FORMULATION AND EVALUATION OF NOVEL MUCOADHESIVE VAGINAL TABLETS OF MICONAZOLE NITRATE

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ABSTRACT

The aim of this study was to formulate a mucoadhesive vaginal tablet of Miconazole Nitrate using a combination of mucoadhesive polymers such as Carbopol 934P, HPMC K15M, Xanthan gum, Gaur gum, and microcrystalline cellulose to achieve an excellent therapeutic effect and patient compliance in the treatment of bacterial vaginosis. Because of the presence of both natural and synthetic, mucoadhesive and rate retarding polymers, the formulation has a sustained-release effect with good mucoadhesion, which aids in decreasing dose frequency. The direct compression method was used to prepare mucoadhesive vaginal tablets. FTIR was used to investigate drug excipient incompatibility. The % swelling index, Muco-adhesive strength, drug content, % drug release, and ex-vivo mucoadhesion time of the mucoadhesive vaginal tablet were all evaluated. The findings of these studies demonstrated the utility of Miconazole Nitrate for local controlled antifungal delivery to the vagina. Our research could lead to a vaginal tablet formulation of Miconazole Nitrate that is effective against Candida albicans.

KEYWORD: Miconazole Nitrate, Bacterial vaginosis, Mucosal drug delivery, Bioadhesive properties, Antifungal Activity.

INTRODUCTION

Vaginal candidiasis is a common condition, with up to 75% of all women experiencing at least one episode during their lifetime. Candida albicans is the most common cause of vaginal candidiasis, accounting for more than 80% of cases. The majority of Candida vaginitis patients respond to topical treatment with Nystatin or Imidazoles (Richardson et al., 2012)
. Miconazole Nitrate is a type of antifungal agent that is used to treat Candida infections (Ringdahl et al., 2000). It comes in tablet, capsule, or suspension form for oral administration, as well as a sterile solution for intravenous injection. Most patients with Candida vaginitis respond to oral miconazole, but they experience GIT side effects in the meantime. Solutions, suspensions, gels, foams, and tablets are examples of traditional vaginal drug delivery systems (Kast et al., 2002). Vaginal creams and gels provide lubrication but are messy and easily removed if water soluble. Suspensions and solutions have an uneven distribution in the vagina. The rapid elimination of topically applied drugs is a major challenge for the successful eradication of vaginal fungal infections. The delivery system in which the drug is incorporated is thus an important consideration that should be designed to maximise drug retention. As a result, an effective drug delivery system that prolongs drug contact with the vaginal mucosal surface has been developed, and flexible mucoadhesive films for topical use have been developed for local drug delivery. Vaginal tablets appear to be useful dosage forms because they are simple to apply, portable, and the user is aware of how many units remain (Parrott et al., 1988; Khan et al., 1998). The most significant advantages of bioadhesive tablets are the controlled release of the drug and the ability to keep them in the vagina for extended periods of time. They also allow for lower dose frequencies (Duchěne et al., 1988). Because of their high bioadhesive strengths, carbomers, hydroxypropylmethyl cellulose, and plant gums are ideal excipients in vaginal bioadhesive tablet formulations. The goal of this study was to create mucoadhesive vaginal tablets of miconazole nitrate that could efficiently deliver drug for an extended period of time against Candida albicans using a combination of mucoadhesive polymers. Swellings, mucoadhesion time, and drug release of tablets containing various proportions of mucoadhesive polymer were measured. The invitro antimycotic activity of various formulations was investigated. (Hui et al., 1985; Akiyama et al., 1995)

MATERIALS AND METHODS

Material

Miconazole Nitrate was provided as gift sample from Leben Laboratories Pvt. Ltd., Akola, Maharashtra, Carbopol 934P Mannitol, Xanthan gum and Gaur Gum were obtained from Mylochem Ltd., Mumbai, while HPMCK15M was obtained from Trio Pharma Chem Paldi, Ahmedabad, Microcrystalline Cellulose, Talc and Magnesium stearate were obtained from SD Finechem Limited, Mumbai.

Methods

A) Preparation of Mucoadhesive Vaginal Tablets

(Jin et al., 2017; Dattatraya et al., 2016; Mohammed, F.A. and Khedr, H., 2003)

Miconazole Nitrate Mucoadhesive Vaginal Tablets each contained 200 mg of drug prepared according to the formula shown in Table 1. Miconazole Nitrate equivalent to 200 mg drug was accurately weighed, and other excipients such as carbopol, xanthan gum, guar gum, HPMC, and microcrystalline cellulose were accurately weighed and thoroughly mixed, followed by addition of magnesium stearate as a lubricant and talc as a glidant. The powder mixture of Miconazole Nitrate and excipients was then compressed into tablets using a 10 Station Rotary Tablet Compression Machine (Chamunda, Ahmadabad) and a suitable set of dies and punches.

Table 1: Formulation of Mucoadhesive Vaginal Tablets of Miconazole Nitrate

Ingredients (mg)	Formulation								
	V1	V2	V3	V4	V5	V6	V7	V8	V9
Miconazole Nitrate	200	200	200	200	200	200	200	200	200
Carbopol 934P	50	100	50	50	100	50	50	100	50
Gaur Gum	50	50	100	-	-	-	-	-	-
Xanthan Gum	-	-	-	50	50	100	-	-	-
HPMC K15M	-	-	-	-	-	-	50	50	100
Microcrystalline Cellulose	190	140	140	190	140	140	190	140	140
Magnesium Stearate	3	3	3	3	3	3	3	3	3
Talc	7	7	7	7	7	7	7	7	7
Total Weight of Tablet	500	500	500	500	500	500	500	500	500

B) Characterization of Pure Miconazole Nitrate and excipients

Infrared Spectroscopy (FTIR): (Qushawy et al., 2018; Gupta et al., 2019)

Pure Miconazole Nitrate, individual excipient and physical mixture of drug and excipients were scanned and recorded in the range of 4000-400 cm^{-1} by using Infrared spectrophotometer, (Bruker, Alfa-T, Germany). The samples were triturated with dried potassium bromide using mortar and pestle. The mixture after grinding into fine powder was kept uniformly in suitable die and compressed into a pellet form by using hydraulic press. The resultant pellet was mounted in a suitable holder in the FTIR spectrophotometer.

C) Evaluation of Vaginal Tablets:

(Lachman et al., 2009; Saeedi et al., 2018; I.P.; USP; Sweety et. al., 2016)

The formulated vaginal mucoadhesive tablets of miconazole nitrate of each batch were evaluated for diameter and thickness using a calibrated dial Vernier caliper. **Tablet Hardness** was determined using the Pfizer hardness tester. **Friability** is the measured accoriding USP by using Roche friability Apparatus (Electrolab, India). **Weight Variation Test** and **Drug Content** was carried out as per procedure given in Indian Pharmacopoeia. For the determination of the **surface pH**, a combined glass electrode is used. The bioadhesive Vaginal tablet was allowed to swell by keeping it in contact with 5 ml distilled water in a petri dish for 2 hr at room temperature. The pH was identified by bringing the electrode into contact with the tablet surface and allowing the surface to equilibrating for 1 min. (Mittal and Pawar, 2018; Patil et al., 2018) **Swelling Index** was determined by placing tablets in petri dishes containing

10 mL of phosphate buffer (pH 4.5) solution. In **Matrix Erosion Test,** tablets initial weight was noted down (W1). Swollen tablets were dried at 60°C for 24 hrs in an oven and kept in desecator for 48 hrs and reweighed (W3) to calculate % matrix erosion. (Balaji et al 2014., Koradia, H. and Chaudhari, K., 2018)

D) Measurement of Bioadhesive Strength:

(Pritchard et al., 1996; Gupta et al., 1992; Garg et al., 2002; Patel et al., 2007)

To assess and contrast the bioadhesive strengths of the mucoadhesive tablets suggested by Sanjay Garg et al., an in-vitro assembly has been created. Using a tensile experiment on a specially constructed assembly, the bond strength between the formulation and the membrane removed from goat Vaginal mucosa was identified.

E) Ex vivo Mucoadhesion Time:

(Shankar et al., 2009; Singh and Ahuja, 2002; Kadam., 2004)

An apparatus for USP disintegration that had been locally modified was used to calculate the ex vivo mucoadhesion time. The medium contained 200 ml of phosphate buffer (pH 4.5) that was kept at a temperature of 37°C. The goat Vaginal mucosa was affixed vertically to the disintegration device and tied to the surface of a glass slab. Using phosphate buffer (pH 6.8) to hydrate the Vaginal tablet, its surface was brought into contact with the mucosal membrane by gently pressing down on it for 30 seconds. The tablet was completely submerged in the buffer solution at the lowest point and was out at the highest point because the glass slide allowed for up-and-down movement. Tablet adhesion was tracked for 12 hours after a slow stirring rate was used to simulate the Vaginal cavity environment after 2 minutes. The mucoadhesion time was measured as the time required for detachment from the goat Vaginal mucosa. The experiments were carried out in triplicate (n = 3), and the ex vivo mucoadhesion time was determined using mean values.

F) Detachment Force Measurement (Madhusudan et al., 1998; Sudarshan et al., 2015)

This technique is used to evaluate the mucoadhesive properties of various polymers in vitro. Martti Marvola created a modified method to evaluate the propensity of mucoadhesive materials to adhere to the oesophagus. The assembly consists of an aerator, a stand for holding the beaker, a reservoir for adding water, and a single organ bath.The force in Newton in calculated by the equation,

$$F = 0.00981\ W/2$$

G) In-Vitro Dissolution Study

Utilizing the USP dissolution testing apparatus II, the release rate of Miconazole Nitrate from Bioadhesive tablets was calculated (Paddle type). At 37 0.5°C and 50 rpm, the dissolution test was carried out with 900 ml of buffer pH 4.5. For a period of 12 hours, a sample (5 ml) of the solution was taken out of the dissolution apparatus hourly and replaced with new dissolution medium. The appropriate dilution of the solution was used to measure the absorbance of these solutions at a wavelength of 272 nm.

H) Kinetic Study

(Suvakanta et al., 2010; Lokhandwala et al., 2013; Paarakh et al, 2018)

The Peppas release rate and the diffusion mechanism for the drug release were said to be followed by the matrix systems. The gathered data was fitted into the Higuchi matrix, Peppas and Hixson Crowell model in order to analyse the mechanism for the release and release rate kinetics of the dosage form. The best-fit model in this case was chosen by contrasting the r-values obtained.

Zero Order Kinetics is represented by the equation $\mathbf{Q_t = Q_o + K_o t}$

First Order Kinetics is studied by fitting the release rate data were fitted to the equation $\mathbf{Log\ C_t = log\ C_o + K_t / 2.303}$

Higuchi Model is studied by equation $\mathbf{Q_t = K_H \times t^{1/2}}$

Korsmeyer - Peppas Model - To study this model, the release rate data is fitted to the equation $\mathbf{Mt / M = K.\ t^n}$

I) Accelerated Stability Studies of Optimized Formulation

(Grimm, 1998; Bagul, et al 2009; Chime et al., 2013)

According to ICH guidelines, short-term accelerated stability testing was performed over a six-month period in a stability chamber at 40 2 °C and 75 5% relative humidity (RH). The initial, intermediate, and final time points were used to test the stability of the mucoadhesive Vaginal tablets of miconazole nitrate of the optimised formulation V9 (e. g., 0, 3, and 6 month). The mucoadhesive Vaginal tablets were once again examined for their outward appearance, assay (%), and in vitro drug release profile at the end of the third and sixth months of the tablets exposed to the stability chamber.

J) Antimycotic Study of Optimized Formulation

(Swamy et al., 1974; Sawyer, et al 1975; Scorzoni et al., 2007)

The activity of selected formulations containing miconazole nitrate was determined. For this, formulation V9 was selected amongst the various formulation as optimized one. 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.

RESULT AND DISCUSSION

FTIR Spectra of Drug and Excipients:

Drug excipient compatibility study was carried out with help of FTIR spectroscopy.Pure drug miconazole nitrate showed the characteristic, when this spectrum compare with spectrum of physical mixture it shows no significant changes in the characteristics peaks of pure miconazole nitrate and other excipients of formulation. This indicates that the miconazole nitrate and different polymers used in the formulation are not having any interactions between them indicates drug and polymer are compatible to each other.

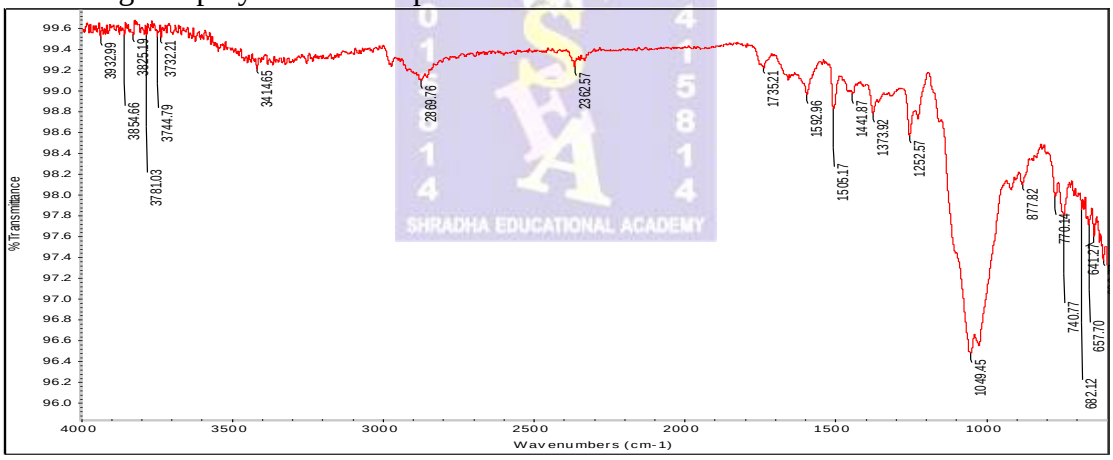

Figure 6.3: FTIR Spectra of Pure Miconazole Nitrate

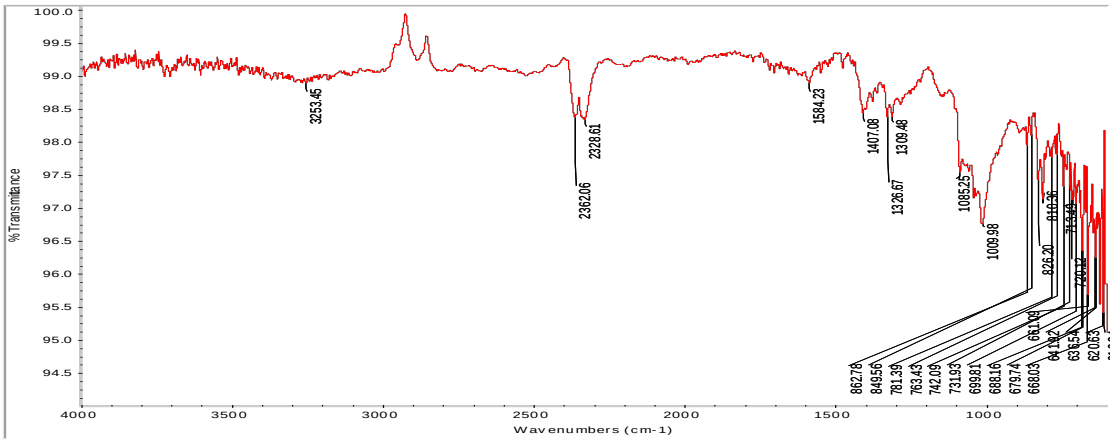

Figure 6.10: FTIR Spectra of MCN Vaginal Tablet Physical Mixture

Evaluation of Mucoadhesive Vaginal Tablets of Miconazole Nitrate: Miconazole Nitrate mucoadhesive Vaginal tablets were prepared using the direct compression method. As shown in Tables 2 and 3, all of the formulations were assessed for key characteristics including diameter, thickness, hardness, friability, weight variation, drug content, surface pH, and others.

Table 2: Evaluation of Mucoadhesive Vaginal Tablets of Miconazole Nitrate

Formulation	Diameter (mm)	Thickness (mm)	Hardness (kg/cm^2)
V1	9.3±0.05	5.1±0.03	5.3±0.05
V2	9.1±0.04	5.0±0.04	5.1±0.04
V3	9.4±0.03	4.6±0.02	5.3±0.06
V4	9.3±0.05	4.6±0.01	5.0±0.02
V5	9.1±0.03	4.7±0.03	4.8±0.02
V6	9.2±0.04	4.8±0.02	5.2±0.05
V7	9.1±0.03	4.6±0.02	4.6±0.03
V8	9.1±0.03	4.5±0.01	4.7±0.04
V9	9.0±0.03	5.0±0.02	5.5±0.01

Table 3: Evaluation of Mucoadhesive Vaginal Tablets of Miconazole Nitrate

Formulation	Friability (%)	Weight Variation (mg)	Drug Content (%)	Surface pH
V1	0.63±0.005	503±1.00	98.37±0.02	6.60±0.006
V2	0.79±0.006	499±0.33	103.24±0.06	6.84±0.03
V3	0.69±0.004	501±0.57	96.51±0.02	6.68±0.05
V4	0.73±0.003	497±0.20	102.67±0.03	6.88±0.008
V5	0.82±0.003	506±1.15	96.45±0.01	6.93±0.02
V6	0.69±0.004	504±0.93	101.31±0.07	6.55±0.01
V7	0.85±0.005	498±0.22	99.21±0.04	6.75±0.05
V8	0.76±0.006	500±0.31	98.98±0.04	6.90±0.08
V9	0.62±0.004	500±0.25	100±0.04	7.25±0.009

Swelling Index and Matrix Erosion Study of Mucoadhesive Vaginal Tablets:
All of the tablet formulations, which contained different amounts of mucoadhesive and rate-retardant polymers, remained stable throughout the swelling period with no signs of disintegration. Due to the low invariance between the formulations' selected polymer compositions, it was discovered that the swelling index of all formulations was more or less superimposable. Table 4 and Figure 1 both display the swelling index profiles of all formulations created in accordance with the experimental plan.

Table 4: Swelling and Matrix Erosion Study of Mucoadhesive Vaginal Tablets of Miconazole Nitrate

Formulation	% Swelling Index After Time (hr)						Matrix Erosion (%)
	2 hr	4 hr	6 hr	8 hr	10 hr	12 hr	
V1	18	27	38	51	59	70	27±0.02
V2	19	29	42	58	65	77	29±0.01
V3	21	43	65	85	99	105	33±0.07

V4	20	46	66	78	88	97	29±0.03
V5	15	21	32	41	57	72	33±0.06
V6	17	40	59	77	90	104	27±0.04
V7	18	36	53	72	91	103	28±0.02
V8	20	35	56	78	95	107	29±0.05
V9	19	39	51	68	83	100	31±0.05

(Standard Deviation, n=3)

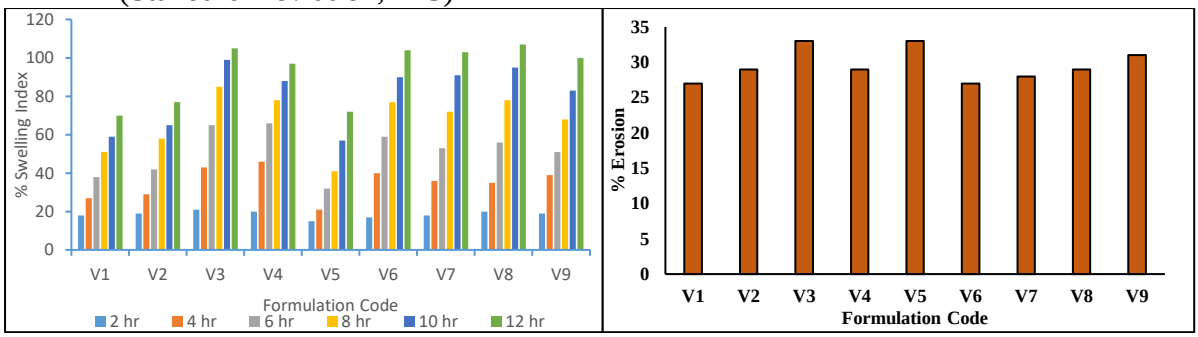

Figure 1: % Swelling Index and Matrix Erosion of Mucoadhesive Vaginal Tablets

Study of Bioadhesive Strength, Ex vivo Mucoadhesion Time and Detachment Force Measurement of Mucoadhesive Vaginal Tablets of Miconazole Nitrate:

Table 5 and Figure 2 displays the tablet's bioadhesive properties as a result. The mucoadhesive strength of tablets increases with the amount of polymer present in the formulation. The ability of mucoadhesive polymers to adhere to the mucosal surface and the polymer concentration used both had an impact on the tablet's strength. To achieve the longest possible duration of bioadhesion, the polymers in the highest concentration were required. The bioadhesive time decreased as the polymer concentration dropped. The most popular mucoadhesive polymer in the pharmaceutical industry is carbopol, which is used in a variety of dosage forms including mucoadhesive films, transdermal bioadhesive patches, tablets, and capsules. Therefore, carbopol was selected in this study to give the tablets mucoadhesive properties. The data obtained showed that increases in the concentration of carbopol resulted in a significant lengthening of the mucoadhesion time.

Table 5: Study of Bioadhesive Properties of Mucoadhesive Vaginal Tablets of Miconazole Nitrate

Formulation	Bioadhesive Strength (gms)	Ex vivo Mucoadhesion Time (hr)	Water Required (ml)	Force of Adhesion (N)
V1	9.52±0.312	11.2±0.03	199.5	0.943
V2	10.45±0.092	11.3±0.01	201	0.999
V3	10.20±0.168	10.5±0.2	210	1.028
V4	9.43±0.543	12.3±0.02	202.5	1.042
V5	9.50±0.741	12.1±0.01	175.6	0.938
V6	9.82±0.221	11.2±0.01	193.5	0.918
V7	11.19±0.323	12.1±0.1	210	0.989
V8	12.65±0.441	12.2±0.01	219.5	1.025
V9	13.28±0.234	12.6±0.23	241.5	1.327

(Standard Deviation, n=3)

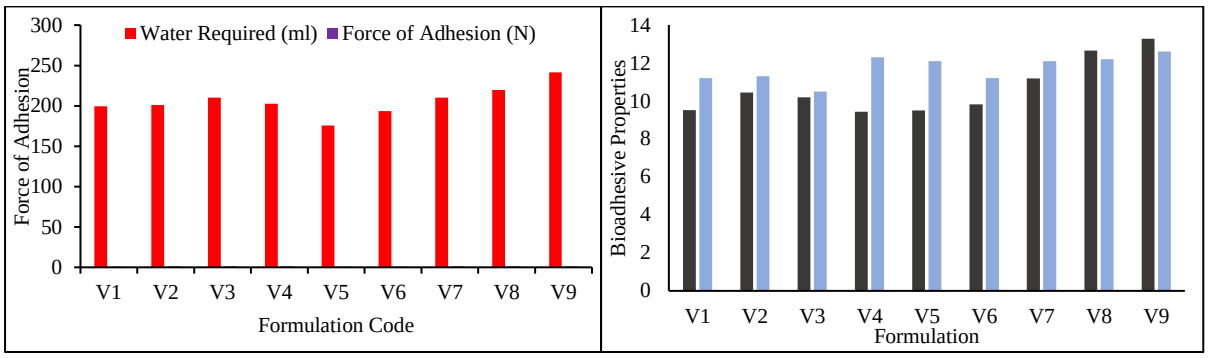

Figure 2: Bioadhesive Strength Detachment Force Measurement of Mucoadhesive Vaginal Tablets of Miconazole Nitrate

In Vitro Dissolution Study of Mucoadhesive Vaginal Tablets of Miconazole Nitrate: When all nine formulations (V1–V9) of tablets were examined, they revealed a sustained release pattern of drug release for up to 12 hours, as shown in Table 6. The findings demonstrated that the amount of drug released was delayed as the concentration of polymer present within the formulation increased. Formulations V1, V4, V5 and V6, which contain the rate-retarder polymer HPMC, guar gum, and Xanthan gum, demonstrated drug release of up to 90% in 12 hours (Figure 3). Utilizing rate-retarded polymer and mucoadhesive HPMC, the overall rate of drug release up to 12 hours. The formulations V2, V3, V7, V8 and V9 had maximum drug release up to 12 hours of 91, 91, 94, 93 and 97%, respectively. Several physicochemical phenomena could be used to compare the mechanisms of drug release from swellable matrices.

Table 6: In vitro Drug Release Study of Mucoadhesive Vaginal Tablets of Miconazole Nitrate

Time (Hrs)	Formulation Code								
	V1	V2	V3	V4	V5	V6	V7	V8	V9
1	8	7	12	11	5	10	8	9	6
2	15	16	24	18	12	19	15	18	17
3	21	26	35	25	24	30	26	30	30
4	28	40	50	35	36	43	37	42	41
5	34	52	61	42	50	56	53	55	54
6	46	63	70	50	61	66	61	64	63
7	56	70	75	59	71	74	71	72	71
8	64	75	80	65	75	80	77	76	79
9	70	80	86	72	81	86	82	82	84
10	76	85	90	79	86	89	87	88	89
11	84	86	91	83	88	89	91	92	92
12	90	91	91	86	90	90	94	93	97

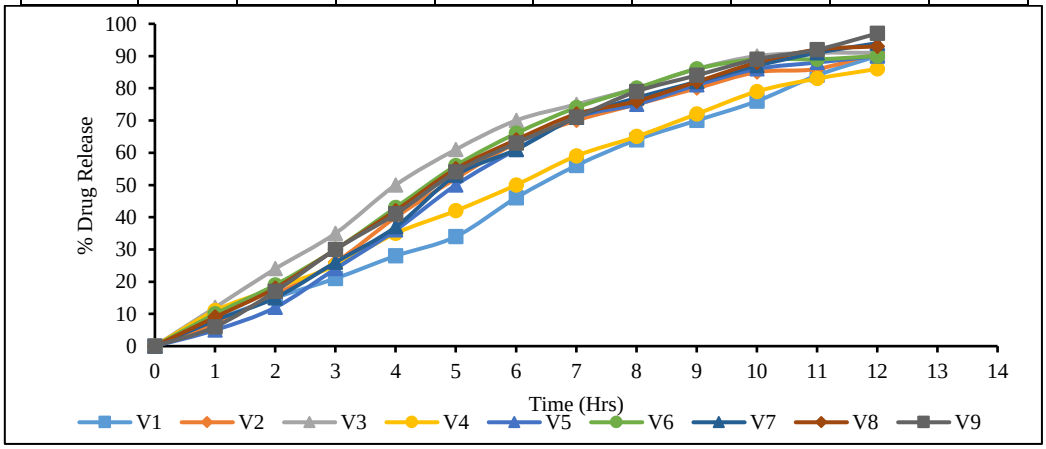

Figure 3: Drug Release Study of Mucoadhesive Vaginal Tablets of Miconazole Nitrate

Drug Release Kinetics of Optimized Formulation: The R2 values for the majority of the formulations were higher for the Zero order model than the First order model, indicating that the formulation's drug release kinetics were in accordance with Zero order kinetics. Higuchi model, which suggests that the diffusion-controlled drug release mechanism from the tablets. Obtained values of n are in the range of 0.5 and 1.0, indicating non-Fickian release kinetics, which is a sign of diffusion-based drug release mechanisms. As a result, the polymers' ability to swell and then allow drug to diffuse through them regulate how much medication is released from the prepared tablets.

Table 7: Drug Release Kinetics of Optimized Formulation V9

Formulation Code	Zero Order	First Order	Higuchi	Korsmeyer - Peppas
V9	R^2	R^2	R^2	R^2
	0.9688	0.9374	0.945	0.8608

Table 8: Drug Release Kinetics of Optimized Formulation V9

Time (Hrs)	Log Time	√ Time	Cumulative % Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remained	Log Cumulative % Drug Remained
0	∞	0	0	∞	100	2
1	0	1	6	0.778	94	1.973
2	0.301	1.414	17	1.230	83	1.919
3	0.477	1.732	30	1.477	70	1.845
4	0.602	2	41	1.612	59	1.770
5	0.698	2.236	54	1.732	46	1.662
6	0.778	2.249	63	1.799	33	1.518
7	0.845	2.645	71	1.851	29	1.462
8	0.903	2.828	79	1.897	21	1.322
9	0.954	3	84	1.924	16	1.204
10	1	3.162	89	1.949	11	1.041
11	1.041	3.316	92	1.963	8	0.903
12	1.079	3.464	97	1.986	3	0.477

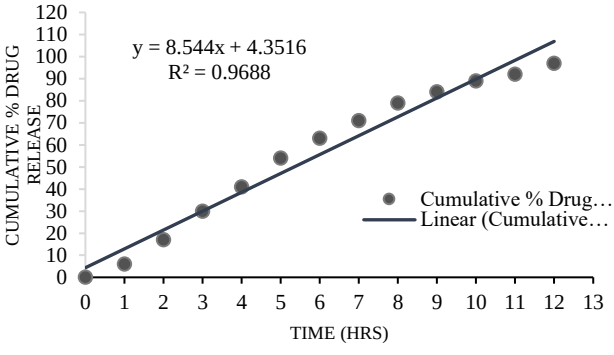

Figure 4: Zero Order Kinetic Plot for Formulation V9

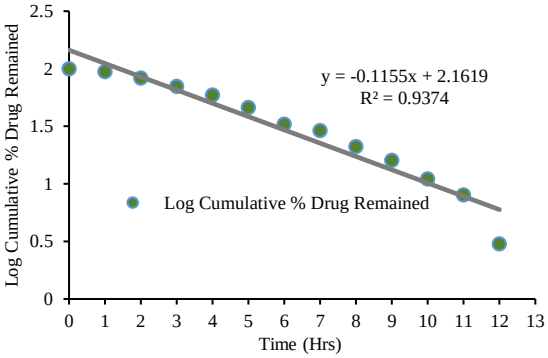

Figure 5: First Order Kinetic Plot for Formulation V9

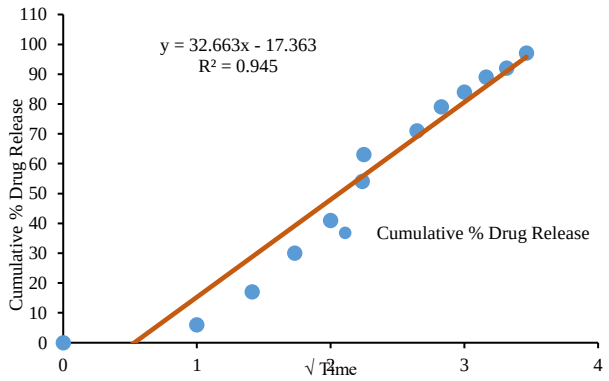

Figure 6: Higuchi Kinetic Plot for Formulation V9

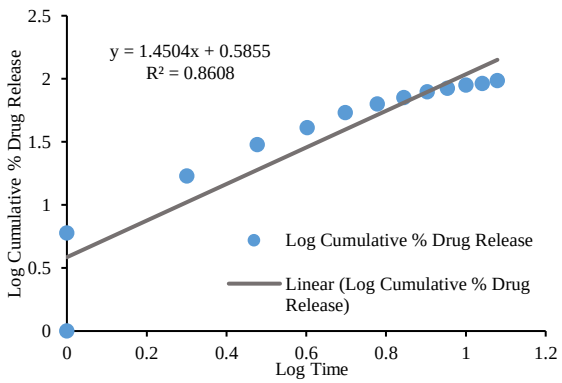

Figure 7: Korsmeyer - Peppas Kinetic Plot for V9

Stability Study of Optimized Formulation: All of the Miconazole Nitrate Mucoadhesive Vaginal Tablets that underwent accelerated stability studies showed negligible physical changes throughout the experiment. All of the mucoadhesive Vaginal tablets' drug content was observed (n = 3) and was fairly stable under accelerated storage conditions. By calculating the percentage content under the previously mentioned accelerated storage condition, the stability of mucoadhesive Vaginal tablets was demonstrated. All Mucoadhesive Vaginal Tablets were stable without any changes to their physical characteristics, according to the values of all parameter changes that were only slightly different.

Table 9: Accelerated Stability Study of Optimized Formulation V9

Evaluation Parameter	Before Stability Storage	After 3 Months Storage	After 6 Months Storage
Hardness (Kg/cm^2)	5.5±0.01	5.4±0.1	5.3±0.2
Friability (%)	0.62±0.004	0.63±0.013	0.66±0.018
Weight Variation (mg)	500±0.25	500±0.28	498±0.09
Drug Content (%)	100±0.04	98±0.07	98±0.06
Surface pH	7.25±0.009	7.20±0.07	7.10±0.03
Swelling Index (%)	100	99	97
Matrix Erosion (%)	31±0.05	30±0.07	29±0.10
Bioadhesive Strength (gms)	13.28±0.234	13.12±0.195	12.78±0.224
Ex vivo Mucoadhesion Time (hr)	12.6±0.23	12.1±0.4	11.4±0.3
Water Required (ml)	241.5	235	226
Force of Adhesion (N)	1.327	1.240	1.195
In vitro Drug Release (%)	97	96.42	95.86

Antimycotic Study of Optimized Formulation: Using the agar-cup diffusion method, the antimycotic activity of the optimised formulation V9 of mucoadhesive Vaginal tablets of miconazole nitrate was assessed. The obtained zone of inhibition diameter is displayed in Table 10 and Figure 8. The tested version of V9, the optimised formulation, was effective against C. albicans. The same tests were performed on a placebo tablet in order to check for any polymer activity. No zone of inhibition was visible in the control placebo pill.

Table 10: Antimycotic Study of Optimized Formulation V9

Sr. No.	Zone of Inhibition (mm)	Mean
1	27	28
2	29	
3	28	

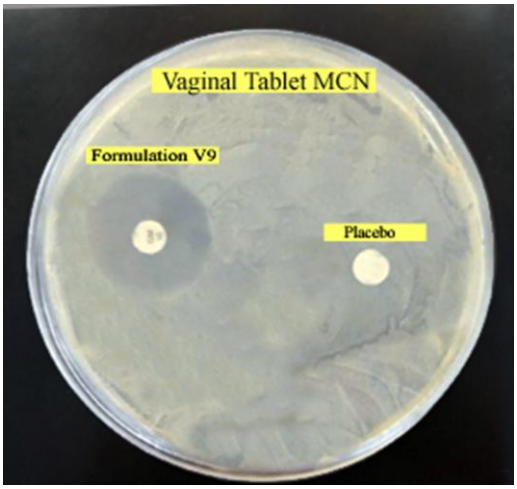

Figure 8: Inhibition Zone of Mucoadhesive Vaginal Tablet of MCN

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