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Formulation and Evaluation of Fluconazole Mucoadhisive Vaginal Tablets

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

The Mucoadhesive drug delivery system has occupied an important place in the field of pharmaceutical research. Mucoadhesive tablets prolong the residence time of the drug at the site of application and provide extended therapeutic effect. Mucoadhesive tablets have been prepared for various sites thus offering localization as swell as systemic control of drug release. The present study focuses on the concept of formulation of fluconazole as a mucoadhesive vaginal tablet, for improving the sustained release of drug and localized action of the drug. Different polymers, such as Hydoxypropylmethylcellulose M 15, Carbopol71G-NFand Guar Gum were used with different concentrations in order to get the desired sustained release profile over a period of more than12 hrs. The tablets were prepared by direct compression method. All the formulations were evaluated for crushing strength, friability, swelling behavior, adhesion time, drug content and *in vitro* drug release profile. All the formulation tested showed good physical and adhesive properties. It was found that the controlled release rate of the formulation increases with increasing polymer concentration. Kinetican modeling of release data supports an anomalous non-fickian release

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behavior. The antimycotic activity of selected formulations containing fluconazole (100 mg) was determined using an agar diffusion technique. Formulations tested showed activity against *C. albicans*.

Keywords: Fluconazole; mucoadhesion; vaginal tablets; in vitro release; antimycotic activity.

1. INTRODUCTION

Vaginal candidiasis is a common condition and up to 75% of all women suffer at least one episode of this infection during their lifetime. Candida albicans is the most important cause of vaginal candidiasis, accounting for over 80% of the infection. Most patients with Candida vaginitis respond to topical treatment with Nystatin or Imidazoles [1]. Fluconazole is one of the subclasses of synthetic triazole anti-fungal agents. The bistriazole anti-fungal agent fluconazole was discovered in 1982 and approved by the US Food and Drug Administration in 1990 for use in treating Cryptococcosis and Candida infections [2]. It is available as tablets, capsules, or suspension for oral administration, and as a sterile solution for intravenous injection. Most patients with Candida vaginitis respond to oral fluconazole, but in the mean time they suffer from GIT side effects of the drug.

Traditional vaginal drug delivery systems include solutions, suspensions, gels, foams and tablets are used [3]. Vaginal creams and gels provide lubrication, but tend to be messy, and are easily removed if they are water soluble. Suspensions and solutions tend to spread unevenly in the vagina [4,5].

Some efforts have been made to formulate the drug in a gel form for topical use. Ellathy and Elshabory [6], have studied the in vitro release and permeation through rat skin of fluconazole formulated into cutina lipogels and gel microemultion for topical application.In another study, Aly and Fouad [7] formulate fluconazole in gel bases for topical use. A major difficulty for the successful eradication of fungal infections of the vagina is the rapid elimination of topically applied drugs. The delivery system in which the drug is incorporated is therefore an important consideration and should be formulated to prolong the retention of the drug. Hence there is the need to develop an effective drug delivery system that should prolong the contact of drug with vaginal mucosal surface, thus flexible mucoadhesive films for topical use had been developed for local drug delivery. Vaginal tablets appear to be useful dosage forms as they are easy to apply, portable and the user knows how many units remain [4,5].

The greatest advantages of bioadhesive tablets are the release of the drug at a controlled rate and the possibility of maintaining them in the vagina for extended periods of time. They also enable lower dosing frequencies [8]. Among the polymers used, carbomers, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, sodium carboxymethyl cellulose, plant gums are ideal excipients in vaginal bioadhesive tablet formulations due to their high bioadhesive strengths [9-11].

Therefore the present work was aimed to develop mucoadhesive vaginal tablets of fluconazole capable to efficiently deliver drug during an extended period of time against *C. albicans*, using a combination of mucoadhesive polymers.

Swellings, mucoadhesion time and drug release of the tablets with different proportions of mucoadhesive polymer were conducted. The in-vitro antimycotic activity for selected formulation were studied.

2. MATERIALS AND METHODS

Fluconazole was supplied from EIPCO, Egypt. Hydoxypropylmethylcellulose M 15 (HPMC15) was obtained Sigma Chemical Co. (USA)). Carbopol71G-NF was Carbopol® 71G-NF (MW, 2,376,000 Da) was kindly donated from Lubrizol Advanced Materials Inc. (Cleveland, OH).. Guar Gum and Magnesium stearate were obtained from Merck, Germany. Calcium Phosphate Dibasic and Avicel PH 102 were kindly supplied by JRSPharma GMBH, Rosenberg, Germany. Other materials and solvents are reagent of analytical grade and they were used without further purification.

2.1 Combatability between the Drug and the Used Polymers Using Differential Scanning Calorimetry (DSC)

DSC scans were recorded for fluconazole, its corresponding physical mixture and the individual

polymers.The samples (3-5 mg) was hermetically sealed in aluminum pans and heated at a constant rate of 10°C/min, over a temperature range of 25°C to 200°C. Thermograms of the samples were obtained using differential scanning calorimetry (DSC-60, Shimadzu, Japan). Thermal analysis data were recorded using a TA 50I PC system with Shimadzu software programs. Indium standard was used to calibrate the DSC temperature and enthalpy scale. N_2 was used as purging gas at a rate of 40 ml/min.

2.2 Preparation of Mucoadhesive Tablets

Fluconazole vaginal mucoadhesive tablets were prepared using different polymers as shown in Table (1). Components of each formula were mixed in the Turbula mix (type S27, Erweka, Apparatebau, Germany) for 15 min and then directly compressed into tablets using a single punch tablet machine (type EKO, Erweka, Apparatebau, Germany) using 9.5 mm flat punches. Tablet hardness was kept within the range of 7-10 kp.

2.3 Tablet Evaluation

2.3.1 Determination of crushing strength and % friability of the prepared fluconazole tablets

For each formulation, 10 random selected Tablets were examined using the Erewka hardness tester, and 20 tablets for friability test according USP using Roche friabilator.

2.3.2 Measurement of water uptake of the prepared tablets

Five tablets were soaked each in 50 ml of Phosphate buffer (pH 5) adjusted at 37.0± 0.5ºC.Tablets were removed at different time intervals, weighed after drying the surface water by filter paper and returned to the medium. The percent increase in weight at different time intervals was calculated as:

[% increase in weight = (Hydrated tablet weight - dry tablet weight/ Dry tablet weight) X 100]

2.3.3 Determination of surface pH of the prepared mucoadhesive tablets

The surface pH of the prepared tablets was determined after soaking tablet from each formula in 1 ml distilled water for 60 seconds. After the time of soaking, the pH of the wet surface was measured by placing the electrode in contact with the surface of the tablet.

2.3.4 *In vitro* mucoadhesion

In vitro bioadhesion of the formulations was examined adopting a previously published method [12] using a chicken pouch as a model mucosal membrane. The tissue was obtained from chicken after slaughter, removed from its contents and surface fats, and stored frozen in simulated physiological fluid (2.38 g $Na_2HPO_4.2H_2O$, 0.19 g KH_2PO_4 and 8.0 g NaCl/L, pH= 6.8). This membrane was thawed to room temperature before use. Circular piece of the tissue was cut and glued with cyanoacrylate adhesive on the surface of the tissue holder disk made of Plexiglas (5.0 cm diameter). The tablet is directly fixed to the upper surface of the tissue. The disk was placed in the bottom of a glass tube fitting the disk diameter. Fifty ml phosphate buffer pH 5.0 was poured on the tissue surface. The whole assembly was immersed in a water bath maintained at 37.0±0.5ºC the buffer solution was continuously circulated over the membrane surface in a closed circuit at a rate of 2.0 ml/ minute using Watson- Marlow peristaltic pump. The adhesion time for each time was recorded. For each formula, experiment was run in triplicate.

2.3.5 *In-vitro* release studies

In each of the flasks of the USP apparatus I1 (LOGIN UDT-814) connected to autosampler. 500 ml of phosphate buffer (1% potassium dihydrogen phosphate and 0.01% disodium phosphate, pH 5) were equilibrated to 37±0.5°C at 25 rpm using a continuous automated monitoring system. This system consists of dissolution apparatus connected to auto-sampler (SCR-DL) with system controller (DSC-800). An accurately weighed tablet of each of the prepared formulations was added to each flask. Samples were withdrawn at time intervals for 12 hours. For each formula, release runs were performed in triplicate and the absorbance was recorded automatically at 260 nm. The cumulative percentage of drug released was determined as a function of time. Also, the placebo tablets were subjected to the same release conditions and samples at different time intervals were used as blank against the drug.

2.3.6 Analysis of the release data

The release data were kinetically analyzed using different Kinetic models (Zero order, first order

and Higuchi diffusion model) to determine the mechanism of drug release from the different mucoadhesive formulations.

2.3.7 Antimycotic activity study

2.3.7.1 Preparation of agar medium

The agar medium was prepared by dissolving 65 gm of Sabouraud Dextrose Agar (Mycological peptone 10 gm; Dextrose 40gm; and Agar No 1) in one liter of distilled water. The Agar was poured into plastic plates (150 mm). The Agar was sterilized by autoclaving at 121ºC for 10 min.

2.3.7.2 Determination of the antifungal activity of selected, prepared formulations

The activity of selected formulations containing FZ (100 mg) was determined. F5 and F12 were selected representing the lowest and the highest in vitro release respectively. An agar diffusion technique was applied using *C. albecans* ATTC 10231 organism. The tablet was placed on the agar surface. The zone of inhibition diameter was measured after 24 h incubation at 35ºC. Also, the placebo tablets were subjected to the same conditions to detect any activity of the used polymers.

3. RESULTS AND DISCUSSION

Differential scanning calorimetry (DSC) offers information about melting, crystallization, decomposition or a change in heat capacity and is useful to assess the physicochemical status of the entrapped drug as well as the interaction among different compounds [13].

DSC scans were performed on FZ, its corresponding physical mixture and the individual polymers. The DSC scan of untreated Fluconazole showed characteristic sharp endothermic peak (Fig. 4A) at 142°C which is corresponding to its melting point. Carbopol, HPMC and guar gum had no any characteristic peaks in the range of temperature study (Fig. 1B, 1C, and 1D). Concerning the corresponding physical mixture (Fig. 1E), characteristic endothermic peaks of the drug were seen nearly at the same positions, but with low intensity which is may be due to dilution effect.

All formulations showed good, and acceptable crushing strength. The hardness values were ranged from 7.2 to 10.8 Kp. Friability of all tablet formulation is within the acceptable range less than 1% (Table 2).

Table 3 shows the effect of polymer type and ratio on the rate and extent of water uptake by the prepared tablets presented as the percent increase in tablet weight versus time. Tablets contain carbopol show higher rate of water uptake. The rate of water uptake is directly proportional to the carbopol content. As an anionic polymer, carbopol swell rapidly at pH 5. Tablets contain guar gum show higher rate of water uptake than HPMC. On the other hand, addition of MCC or Dibasic Calcium Phosphate slightly retards water uptake.

All the formulation tested showed good adhesive properties. The adhesion time ranged from 16 to 24 hours, this could be attributed to the good bioadhiseve properties of carbopol as well as the cellulosic polymers at pH 5 [14]. The chicken pouch tissue was used instead of vaginal mucosal tissues because of its availability and the two tissues posses similar mucoadhesive properties [15].

The measured surface pH was between 4.2 to 5.3 which resembles the pH of the vagina,thus it will be not irritant [16].

FZ release profiles from the prepared tablets are shown in Figs. 2 and 3. No interference of the used polymers was observed at the measuring wave length. The drug was gradually released from all formulations over a period of more than 12 hours. Therefore, all the prepared tablets could be adequately sustained. The sink condition was maintained all over the release period because the solubility of FZ at pH 5 was reported as 5 mg/ml [17].

It was apparent from the plots that an increase in the bioadhesive polymer contents was associated with a corresponding decrease in the drug release rate. This could be attributed to the extensive swelling of the polymers at high concentrations. This extensive swelling created a thick gel barrier for drug diffusion. These observations were in good agreement with those obtained by other workers [18,19]. Formulations F1-F8 showed less than 50% of drug release after 12 hours. However, increasing the amount of avecil (F9-F12) resulted in an increase in drug release. Formulae F12 that contains the highest amount of avecil (250 mg) showed about 56% FZ released after 12hours.This could be attributed to decrease in swelling as shown in Table 3.

In order to determine the release model which best describes the pattern of drug release, the *in-vitro* release data were fitted to zero order, first order and diffusion controlled release mechanisms according to the simplified Higuchi model.

a- Zero-order Kinetic model: -

$$C = Co - Ko\ t.$$

b- First order Kinetic model: -

$$\log C = \log Co - Kt/2.303$$

c- Higashi diffusion model: -

$$Q = 2\ Co\ (Dt/\pi)\ ½$$

Where: -

Co = initial drug concentration
C = drug concentration (remaining) at time t.
t = time of release
Q = amount of drug released /unit area
Ko = zero order rate constant
K = first order rate constant
D = diffusion Coefficient , it was calculated according to the following equation.
D = (Slope/2Co) 2 π

The preference of a certain mechanism was based on the correlation coefficient (r) for the parameters studied, where the highest correlation coefficient is preferred for the selection of mechanism of release.

Successive evidence of the relative validity of diffusion and first order models obtained by analyzing the data using the Korsmeyer-Peppas equation:

$$M_t/M_\infty = K\ t^n$$

Where Mt/M∞ is the fraction released by the drug at time t, K is a constant incorporating structural and geometric characteristic and n is the release exponent characteristic of the drug transport mechanism. When n =0.5 fickian diffusion is observed and the release rate independent on (t), while 0.5<n<1.0 indicate anomalous (non fickian) transport and when n =1, the release is zero order [20].

The mechanism of drug release from matrices containing swellable polymers is complex. Some systems show either purely diffusion or erosion controlled, and other systems exhibit a combination of the two mechanisms. Higuchi model is applicable if the release of drug is largely controlled by diffusion through water-filled pores in the matrix. A good fit to Korsmeyer-Peppas equation could indicate combined effects of diffusion and erosion mechanisms of drug release.

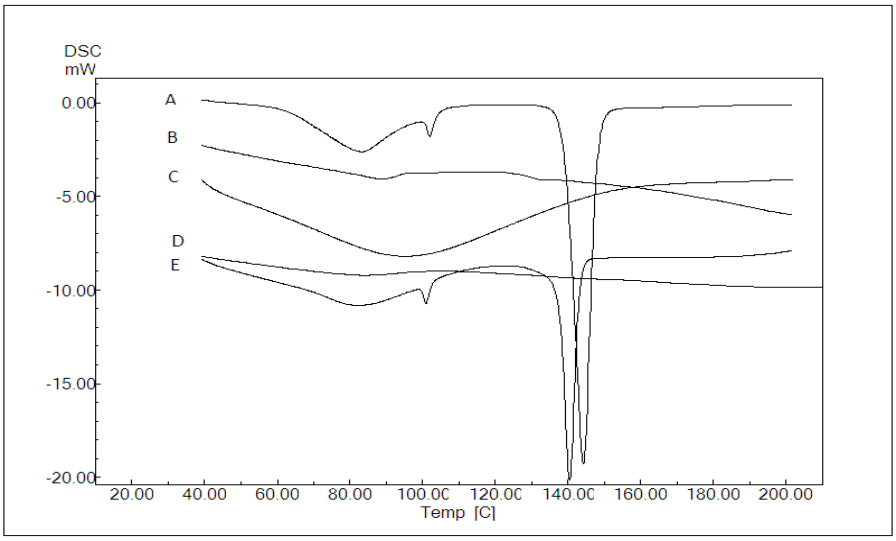


Fig. 1. DSC thermogram of fluconazole and the used polymers
A : Fluconazole ; B: Carbopol ; C: Gaur gum ; D: HPMC ; E : mixture

Table 1. Composition of different fluconazole mucoadhesive vaginal tablets

Materials	Formula (mg)												Control
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	
Fluconazole	100	100	100	100	100	100	100	100	100	100	100	100	-
Carbopol 934	200	200	200	200	100	100	100	100	100	100	100	100	100
HPMC	-	100	-	50	-	100	100	-	100	-	100	100	100
Guar gum	100	-	50	-	100	-	-	100	-	100	-	-	-
Ca phosphate dibasic	100	100	150	150	150	150	100	100	50	50	-	-	-
Avicil PH 102	-	-	-	-	50	50	100	100	150	150	200	250	250
Mg stearate	4	4	4	4	4	4	4	4	4	4	4	4	4

Table 2. Hardness and friability values of fluconazole mucoadhesive vaginal tablets

	Formula											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Hardness(kp)	7.18	8.61	10.8	10.5	8.76	9.6	9.35	8.72	9.65	8.05	7.9	7.6
Friability %	0.3	0.4	0.4	0.46	0.6	0.57	0.6	0.74	0.26	0.29	0.1	0.5

Table 3. % Water uptake values of fluconazole mucoadhesive vaginal tablets

	Formula											
Time (h)	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	88.7	107	134	101	98	107	122	151	133	160	125	143
2	135	192	219	175	151	149	168	202	174	191	164	162
3	192	231	276	240	200	206	195	241	192	222	212	194
12	625	550	575	625	500	425	450	575	300	425	275	275

Table 4. pH values and adhesion time (h) of selected fluconazole mucoadhesive vaginal tablets

	Formula					
	F 1	F 3	F 5	F 6	F 9	F 12
pH	4.5	4.2	4.7	4.6	4.5	5.3
Adhesion time (h)	24	24	18	18	16	16

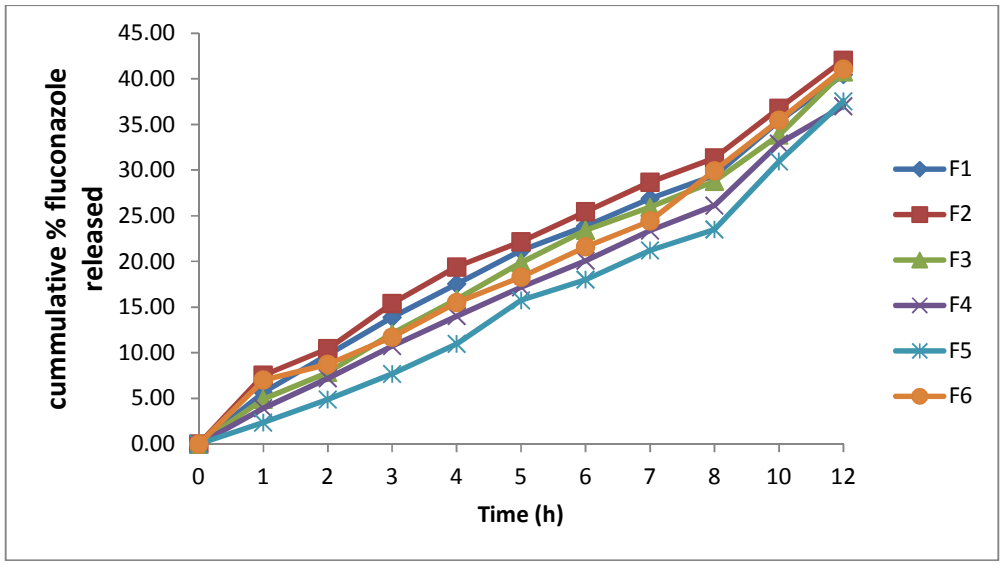


Fig. 2. *In-vitro* fluconazole release from fluconazole vaginal tablet formulations (F1- F6)

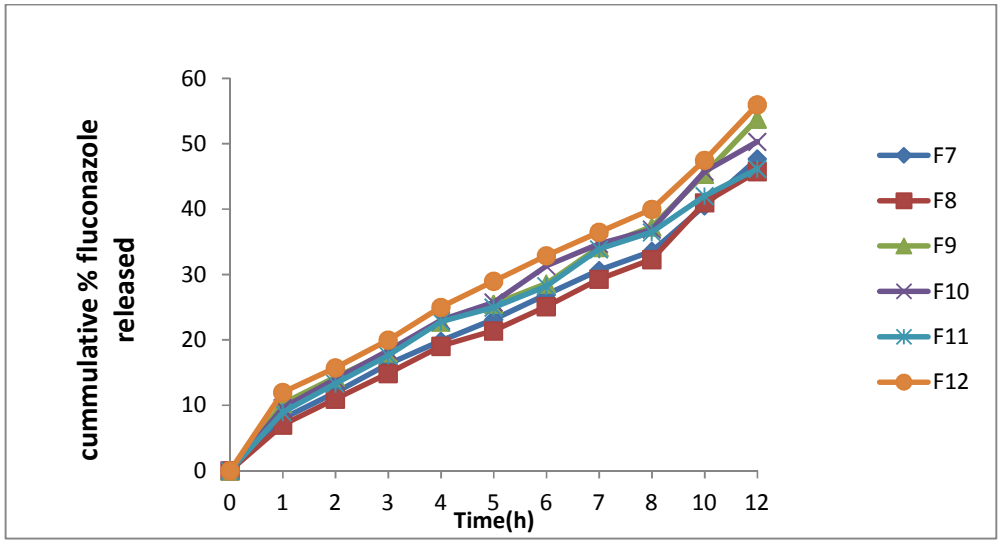


Fig. 3. *In-vitro* fluconazole release from fluconazole vaginal tablet formulations (F7- F12)

Table 5. Diameters of zones of inhibition obtained by the selected fluconazole mucoadhesive vaginal tablets

Zones of inhibitions (mm)	
F 5	**F 12**
30	19
28	20
29	18
Mean= 29	Mean= 19

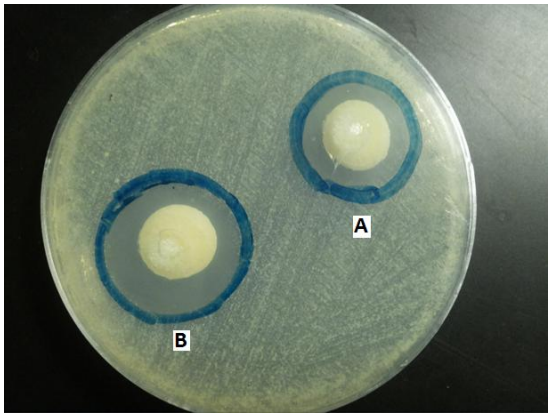
The mathematical treatment of the vitro release data of FZ from the prepared tablets is presented in Table 6. Based on the correlation coefficient values (r), the results of formulations (F1, F2, F4, F6, F7, F9, F10, F11) are in favor of the first order. In the meantime, the results of formulations (F3, F5, F8, F12) are in favor of zero order. However, n values of all formulations were in the range of (0.51-0.83) which support an anomalous non-fickian release behavior controlled by a combination of diffusion and chain relaxation mechanism [17].

Table 6. Kinetic modeling of drug release from vaginal tablets containing Fluconazole

	Release model	Formula no.											
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Zero order	r	0.993	0.990	0.9977	0.9982	0.9967	0.9949	0.9961	0.9937	0.9897	0.9849	0.9899	0.9989
	K_o(mg%/min)	0.0548	0.056	0.0555	0.0519	0.0528	0.0626	0.0620	0.0692	0.0671	0.0621	0.0714	0.0626
First order	r	0.9989	0.9978	0.9960	0.9993	0.9943	0.9959	0.9974	0.9930	0.9975	0.9956	0.9957	0.9959
	K1 (min-1) x10^3	.0.690	0.696	0.69	0.644	0.6450	0.691	0.713	0.828	0.920	0.943	0.8464	1.034
Higuchi diffusion	r	0.9813	0.9853	0.9716	0.9661	0.9427	0.9787	0.9731	0.9762	0.989	0.9881	0.9847	0.9787
	Kh(mg%)/$min^{1/2}$	1.566	1.616	1.576	1.4550	1.4441	1.7846	1.7527	1.9671	1.9341	1.8045	2.0557	1.7846
Log Q Vs log t	r	0.962	0.7920	0.9670	0.9653	0.9644	0.9897	0.9772	0.9884	0.9777	0.9979	0.9930	0.9897
	n	0.580	0.532	0.6450	0.6746	0.8343	0.5806	0.5737	0.5098	0.5125	0.6823	0.6331	0.5806

Antimycotic activity of selected tablet formulations:

The activities of the investigated formulae (5 and 12) were determined using agar-cup diffusion method. Table 5 and Fig. 4 show the zone of inhibition diameter obtained.Both formulations (F5 and F12) tested showed activity against *C. albicans*. It is clear that the zone of inhibition obtained by the formula No. 12 is higher than that obtained by formula No. 5. These results are in accordance with in vitro release release data. The control placebo tablet showed no zone of inhibition.



A : Formula 5 **B : Formula 12**

Fig. 4. Inhibition zone of two selected fluconazole vaginal tablet formulation

4. CONCLUSION

The present study was an attempt to develop a mucoadhesive vaginal drug delivery system for an antifungal drug (Fluconazole). The main advantage achieved by this tablet dosage form resulted from its ability to prolong the local release of the drug in the vaginal cavity. The results suggest that fluconazole-containing mucoadhesive vaginal tablets would be useful for effective and safe treatment of vaginal candidiasis with reduced dosing intervals, lower systemic side effects and hence, improved patient compliance. The compatibility studies revealed that Fluconazole is physically compatible and stable in the presence of the used bioadhesive polymers.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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