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Formulation and Evaluation Once Daily Mucoadhesive Vaginal Tablet of Clotrimazole Using Natural and Synthetic Polymers

Dangi Amish. A*[1], Navin R Sheth[1], Patel Hardik J[2], Shukla Tapan M[2], Patel Hardik M[2]

[1]Department of pharmaceutical Sciences, Saurashtra University, Rajkot – 360005, India.
[2]Department of Pharmaceutics, B.Pharmacy College, Navalgadh, Ta: Dhrangadhra – 363310, India.

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***Corresponding author:**

E-mail: amishdangi@gmail.com
Phone: +91 9428236404

ABSTRACT

Clotrimazole was formulated in mucoadhesive vaginal tablet by direct compression technique using natural and synthetic polymer. Tablets were prepared by directly compression using chitosan as natural polymer and HPMC K15 M as synthetic polymer together with or without addition of microcrystalline cellulose (MCC). The drug content in the tablet was kept 20% each. Drug dissolution rate studies from tablets were carried out in buffer pH 4.8 and distilled water. The mucoadhesive strength was evaluated by detachment force measurement using porcine vaginal mucosal membrane. Chitosan showed maximum bioadhesion and was directly proportional to its total content. The formulations were tested for their swelling behavior using agar - agar plate technique. Swelling study data revealed that swelling index increased with an increase in the content of HPMC K15 M. The formula containing 3:1 % polymer ratio shoed adequate release properties in both media and gave lower values of swelling index compared with the other formulations. The biopharmaceutical studies showed that F1, F3, F4 and F5 formulation released the drug up to 20, 26, 27 and 29 hours respectively, while the F2 formulation was able to release the drug for 24 hours so it is best suitable for once a day dosing frequency. Similarly F2 was negligibly affected by aging. Thus F2 formulation may be considered a good candidate for the vaginal mucoadhesive dosage forms.

INTRODUCTION

Improvement in technology to develop the controlled drug delivery system have been ongoing for decades, with the formulation ranging from simple matrix, or reservoir type devices to transdermal, osmotic pumps, nanoparticles, liposomes, microspheres, bioadhesive, implants and more [1]. Pharmaceutical aspect of mucoadhesion have been the subject of great interest during recent years because mucoadhesion could be solution for bioavailability problems that result from a too short length of stay of the pharmaceutical dosage form at the site of application. It was hoped that bioadhesive vaginal tablet dosage forms release the active ingredients slowly, so that the vaginal would not be immediate exposed to entire dose of active ingredient thereby minimizing its possible toxic effects on the vaginal epithelium [2].

For vaginal delivery systems of antifungal agents to be more effective, they need to reside at the sites of infection for a prolonged period. In addition, convenience of dosing method is an important factor in the design of vaginal application forms. Of vaginal dosage forms, patients are known to better tolerate gels than inserts or ointments. However, the direct application of gels onto the infected sites of the vagina might be difficult as well as inconvenient. This investigation highlights the utility of vaginal delivery of antifungal agents as compared to oral therapy [3]. In view of this, it is desirable to develop a suitable delivery system for vaginal delivery of Clotrimazole (CT). The vaginal delivery of CT would provide high local tissue levels, more rapid drug delivery, and lower systemic exposure. This may be especially important for treating pregnant patients [4,5].

The use of natural polymer is valuable based on proven bioavailability and safety. In this respect, the polysaccharides chitosan, a cationic agent, have received particular attention. Chitosan possesses favorable properties and hence has application in the pharmaceutical and biomedical fields. It is a promising bioadhesive material at physiological pHs. This polymer possesses OH and NH_2 groups that can give rise to hydrogen bonding. Its linear molecule expresses sufficient chain flexibility and their confirmation is highly dependent on ionic strength. These properties are considered for the mucoadhesion [5,6]. Moreover it was observed that chitosan achieves a sustained release behavior at a concentration $\geq 50\%$ of tablet weight. Although chitosan has been used in the tablet intended for

oral sustained release preparation. Its combination with HPMC K15 M has not been reported yet for the vaginal preparation [8,9]. This study accounts for the possible use of chitosan in mixture of different ratios with synthetic polymer (HPMC K15 M) for the preparation of mucoadhesive tablets to be used as a vaginal delivery system for clotrimazole.

Here, the aim of the present study was to develop once daily mucoadhesive vaginal delivery system for the drug clotrimazole, which is designed to improve the adhesion to the vagina in order to prolong the residence time and consequently to obtain a long therapeutic concentration at the site of infection. Formulated vaginal tablets were evaluated for bioadhesive properties, in vitro release studies, in vitro swelling studies and stability studies[10,11].

MATERIALS AND METHODS

Chemicals

Clotrimazole was obtained as a gift sample from JB chemicals and Pharmaceuticals Ltd, Mumbai. Chitosan of low viscosity grade (molecular weight = 625000 dal) was obtained from Biological E Ltd, Hyderabad. HPMC K15 M was obtained as a gift sample from Alex Pharmaceutical Pvt. Ltd, Sanand. Potassium dihydrogen phosphate (Chem. dyes corporation), agar powder (Hi – Media labs Pvt. Ltd.), magnesium stearate (Umiya Chemicals), were obtained from commercial sources. All the reagents and chemicals used were of analytical grades.

Preparation of clotrimazole vaginal tablet

Chitosan (0.4g) was soaked in 5.5ml if 10% acetic acid for 48 hours; the lumps were homogenized using a spatula and left for 1 hour at room temperature. The mass was then taken by a plastic syringe and extruded onto a Teflon plate for 1 hour at room temperature, then dried in oven at 50°C for 8 hours. Rods obtained were cut into small pieces and soaked in 5% gluteraldehyde for 1 minute (≈ 1.5ml / 0.4g chitosan). They were then filtered, left to dry in desiccators overnight and powdered in mortar. The vaginal mucoadhesive tablet of clotrimazole was prepared by using powdered chitosan and other excipient like HPMC K15 M, magnesium stearate and MCC. Tablets were prepared by direct compression method. The required weighed amount of drug, other materials were sieved through # 80mesh and mixed for 5min. Mixture is compressed using double punch tablet machine (Cadmach Machines, Ahmedabad) which is fitted with flat – forced punches [13,14,15]. The composition of all the formulation is given in table

Table No.1: Composition of different investigational mucoadhesive vaginal tablets

Formulation	Drug (%)	Polymer ratio (%)	
		Chitosan	HPMC K15 M
F1	20%	80	0
F2	20%	60	20
F3	20%	40	40
F4	20%	20	60
F5	20%	0	80

Evaluation of prepared tablet formulations

UV analysis of Clotrimazole

Preparation of standard curve in PBS (pH 4.8): Methanol (6:4)

10 mg accurately weighed clotrimazole was dissolved in the PBS (pH 4.8): methanol (6:4) and volume was made up to 100 ml with PBS (pH 4.8): methanol (6:4) [Stock A]. From stock A, different dilutions were prepared in the concentration range of 10,20,30,40,50,60,70,80 µg/ml and absorbance was recorded in Shimadzu-1700 UV/Visible spectrophotometer at $\lambda_{max,}$ 260.5 nm.

Preparation of standard curve in methanol

10 mg accurately weighed CT was dissolved in the methanol and volume was made up to 100 ml with methanol [Stock A]. From stock A, different dilutions were prepared in the concentration range of 10, 20,30,40,50,60,70,80 µg/ml and absorbance was recorded in Shimadzu-1700 UV/Visible spectrophotometer at λ_{max}, 261 nm.

IR Spectroscopy

The infrared spectra of CT and chitosan were obtained by FTIR (Jasco – 470 plus) The study was performed to check the interaction of chitosan with CT. In this study KBr (Uma chemicals, Baroda, India) was used as a reference to study the interaction.

Average drug content

Tablets of each formulation were ground in a mortar to a powder form. An accurately weighed amount of the powder, equivalent to 100mg of clotrimazole, was transferred to a 100 ml volumetric flask. The powder was dissolved in 10% acetic acid using a magnetic stirrer overnight. After filtration, the solution was assayed spectrophotometrically (shimadzu-1700) at 260.5 nm against 10% acetic acid as blank. The content was calculated using a calibration curved for the drug [16]. No interference from any of the tablet component was observed under assay condition procedure.

Dissolution rate study

In order to determine *in vitro* release of clotrimazole from different vaginal tablets, dissolution test apparatus USP *type II* (paddle type) (Elecro Lab, Mumbai) was used. A tablet (≈500mg) was glued in the center of a 9 cm diameter glass disc. Dissolution media were 650ml of either distilled water or phosphate buffer (pH 4.0 ± 0.1) at 37° C was used with constant stirring speed (25rpm) for up to 100% drug release from tablet. Sample of 5ml were withdrawn at suitable time intervals in triplicate and were compensated with fresh dissolution medium at 37°C. The amount of clotrimazole was analyzed spectrophotometrically at λ_{max} 260.5 nm (shimadzu-1700). No interference occurred due to tablet excipients or to cyanoacrylate glue at this wavelength. Dissolution tests were performed in triplicate and standard deviation was applied [16].

Swelling study

The swelling rate of vaginal bioadhesive tablets were evaluated by using 1% w/v agar gel plate method. Each tablet was placed separately on gel surface in petridis, which were placed in an incubator and allowed to swell at 37°C for at least 25 hours. The tablets were periodically removed and their weights were checked before and during the swelling by using electronic

balance. Finally swelling indexes of all investigational formulations were calculated [18,19,21]. Each experiment was performed in triplicate.

Swelling index = w_2-w_1/w_1

Where,

W_1 = Weight of medicated tablet before swelling study

W_2 = Weight of tablet during swelling study

Determination of bioadhesive properties

A modified balance method was adapted to measure bioadhesion properties. The vaginas of freshly sacrificed porcine were removed and mucous membrane (2mm thick) were excised by removing the underlying connective tissues and thoroughly washed with phosphate buffer (pH 4.8 ± 0.1). The membrane was glued to moving platform with α- cyanoacrylate glue. Tablets were glued to different weight with α- cyanoacrylate glue by following tarring of the balance. A volume (0.1ml) of buffer pH 4.8 was slowly added using a plastic syringe over the mucosal sample. The platform was slowly raised until the tablet touched the mucosa. The tablet and mucosa were left in contact for 15 minutes, after which the balance was again tarred and corresponding weights were added to the pan. The addition was stopped upon detachment of the tablet from the mucosa. The equivalent adhesion force was then calculated in g/cm^2. Each adhesion experiment was repeated 6 times [19,20,22].

Stability study

The best batch was subjected to stability studies at elevated temperature (i.e. 60°C / ambient humidity) for six weeks. The samples of the dosage form were withdrawn at end of sixth week and evaluated for the changes in physical characters and drug release pattern [24].

RESULTS AND DISCUSSION

UV analysis of clotrimazole

An absorption maximum of drug was determined by UV spectrophotometric method using shimadzu-1700 UV/Visible spectrophotometer. The standard curve of drug were prepared in PBS (pH7.4): methanol [6:4] and in methanol in the concentration range of 10 to 80 µg/ml. A straight line with correlation coefficient 0.9994 for PBS (pH 4.8) : Methanol [6:4] and 0.9996 for methanol, indicate that the drug follows Beer's law within the specified concentration range. It has been found that the λ_{max} for drug in PBS (pH 4.8) : methanol [6:4] was 260.5 nm and in methanol was 261 nm. Equations are as follows;

In PBS (pH 7.4) : methanol [6:4]-

$ABS = K_1C + 0.0007$ $K_1 = 0.0022$

In methanol $-ABS = K_1C + 0.00073$ $K_1 = 0.0023$

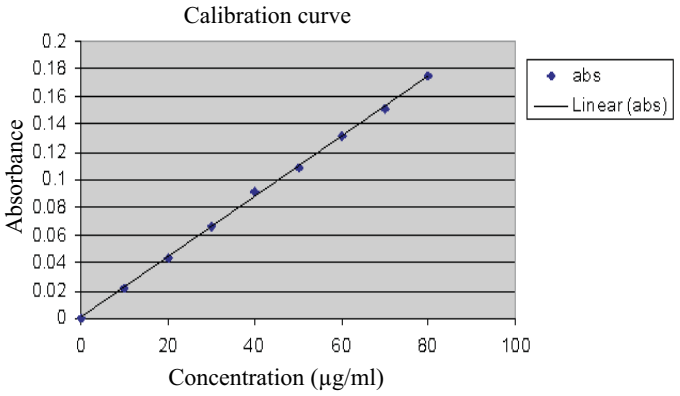

Fig.1: Calibration curve in (pH 4.8) : Methanol (6:4) at λ_{max} (260.5nm)

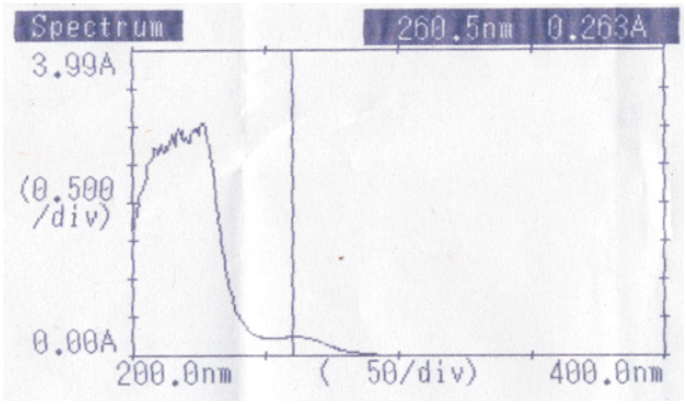

Fig. 2: UV spectrum of clotrimazole in PBS pH 7.4: Methanol (6:4) solution in methanol

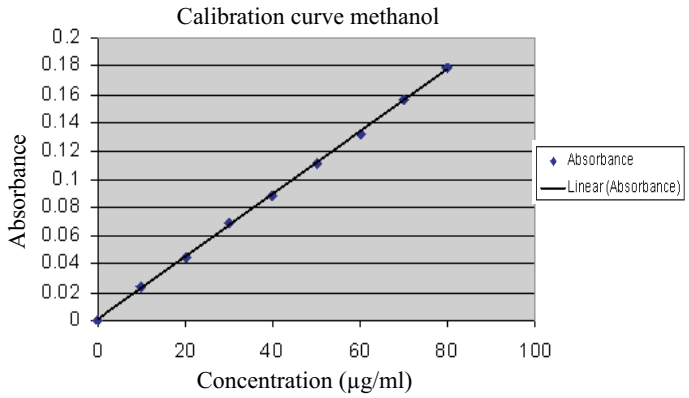

Fig. 3: Calibration curve in Methanol at λ_{max} (261 nm)

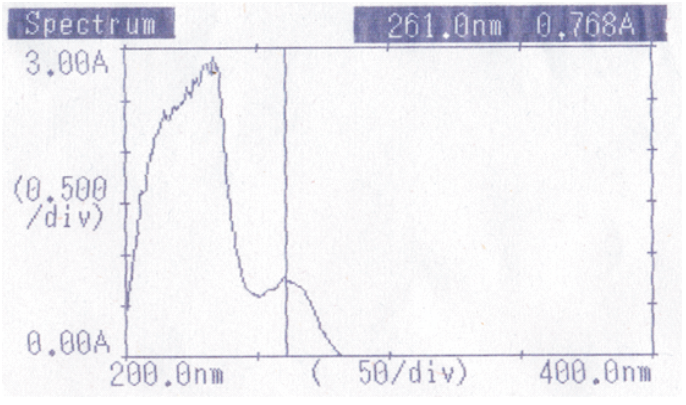

Fig.4: UV spectrum of clotrimazole in Methanol

IR Spectroscopy

The IR Spectroscopy was used as a mean of studying drug-excipient compatibility and also to confirm the structure of drug in the given dosage form. The study reveals that as identified by IR spectrum and the main peaks found at 765, 752, 708, 1075, 741, 1205 cm^{-1} of sample which is identical to standard spectra reported. The IR spectra of the chitosan showed a strong peak of the primary amino group (N-H bending) at 1645.95 cm^{-1}. The presence of this group confirmed the structure of chitosan.

Average drug content was 101.02% ± 1.2, and the results of content uniformity test proved that there was homogeneous drug distribution.

Dissolution rate study

The release of clotrimazole in either buffer pH 4.8 or distilled water from different matrix formulation is shown in figures 8 and 9 respectively. No lag time was observed in any of the formulations studied in both dissolution media. Table 2 shows values of dissolution efficiency (DE) of the different formulation in both media.

In all the formulations it was found good drug release profile. Obviously, in the absence of or at low level of HPMC K15 M (especially in batch A & B), the cellulose ether could not maintain the integrity of the matrix in the presence of higher levels of chitosan resulted in burst release as compared to the formulations containing higher HPMC release.

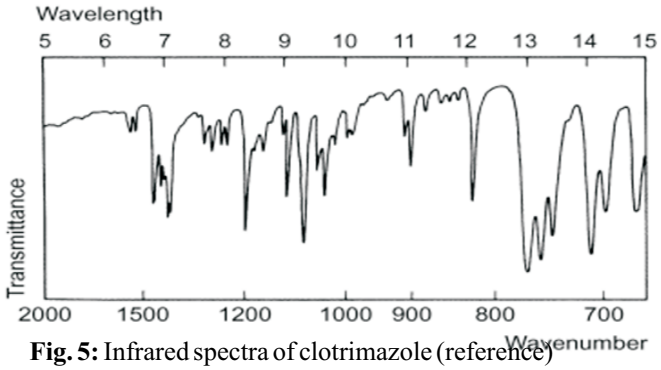

Fig. 5: Infrared spectra of clotrimazole (reference)

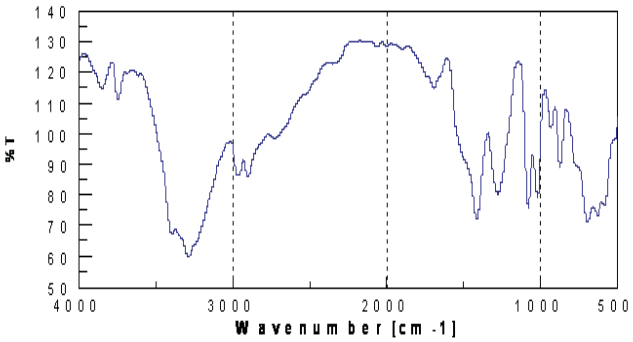

Fig.6: Infrared spectra of clotrimazole (working standard)

Table.No. 2: Selection of best formulation on its bioadhesive strength and in vitro drug release profile data

Sr. No.	Time	DISSOLUTION DATA (Drug release study)									
		Buffer pH 4.8					Distilled water				
		F1	F2	F3	F4	F5	F1	F2	F3	F4	F5
1	0	0	0	0	0	0	0	0	0	0	0
2	2	9.41±0.25	13.51±0.09	5.01±0.24	6.08±0.71	4.01±0.11	9.25±0.19	8.45±0.36	7.09±0.41	6.19±0.56	3.95±0.61
3	4	18.21±0.14	24.12±0.16	12.03±0.29	10.11±0.33	9.24±0.39	16.01±0.14	17.89±0.44	14.33±0.19	10.36±0.14	8.12±0.90
4	6	27.15±0.17	37.21±0.22	16.78±0.78	15.85±0.64	13.22±0.88	26.03±0.73	23.55±0.21	23.55±0.91	16.14±0.16	14.26±0.12
5	8	36.45±0.37	52.26±0.84	24.58±0.78	24.02±0.68	22.14±0.14	34.11±0.25	32.74±0.38	31.81±0.85	26.78±0.57	24.15±0.68
6	10	48.25±0.19	61.24±0.54	32.66±0.45	30.25±0.54	28.89±0.21	43.12±0.17	43.10±1.02	38.19±0.29	32.43±0.63	30.01±0.33
7	12	59.27±0.55	68.78±0.47	39.89±0.59	37.69±0.81	35.62±0.83	50.12±0.18	59.99±0.99	46.34±1.23	40.99±0.18	38.56±1.11
8	14	68.26±0.45	77.89±0.84	47.21±0.47	43.24±0.36	41.10±0.86	59.35±0.16	62.32±0.74	54.12±0.11	46.22±0.29	44.38±0.32
9	16	76.12±0.80	82.45±0.24	55.12±0.40	51.26±0.90	49.26±0.74	67.12±0.60	71.11±0.66	61.22±0.83	54.12±1.25	54.77±1.36
10	18	80.24±0.17	89.26±0.50	63.89±0.47	59.58±0.36	57.89±0.49	77.12±0.14	78.22±0.30	70.49±0.20	63.19±1.24	60.14±1.05
11	20	83.24±0.24	92.58±0.98	72.22±0.91	65.14±0.83	64.35±0.81	84.12±0.73	84.14±0.87	79.42±0.61	67.89±0.60	65.08±0.84
12	22		96.58±0.58	82.14±0.14	71.26±0.75	69.78±0.19	94.56±0.38	88.01±0.19	84.02±0.68	76.03±0.82	70.18±0.45
13	24		98.60±0.82	89.26±0.74	79.25±0.52	77.89±0.10		93.89±0.35	87.69±0.58	82.33±0.54	76.45±1.88
14	26			98.10±0.58	88.25±1.25	84.26±1.69		96.45±0.99	92.11±1.06	87.05±1.58	81.02±0.58
15	28				98.10±1.09	90.21±0.65			94.78±0.68	91.02±0.54	86.44±1.02
16	30					98.81±1.00				93.45±0.98	91.25±0.68
17	32										98.15±1.09

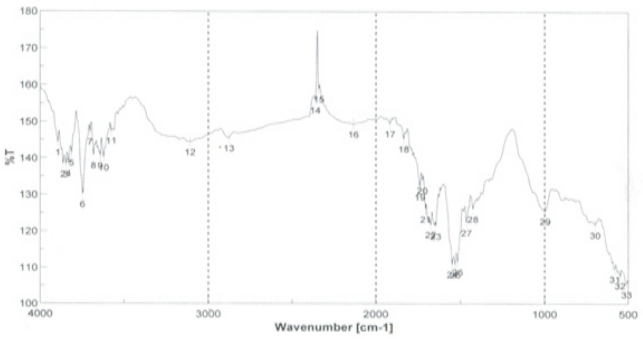

Fig. 7: IR Spectra of chitosan sample.

An inverse relationship was found between swelling index and percent release of clotrimazole in all formulations. When the amount of HPMC in the matrix is high, it causes a greater degree of swelling. This is turn reduces the drug release, as the diffusion path length of drug is now longer, resulting in controlled release. The results also indicated that as the chitosan content increased there was slight decrease in percent drug release and it can be explained by swelling behavior of HPMC and chitosan matrix system.

In vitro swelling studies

Swelling is the important parameter to be studied before considering mucoadhesion. While some reports showed direct relation between swelling and mucoadhesion, other did not. The swelling results expressed in term of swelling index at 25°C and 37°C. The swelling index of the formulation mainly depends upon the amount of HPMC. As shown in figure 10 and Table No.3, swelling of tablet with HPMC K15 M was higher and increased with increase in HPMC K15 M content. On the other hand, formulations with higher concentration of hydrophilic polymer (HPMC K15 M), due to its lower cross – link density, has increased chain flexibility thereby resulting in more swelling of the tablet.

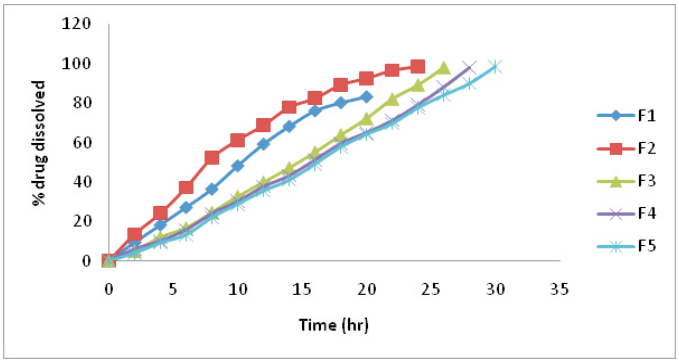

Fig. 8: Clotrimazole release profile from different tablet formulations in buffer pH 4.8

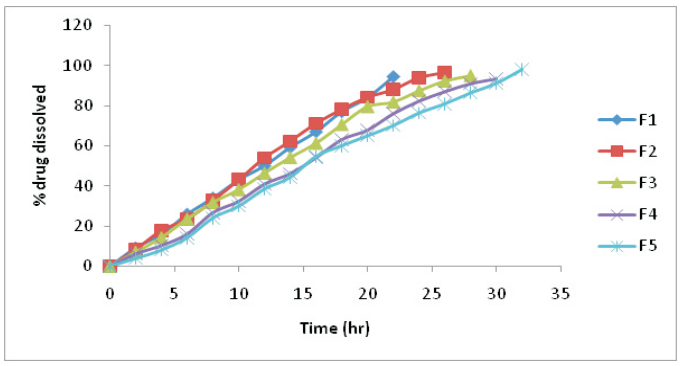

Fig. 9: Clotrimazole release profile from different tablet formulation in distilled water

Table. No. 3 Observed swelling index of investigational formulations using agar gel plate method

Sr. No.	Time (hr)	Swelling index of all formulations				
		F1	F2	F3	F4	F5
1	0.5	0.072 ± 0.003	0.066 ± 0.023	0.085 ± 0.034	0.091 ± 0.014	0.095 ± 0.010
2	1.0	0.108 ± 0.023	0.094 ± 0.009	0.120 ± 0.022	0.145 ± 0.024	0.184 ± 0.009
3	2.0	0.241 ± 0.035	0.274 ± 0.015	0.281 ± 0.056	0.308 ± 0.008	0.351 ± 0.032
4	4.0	0.302 ± 0.010	0.364 ± 0.022	0.041 ± 0.006	0.047± 0.051	0.059 ± 0.071
5	6.0	0.572 ± 0.024	0.644 ± 0.059	0.718 ± 0.019	0.872 ± 0.045	1.102 ± 0.148
6	8.0	1.148 ± 0.089	1.763 ± 0.145	1.821 ± 0.243	2.140 ± 0.328	2.284 ± 0.411
7	10.0	2.125 ± 0.224	2.150 ± 0.246	1.786 ± 0.045	2.321 ± 0.214	2.712 ± 0.248
8	12.0	2.310 ± 0.384	2.258 ± 0.874	2.113 ± 0.045	2.425 ± 0.352	2.912 ± 0.315
9	24.0	2.471 ± 0.257	2.673 ± 0.256	2.931 ± 0.024	2.947 ± 0.187	3.124 ± 0.045
10	30.0	2.644 ± 0.448	2.710 ± 0.208	3.012 ± 0.100	3.084 ± 0.066	3.399 ± 0.387

Adhesion study

It was suggested by several workers that the initial interaction between the polymer and the biological surface is through electrostatic interaction followed by mechanical interlocking of polymer chains. Therefore, the surface change density of polymer is important for electrostatic behavior during the adhesion process. At acidic pH simulating that of the vagina (buffer pH 4.8), chitosan has been identified as a linear polycation that readily adheres to negatively charged surfaces. In the study it was

seen that as the amount of HPMC K15 M increased adhesion also increased. The values of adhesion force showed a very slight variation. From the study it was found that adhesion occurs shortly after the beginning of swelling, but the bond formed may not be very strong. In the case of F2, this was the least hydrated as shown from the results of swelling index. F2 would be pressed in to cell surface instead of interacting with only the mucin layer, consequently, this could result in a higher force required for its detachment. The formation of rigid network due to cross linking with CMC, associated with F2's restricted hydration, may have enhanced mucoadhesion properties of F2.

Stability Study

The batch B has been selected as the best batch among all investigational formulation based on different studied parameters, which was able to release the clotrimazole more than 96% in an optimum time period with sufficient adhesive strength. Accelerated stability study testing on selected batch was carried out to determine the rate of degradation of the formulation. There was no physical change in the tablets after 6 weeks. Since the resulting similarity factor was 80.21 and it lies between 50 and 100, both fresh and aged samples of selected batch were not significantly different as respect of their drug release profiles.

CONCLUSION

In conclusion, F2 containing 60% chitosan and 20% HPMC K15 M was found to be the best formulation regarding all the properties evaluated in order to achieve the aim of this study. Drug was released about 98% of clotrimazole content over a period of 30 hours in buffer pH 4.8. Moreover, maximum adhesion was obtained with a minimum pressure applied. This lack of pressure effect may be of value during insertion in vagina, as it differentiates this formulation from other pressure sensitive adhesive formulations. Tablets were prepared by direct compression, which is an easy, rapid and cheap method. No organic solvent was used during the preparation of formulations. All excipients used are safe and easy available.

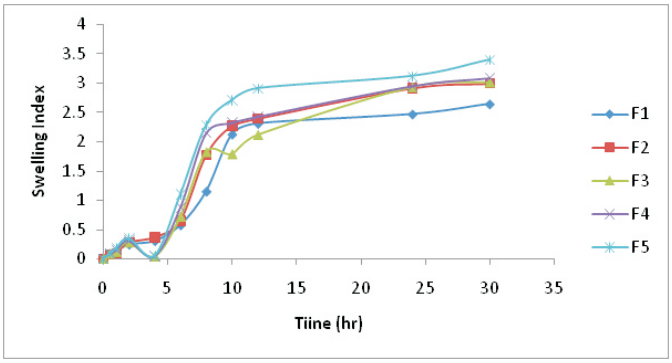

Fig. 10: Swelling index profile of clotrimazole tablet formulations at 37° C in buffer pH 4.8

Table No. 4: Adhesion force profile of all clotrimazole formulations

Sl. No.	Investigational Formulation	Adhesive force
1	F1	29.14 ± 2.25
2	F2	26.45 ± 1.75
3	F3	21.48 ± 1.09
4	F4	16.87 ± 1.16
5	F5	11.33 ± 1.88

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