effectively. Therefore, delivery system which is used to deliver the drug is a major problem and delivery system should be as much to provide prolonged retention time of the drug. There should be a delivery system that can increase the time of the adhesion of the dug with the vaginal mucosal membrane. A mucoadhesive film appears to be helpful in this regard, as it can prolong the adhesion time topically

for local delivery of drug. Also, as compared to gels, vaginal tablets appear to be more useful and easier to use as they can be applied easily, handled easily and the patient always knows how many are left **[5, 6]**. One of the greatest advantages mucoadhesive tablets offer is they adhere for long period of time providing controlled and sustained release of drug. Another one is that they lower the frequency of dosing**[7]**. Ideal polymers that can be used in mucoadhesive tablets are carbomer, hydroxy propyl methyl cellulose, sodium carboxy methylcellulose and plant gums, as they have relatively high adhesive strength to biological membranes **[8, 9]**. So, our work was aimed to formulate fluconazole mucoadhesive vaginal tablets that can provide enough adhesion to the drug to treat vaginal fungal infections, with the help of polymers. Different proportions of polymers were used to study the swelling, release of drug and mucoadhesive strength and time. As well as the antimicrobial activity for the formulation that was selected.

MATERIALS AND METHODS

Drugs, Chemicals and Instruments

Fluconazole, HPMC K15, Carbopol 934 NF, Mg Stearate, Talc MCCP 200, PEG6000 and Avicel PH102 were purchased from the Merk Pakistan. Chemicals as well as the reagents that were used were of the analytical grade. Tablet hardness tester (YD-1), Friabilator (Veego VFT-DV), dissolution apparatus, Shimadzo UV visible spectrophotometer and Bruker FTIR alpha spectrophotometer were used to conduct this study.

Formulation of Fluconazole Mucoadhesive Tablets

All the ingredients were weighed carefully and accurately. At first, the API was mixed with the carbopol. The remaining chemicals were mixed with the talc separately. Both of the mixtures were mixed to-gather. Drop wise water was added until dough was attained. It was passed through mesh and granules were formed. Granules were dried and made fine in pestle and mortar. The resulting fine granules were punched b tablet press to form tablets.

Evaluation of Tablet Properties

To assess the quality of the different mucoadhesive formulations, different processes of quality control were used to determine the physiochemical properties of tablets.

Weight Variation

From each of the prescribed formulations twenty tablets (n=20) were weighed separately and average weight was determined. Then percentage deviation was measured for each tablet from average weight.

Friability

Tablets were weighed initially and then placed in the friabilator for 4 mins at 25rpm. After that tablets were weighed again and final weight was noted.

$$\%\ Friability = [(Initial\ weigh - Final\ weight)\ /Initial\ weight] * 100$$

Hardness

Hardness was measured by using hardness tester. Five tablets (n=5) from each formulation were placed separately in hardness tester. The force on the screen was recorded for each tablet.

Surface pH Studies

Three tablets (n =3) were selected from every formulation and their pH from each. They were kept in a pH 6.8 for 2h in distilled water. The pH meter electrode was used to determine the surface pH of the tablets.

Drug Content

Two tablets from each formulation (F1-F5) were crushed and mixed separately. About 20% of the total weight of mixed contents was weighed from each formulation. This mixture was added to 10 ml phosphate buffer of pH 6.8 and left for 24 hours. After 24 hours, 1 ml sample was taken from each dilution and it was further diluted with 10 ml phosphate buffer of pH 6.8. Then it was observed on UV spectrophotometer and absorbance values were noted for each formulation. The actual drug content was calculated and compared with the theoretical drug content present in the formulation by using following formula:

$$\%\ age\ drug\ content = (Actual\ drug\ content / Theoretical\ drug\ content) * 100$$

Table 1: Composition of various fluconazole mucoadhesive vaginal tablets.

Formulations	Fluconazole (mg)	HPMC K15 (mg)	Carbopol 934 NF (mg)	Mg stearate (mg)	Talc (mg)	MCCP 200 (mg)	PEG 6000 (mg)	Avicel PH102 (mg)
F1	100	60	30	5	5	50		
F2	100	30	30	4				90
F3	100	95	45	5	5			
F4	100	80	15		5		50	
F5	100	90	40	5	5			10

Mucoadhesion Test

The chicken intestinal mucosa was used for bioadhesion test. For this test 3 tablets were selected. Modified pan balance was used to determine mucoadhesive forces. On one test tube the intestinal mucosa was attached by bilayered adhesive tape. The formulation was attached on its exposed surface separately and a uniform force applied to attach tablet for 2 minutes. The second vial attached to balance with the space between them equal to thickness of tablet. The weight was increased by 0.5 g on pan. Maximum weight was noted when two vials get detached for the formulation F1 to F5 separately to determine muccoadhesive strength.

Swelling Test

Three tablets were selected from every formulation and they were weighed carefully. It was termed as W1. Then these selected tablets were placed in petri dishes having a pH 6.8 phosphate buffer in a volume of 5 ml. Then they were taken out from the Petri dish and then filter paper was used to remove excess water. These tablets were weighed again and it was designated as (W2) and the percentage of hydration was calculated for each tablet, using the Eq. Swelling index= $[(W_2 - W_1)/W_1 * 100]$

In vitro Dissolution Studies

Release properties of formulations F1-F5 were analyzed by obtaining dissolution samples at specifies intervals and then evaluating percentage drug release as a function of time. The rotating paddle apparatus or USP type II dissolution apparatus was used to study drug release from the tablets. Two tablets were chosen for the analysis. Dissolution media was composed of Phosphate buffer having pH 6.8. The temperature was maintained 37 °C ± 0.5 °C throughout the procedure with a constant rate of 50 rpm. A Total of 5 ml samples were withdrawn at every hour and the same volume was replaced with a fresh dissolution medium. Samples which were withdrawn were diluted to 10times of their original concentration with the same phosphate buffer. The spectrophotometer was turned on and allowed to auto calibrate itself by pressing the auto-zero. After it was calibrated, dilution samples containing fluconazole were analyzed at a wavelength of 210 nm and absorbance was noted. The percentage of drug release was calculated using the calibration curve b/w absorbance and concentration. A filter paper was used to filter these collected samples and then a UV-Visible spectrophotometer was used to analyze them at 210 nm. The calibration curve obtained was used to analyze the amount of drug released. For the calibration curve. A stock solution was prepared at a concentration of 50 mg/50ml in phosphate buffer pH 6.8. The diluted stock solution was used to obtain the solution of different concentrations from 2mcg/ml to 10mcg/ml.

Differential Scanning Chromatography (DSC)

Differential scanning calorimeter was used to conduct DSC. In this procedure a weighed sample of 10 mg was in an aluminum pan. Then the pan was sealed carefully, temperature scanning was carried out between −40◦C and 180 ◦C by performing a DSC heating/cooling/heating cycle (1st heating, 1st cooling, and 2nd heating) with a fixed rate of 10 ◦C/min as the nitrogen gas flows (30 mL/min). Pyris program was used to analyze the heat flow against the temperature by plotting a graph.

FTIR

FT-IR spectra were obtained in the range of 4000-400 cm^-1 for 30 times for pure drug and mixture of pure drug with the polymers. Compatibility was analyzed **b**y comparing these spectra.

Determination of Release Kinetics

The dissolution testing data was used to determine release kinetics of the formulations using DDS solver. Zero-order, first-order, Higuchi and Korsmeyer-Peppas and Hixson Crowell models were used to determine the rate and mechanism of fluconazole release. R2 is a statistical entity of the accuracy with which the data are to the fitted regression line. The value close to 1 was considered as the most suitable and preferable.

RESULTS

Evaluation of Tablet Properties

Weight variation, friability, hardness, and surface pH of the tablets. The weight variation with the values between 0.1% to 0.4% was within the pharmacopeia limit which is ±5 for the tablets above 325 mg as per the USP. Friability values of formulations F1 to F5 ranged from 0.02% to 0.05%, which was in the given acceptable range as per the USP. This shows that tablets had the good compaction properties Hardness values of formulation F1 to F5 were found between 7.2 kg to 8.9 kg, which were in the pharmacopeia limit (5 kg). The surface pH of selected formulations was in the range of 6.72 to 6.96, and all the formulations were in the acceptable range of vaginal pH 6.5 to 7.5.

Drug Content

The drug content of the formulations (F1-F5) was in the range of 96.9 to 103%, which shows the efficacy and the precision of the process of making formulation and little wastage of any materials during formulation.

Table 2: Quality control parameters evaluation numerical data.

Formulation	Weight Var (%age)	Hardness (kg)	Friability (%age)	Surface pH	Drug Content (%age)	Swelling Test at 12 Hrs (%age)	Mucoadhesive Strength (g)
F1	0.35	7.9	0.05	6.72	96.90143	59.14	40
F2	0.1	8.9	0.03	6.76	96.96353	56.73	40
F3	0.3	7.2	0.02	6.74	103.1525	70.34	42
F4	0.4	8.4	0.035	6.85	99.17566	66.83	37
F5	0.2	7.7	0.04	6.96	100.4105	69.64	46

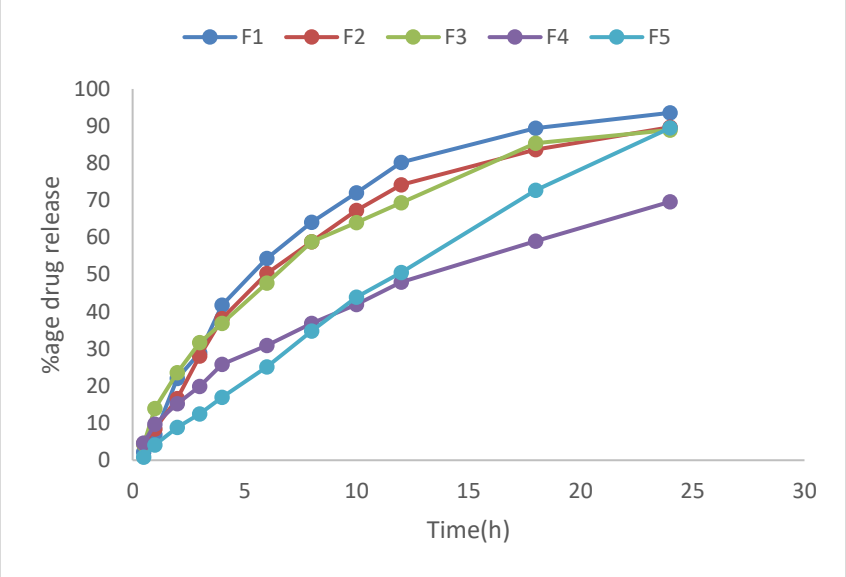

Figure 1: Release kinetics of mucoadhesive fluconazole vaginal tablets.

Mucoadhesive Strength

The mucoadhesive strength was found to be between 37g to 46g for the formulations (F1 to F5). The formulation F4 incorporated the lower amount of carbopol hence it has less mucoadhesive property with a value of 37 g. While in formulation F5 the carbopol is used in highest amount so its mucoadhesive properties are highest showing result at around 46 g (**Table 2**).

Swelling Test

All the batches showed considerable swelling effect during the study which was proportional to the time. However, no remarkable alternations were noticed in the shape of the tablets from any batch. It was appeared to be influenced by the presence of relative amount of HPMC and carbopol in respective formulations. Maximum values of it were shown at 12h. The highest swelling index is shown by the formulation F3 (70.34%) that is due to the high amount of the HPMC and the carbopol in the formulation. While the formulation 2 showed lowest swelling index (56.73%) due to lesser amount of the HPMC and Carbopol (**Table 2**).

In vitro Dissolution Studies

The drug release was in the range of 93.5% to 69.6% at the 24 h interval for the formulations F1-F5. At 24h the highest drug release 93.5% was of the formulation F1 due to presence of HPMC, carbopol and MCCP in it. The formulation F4 showed the lowest drug release at 24 h that was about 69.6% and this is because due to presence of binder PEG6000 along with the HPMS and carbopol. The drug release for the formulation F2 at 24 h was 89.6% which accounts for the presence of the avicel in its composition. Avicel creates pores at different levels in the tablet structure and this leads to the water permeation of the tablet matrix resulting in quick dissolution and disintegration. The drug release values for the formulations F3 and F5 at 24 interval were found to be 88.9% and 89.4% respectively. This is due to presence of HPMC and CP in their formulations in respective amounts (**Fig. 1**).

The formulation F1 followed the First order mechanism of drug release that clearly shows that the release of the drug is dependent on the concentration of the drug. The diffusion of the drug from the system is dependent on the concentration of drug present in the system. Hence it is showing that the formulation is sustained release formulation. Formulation F2 followed he first order mechanism of drug release. It means the drug is following the concentration dependent diffusion. So drug is released by Fickian method and follows the dissolution by erosion. Formulation F3 is following the first order of drug release which shows that the drug is released from the matrix as a function of concentration. So, all these formulations are following drug concentration dependent and Fickian method of drug diffusion. The formulation F4 is following two models i.e. Higuchi model and Korseymer Pepass Model. The value of n is 0.598 which confirms that the formulation is following Higuchi model where drug is released by both dissolution and diffusion. Higuchi model shows that the drug release is dependent on time and it is Fickian release. The korsmeyer Peppas model is showing that drug is first released by non-Fickian anamolous diffusion and followed by dissolution. Formulation F5 followed zero order model and Korsmeyer Peppas Model of drug release. This formulation followed zero order model keeping in view the regression co-efficient and Korsmeyer Peppas Model of drug release. This is the reason that drug is released by non-Fickian zero order diffusion. But the formulation is also following the Korsmeyer Peppas model with n value being closer to 0.9 confirming that the drug release is following zero order kinetics and is independent of the concentration of drug.

Differential Scanning Chromatography (DSC)

Differential scanning calorimeter is a useful instrument to study the physiochemical nature of the drug and the interaction between its various components. Not just that it gives us information about the melting of the drug its crystallization and its decomposition. We performed DSC scans on fluconazole, physical mixture of fluconazole and its various components. The untreated fluconazole gave a sharp endothermic peak at 142. And another peak at 140 was observed. Peak at 140 gave us the melting point of our drug fluconazole (**Fig. 3**). Carbopol, HPMC showed no characteristic peak in the temperature study. About the physical mic tire, endothermic peaks were near to each other, and of low intensity which can be due to dilution. Which tell us there is no interaction between ingredients and the excipients have no effects on the physiochemical nature of the drug.

Table 3: Release kinetics of the formulations.

Models	**Formulations**					
		F1	**F2**	**F3**	**F4**	**F5**
Zero Order	k0	5.245	4.925	4.872	3.464	3.971
	Rsqr_adj	0.6665	0.6956	0.6545	0.8048	0.9909
	AIC	91.7765	89.2284	89.1074	75.8787	49.6490
	MSC	0.9162	1.0074	0.8810	1.4519	4.5217
First Order	k1	0.127	0.110	0.108	0.056	0.062
	Rsqr_adj	0.9943	0.9953	0.9900	0.9664	0.9642
	AIC	47.0825	43.2604	50.1494	56.5221	64.7699
	MSC	4.9793	5.1863	4.4226	3.2116	3.1471
Higuchi	kH	20.692	19.367	19.245	13.457	14.619
	Rsqr_adj	0.9363	0.9461	0.9734	0.9786	0.8507
	AIC	73.5610	70.1926	60.8896	50.5727	80.4706
	MSC	2.5722	2.7380	3.4462	3.6615	1.7197
Hixson Crowell	kHC	0.036	0.031	0.030	0.016	0.018
	Rsqr_adj	0.9874	0.9790	0.9641	0.9355	0.9854
	AIC	55.7580	59.7995	64.1990	63.6901	54.9037
	MSC	4.1906	3.6828	3.1454	2.5600	4.0440
Korsmeyer Peppas	kKP	18.293	16.699	17.812	10.537	5.219
	n	0.550	0.560	0.531	0.598	0.903
	Rsqr_adj	0.9352	0.9485	0.9731	0.9966	0.9963
	AIC	74.5882	70.5239	61.8829	32.1571	40.7194
	MSC	2.4788	2.7079	3.3559	5.4266	5.3335

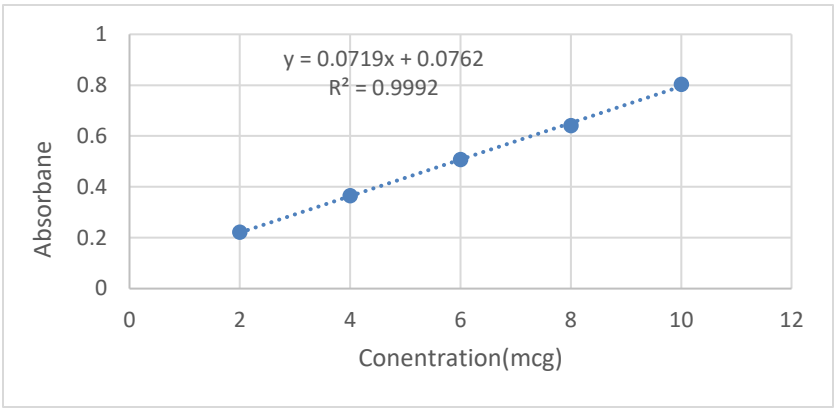

Figure 2: Dissolution of mucoadhesive fluconazole vaginal tablets.

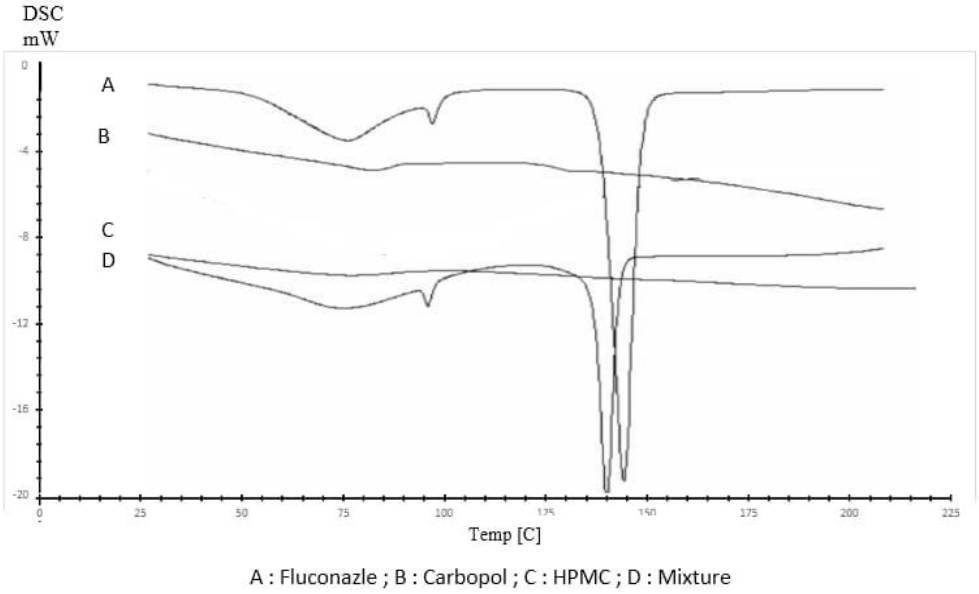

Figure 3: DSC of mucoadhesive fluconazole vaginal tablets components/mixture.

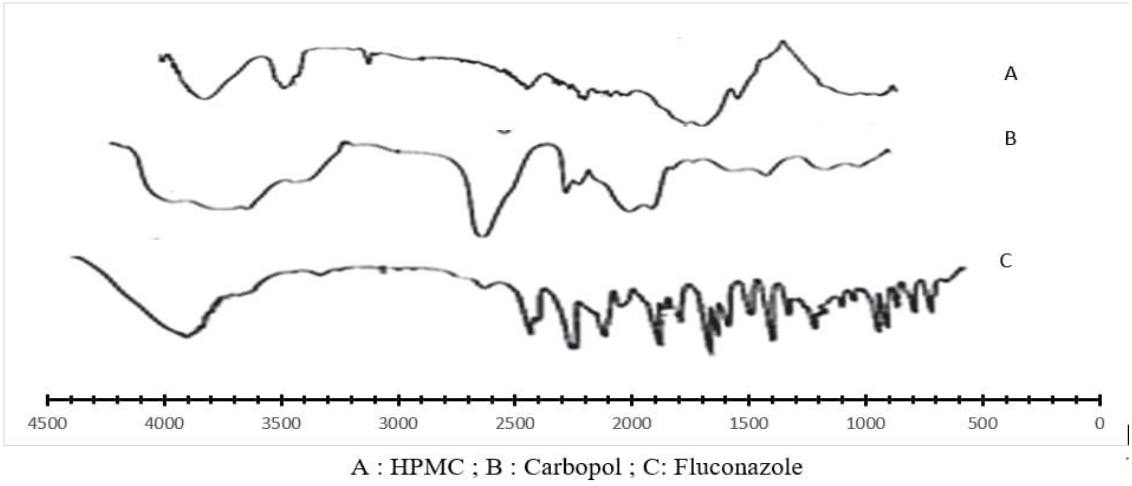

Figure 4: FTIR curve.

FTIR

FTIR analysis of fluconazole vaginal tablets along with the excipients used was performed. The results are shown in the figure below. The excipients used were Carbopol 934, HPMC K15. At high frequency absorption spectra at wavelength of 3200 cm^{-1} was observed because of the OH group. At high frequency similar sharp bands were observed at 3062.96cm^{-1} and 3020.53cm^{-1} indicating C-H bonds. The presence of aromatic groups was shown by vibrations. Due to aromatic C-N stretching vibration at 1620.21 cm^{-1} and aromatic C-C stretching vibration at 1504.48 cm^{-1} broad bands were shown in FT-IR spectrum. At low frequencies bands at 1138 cm^{-1} show C–O stretching vibration and bands at (1249.87–1211.3) cm^{-1} show C-F Bond stretching. In the Carbopol spectrum, free hydroxyl groups were shown by the broad bands at about 3433.29–3097.68 cm^{-1}. The carbonyl band of Carbopol which corresponds to the the intra-molecular hydrogen bonding among the carboxyl groups of Carbopol appeared at 1708.93 cm^{-1}. The IR spectrum of HPMC gives an absorption band at 3444.87 cm^{-1} which is due to the stretching frequency of the –OH group (**Figure 4**).

At the same position, the spectra showed the absorption bands of both fluconazole, the tablet excipients and the used polymers which indicate that there is absence of any interaction between fluconazole the excipients of tablet and the used polymers upon mixing them together.

DISCUSSION

Bio-adhesive tablets including muco-adhesive, bucco-adhesive formulations are characterized by high residence time and sustained release over a prolonged time **[10, 11]**. To achieve these characteristics multiple mucoadhesive tablets of fluconazole were formulated and investigated for different physicochemical characteristics abet their physcial strength as well as uniformity of active moiety to determine their performance and to validate the optimal formulation. The physical appearance of tablets from all batches was uniform i.e white, flat faced and with no visible cracks and flakes. Hardness of all prepared formulations F1-F5 was found to be in the range of 7.2 kg to 8.9 kg which is ideal for a bio-adhesive formulation to prevent if from cracking and dissolving rapidly. Such preferable parameters were mostly correlated to the optimal amounts of HPMC and Avicel (MCC) in the formulations **[12]**.

Further mechanical strength was confirmed by Friability values of all the formulations ranging from 0.02% to 0.05% (**Table 2**), which is much less than the 1% prescribed range which furthers confirms the optimal mechanical strength and composition of the tablets as per the USP. It depicts that all the tablets had good compaction properties because of HPMC, Carbopol 934 along with Avicel **[12]**.

Further assessing the pharmaceutical equivalency and compatibility of formulations, the tablets had weight variation in the range of ±5% and content uniformity in the range of +-10 percent in all the formulations. These results depict that all the formulations were prepared in a controlled and optimized manner ensuring uniformity of all the processes.

A bio-adhesive tablet should have a considerable amount of bioadhesive strength to render it optimal in its use. Bio-adhesive strength of formulation F5 had a respectable amount of mucoadhesive strength coming out to be 46g, which is falling within the range prescribed for good mucoadhesive properties of a prepared tablet. This occurred due to presence of carbopol 934, which gives an excellent muco-adhesive strength to the tablets if used in a formulation due to its wetting and sticking properties**[13]**.Similarly, swelling of a tablet ensures that the tablet sticks and then releases the drug at optimal concentration from the tablet matrix. Swelling test was performed on all the formulated tablets and most of them showed considerable swelling except F2 which showed less swelling (34%) as compared to F3 which showed highest swelling of 54.6%. All of this swelling was attributed to certain amount of carbopol used in the formulation which causes swelling **[14, 15]**. Drug release studies were performed to analyze the dissolution and release properties of the dosage forms. Ideally a formulation should release more than 50 percent of its active content within the first 12 hours from all of the formulations to prevent multiple dosing within the day and organize patient compliance. The drug release was in therange of 93.5 % to 69.6% at the interval of 24 hours. F1 showed highest release at 24h due to presence of HPMC carbopol and MCCP**[16]**. F4 showed lowest release due to the presence of PEG6000 **[17]**. F2 showed drug release of 89.6% at 24h due to the presence of avicel which creates pores in tablet and allows water penetration resulting in quick dissolution and disintegration **[18, 19]**. The drug release curve of all the formulations at 24h is given in the fig2. From dissolution data release kinetics of the formulations were obtained and it was seen that F1, F2, and F3 showed first order kinetics which means that drug is following concentration dependent diffusion so drug is released by Fickian method and follows the dissolution of erosion. F4 is following Higuchi and Korsmeyer Peppas model with n value 0.598 showing that release is by both

diffusion and dissolution method. F5 followed zero order and Korsmeyer Peppas model (**Table 3)**. This showed that the drug is released by zero order non Fickian diffusion and it is independent of concentration of drug **[20]**. Compatibility studies were performed by FT-IR spectrophotometer and differential scanning calorimeter. The IR spectrum of fluconazole and different polymers is shown in fig4 with characteristic bands. The DSC thermogram of fluconazole and polymers used as shown in **Fig. 3** gave us the melting point of drug at peak of 140. No interaction was observed between the ingredients and excipients showed no effect on physicochemical properties of the drug.

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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