Development and Evaluation of Acid-buffering Bioadhesive Vaginal Tablet for Mixed Vaginal Infections

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ABSTRACT

An acid-buffering bioadhesive vaginal tablet was developed for the treatment of genitourinary tract infections. From the bioadhesion experiment and release studies it was found that polycarbophil and sodium carboxymethylcellulose is a good combination for an acid-buffering bioadhesive vaginal tablet. Sodium monocitrate was used as a buffering agent to provide acidic pH (4.4), which is an attribute of a healthy vagina. The effervescent mixture (citric acid and sodium bicarbonate) along with a superdisintegrant (Ac-Di-sol) was used to enhance the swellability of the bioadhesive tablet. The drugs clotrimazole (antifungal) and metronidazole (antiprotozoal as well as an antibacterial) were used in the formulation along with *Lactobacillus acidophilus* spores to treat mixed vaginal infections. From the ex vivo retention study it was found that the bioadhesive polymers hold the tablet for more than 24 hours inside the vaginal tube. The hardness of the acid-buffering bioadhesive vaginal tablet was optimized, at 4 to 5 kg hardness the swelling was found to be good and the cumulative release profile of the developed tablet was matched with a marketed conventional tablet (Infa-V). The in vitro spreadability of the swelled tablet was comparable to the marketed gel. In the in vitro antimicrobial study it was found that the acid-buffering bioadhesive tablet produces better antimicrobial action than marketed intravaginal drug delivery systems (Infa-V, Candid-V and Canesten 1).

KEYWORDS: Bioadhesion, Bioadhesive polymers, Vaginal infections, Acid-buffering bioadhesive tablet, Mixed vaginal infections.

INTRODUCTION

Vaginitis is a common gynecological problem in women of all age groups. It may result from microbial infections, contact dermatitis, atrophic vaginitis, or allergic reactions.[1] The infectious vaginitis is of 3 types: candidiasis, trichomoniasis, and bacterial vaginosis. Vaginal infections are usually characterized by vaginal discharge, vaginal irritation or vulvar itching, and vaginal odor.[2,3] Vaginal infections are diagnosed by vaginal discharge, pH measurement, and microscopic examination.[2] In bacterial vaginosis and trichomoniasis, the pH of vaginal secretions is reported to rise.[2]

Several drug delivery systems are used for contraception, vaginal infections, and vaginal health and hygiene maintenance. Marketed vaginal dosage forms include tablets, tampons, films, sponges, foams, creams, gels, solutions, ointments, ovules, soft gelatin capsules, pessaries, douches, suppositories, and vaginal rings.[4,5] Tablets and gels are the most common vaginal formulations. The conventional drug delivery systems (exemplified by tablets, creams, gels, pessaries, and foams) suffer from poor retention in the vaginal tract, as they are removed in a short time by the tract's self-cleansing action.[6] Multiple daily doses of conventional formulations result in poor patient compliance. To overcome such problems, delivery systems with bioadhesive polymers that prolong drug permanence on the vaginal mucosa were developed. Such systems have increased patient compliance as well as therapeutic success.[7,8] Hence, the present work was envisaged to develop a stable, novel, and aesthetic bioadhesive vaginal delivery system with improved efficacy. The following bioadhesive polymers were screened to develop a vaginal delivery system: polycarbophil, carbopol, sodium carboxymethylcellulose, sodium alginate, xanthan and guar gums, hydroxypropyl cellulose, and hydroxypropyl methylcellulose. The polymers hydroxypropyl methylcellulose, sodium carboxymethyl cellulose, sodium alginate, and xanthan and guar gums have good stability at pH 3 to 10 and, hence, are good candidates for vaginal delivery systems (pH 4 to 4.5). Clotrimazole is a Food and Drug Administration (FDA)-approved over-the-counter (OTC) antifungal drug; metronidazole is an FDA-approved antibacterial drug for vaginal infections. Clotrimazole and metronidazole are broad-spectrum antibiotics recommended for treatment of candidiasis and bacterial vaginosis/trichomoniasis, respectively.[1-3] *Lactobacilli* are normal microflora of the vaginal tract responsible for the acidic pH of the vagina.[1,9] Hence, it was thought to be worthwhile to include spores of *Lactobacillus acidophilus* in the formulation to be developed.

MATERIALS AND METHODS

Drugs and polymers were obtained as gift samples from Indian pharmaceutical firms (metronidazole, clotrimazole, and

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Table 1. Tablet formulations of metronidazole (500 mg) and clotrimazole (100 mg)

	Tablets formulations (quantity in mg)																
Ingredients	T-1	T-2	T-3	T-4	T-5	T-6	T-7	T-8	T-9	T-10	T-11	T-12	T-13	T-14	T-15	T-16	T-17
HPMC-K 4M	72	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
HPMC-K 15M	—	72	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
HPMC-100cp	—	—	72	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Xanthan gum	—	—	—	72	—	—	—	—	—	—	—	—	—	—	—	36	—
Sod. Alginate	—	—	—	—	72	—	—	—	—	—	—	—	—	—	—	—	—
HPC (M)	—	—	—	—	—	72	—	—	—	—	—	—	—	—	—	—	—
Sod. CMC	—	—	—	—	—	—	72	—	—	—	36	—	—	—	36	—	—
Carbopol-971	—	—	—	—	—	—	—	72	—	—	36	36	36	—	—	—	—
Polycarbophil	—	—	—	—	—	—	—	—	72	—	—	—	—	36	36	36	36
Guar gum	—	—	—	—	—	—	—	—	—	72	—	—	36	36	—	—	—
HPMC-5 cp	—	—	—	—	—	—	—	—	—	—	—	36	—	—	—	—	36
Sod bicarbonate	—	—	—	—	—	—	—	60	60	—	30	30	30	30	30	30	30
MCC-PH 112	462	462	462	462	462	462	462	402	402	462	432	432	432	432	432	432	432

Each formulation of Table 1 contains 6 mg of magnesium stearate and 60 mg Ac-Di-Sol.

Lactobacillus acidophilus spores from Lark Laboratories [Bhiwadi, Rajasthan, India]; bioadhesive polymers from Ranbaxy [Gurgaon, Haryana, India]; and sodium monocitrate from Oscar Laboratories [New Delhi, India]). Infa-V vaginal tablets (a combined formulation of clotrimazole, metronidazole, and *Lactobacillus acidophilus*) were purchased from a Chemist shop. Instruments used were a texture analyzer (TAXT2i/; Stable Micro Systems, Surray, UK), surface pH electrode (Orion 9135AP; Thermoelectron Corporation, Ecublens, Switzerland), Shimadzu UV-Spectrophotometer 1601 (Shimadzu, Singapore Science Park, Singapore), 16-station rotary tablet machine (Clit, Amedabad, India), and BOD incubator (Nirmal International, New Delhi, India).

Development of Bioadhesive Tablet

Bioadhesive tablets were formulated by using polymers alone and in combination. The tablet compositions were compressed directly on a 16-station rotary tablet machine by using 16-mm flat-faced round punches. The composition formulas for the bioadhesive tablets are given in Table 1.

Preparation of Simulated Vaginal Fluid

The simulated vaginal fluid (pH 4.2) was prepared as described by Owen and Katz.[10]

Method for Estimation of Drugs

Clotrimazole and metronidazole were individually estimated at 2 different wavelengths (λ_{max}). A new colorimetric method was developed for estimating clotrimazole: Samples containing clotrimazole were diluted using 70% wt/wt perchloric acid and heated for 5 minutes on a boiling water bath. The intensity of the resultant yellow color tint was estimated at 448 nm. In test solutions of clotrimazole in perchloric acid (70% wt/wt), the percentage of methanol/water *must not* exceed 8.0% (vol/vol), otherwise the intensity of the color development decreases. For estimation of metronidazole, samples were prepared in distilled water and absorbance recorded at 320 nm.

Validation of Analytical Method

Analytical methods were validated for accuracy, recovery, precision, linearity, and limit of detection (LOD) / limit of quantitation (LOQ) determinations.[11]

Evaluation of Bioadhesive Tablets

Tablets were evaluated on the basis of bioadhesive strength, release properties, and hardness. The bioadhesive strength was measured using a texture analyzer. Dissolution studies were performed in 900-mL dissolution media (0.5% sodium laurylsulphate [SLS] wt/vol in distilled water) using a 6-vessel dissolution rate test apparatus (USP II) at 50 rpm and 37 ± 0.5°C. The hardness of the bioadhesive tablet was measured by using a Pfizer hardness tester D6426 (New Delhi, India).

In Vitro Adhesion Tests

The mucoadhesive properties of tablet formulations were assessed on the vaginal mucosa of buffalo using a texture analyzer (pretest and test speeds: 0.5 and 0.1 mm per second, respectively, contact 3.0-minutes, contact force 1.0 Newton,

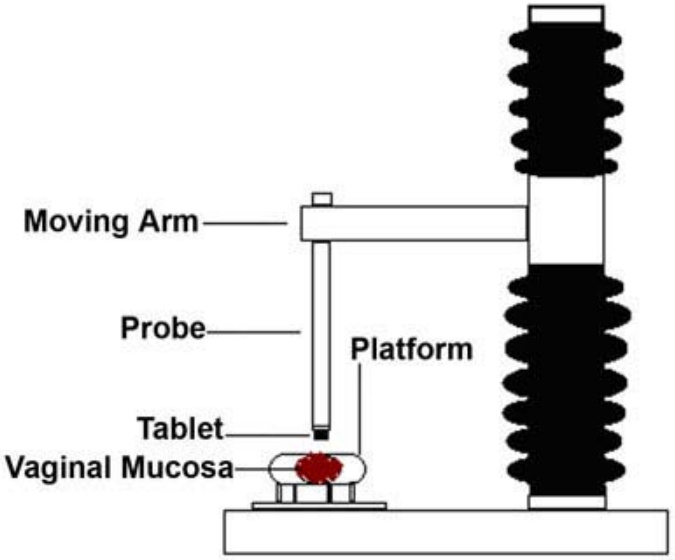

Figure 1. Outline diagram of texture analyzer showing the set up of in vitro bioadhesion experiment for tablets.

and load cell 500 Newtons). Vaginal mucosa free from supporting tissues was stored in a deep freezer at –20°C. For experiments, the vaginal tube (thawed in normal saline with 0.1% wt/vol sodium azide preservative) was incised longitudinally and held on the lower platform of the texture analyzer. The tablet was applied to the upper probe with the help of a double-sided adhesive tap (Figure 1). The vaginal mucosa was moistened with simulated vaginal fluid. The force required to detach the formulation from the tissue surface was determined as the peak value in resultant force-time plot (as shown in the graph in Figure 2).

Development of the Acid-buffering Bioadhesive Tablet

The compositions (Table 2) were directly compressed on the rotary machine by using flat-faced round punches.

Table 2. Composition of acid buffering bioadhesive vaginal tablet

Pharmaceutical Ingredients	Qty in mg/Tablet	pH
Metronidazole	500	
Clotrimazole	100	
Spores of *Lactobacillus acidophilus*	25	
Polycarbophil	36	
Sodium CMC	36	4.4
Microcrystalline cellulose	282	
Sodium monocitrate	125	
Sodium bicarbonate	30	
Ac-Di-sol	60	
Mg-stearate	6	

pH of Tablet Formulation

The acid-buffering bioadhesive tablet was kept in 2 mL distilled water and the pH of the swelled tablet was measured. The conventional tablet was crushed into a powder and dissolved in 2 mL of distilled water. The tip of the electrode was brought into contact with the wet mass of the conventional tablet for pH measurement.

Optimization of Tablets

The acid-buffering bioadhesive tablet was optimized on the basis of hardness, bioadhesion, and release profile. The release profile of the bioadhesive formulations was studied in 900 mL of simulated vaginal fluid containing 0.5% wt/vol sodium lauryl sulfate using USP dissolution II apparatus at 50 rpm and 37°C.

Apparatus for Ex Vivo Retention Studies

The apparatus for ex vivo bioadhesion/retention studies consisted of a glass cell (length 11.0 cm; external diameter 5.0 cm;

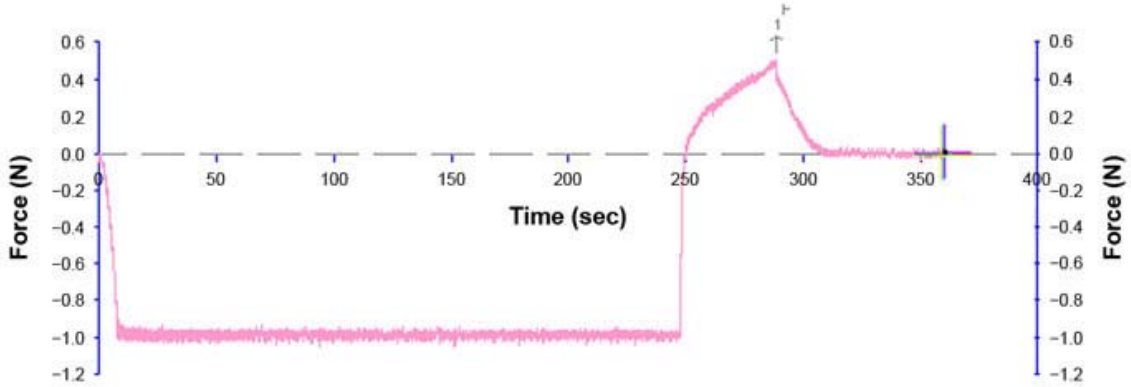

Figure 2. Representative graph of in vitro bioadhesion test.

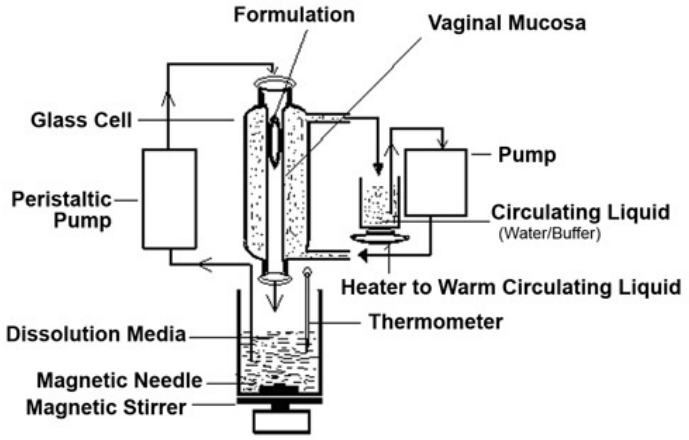

Figure 3. Apparatus for ex vivo bioadhesion experiment.

internal diameter at upper and lower ends: 2.4 and 1.0 cm respectively) open at both the ends (Figure 3). The edges of the upper and lower ends were tapered to tie the tissue properly. The cell had 2 small side arms (lower as inlet and upper as outlet) separated by a distance of 4.5 cm. Distilled water circulated through these side arms into the glass cell by using a pump (Miellins, India). Peristaltic pumps were used to circulate simulated vaginal fluid/distilled water at 37°C. This assembly was a modified version of the Setnikar and Fantelli apparatus.[12]

Ex Vivo Retention Measurement

Ex vivo retention studies were performed by using the assembly shown in Figure 3. The excised and cleaned buffalo vaginal tube was vertically suspended in the glass cell. The ends of the vaginal tube were averted on the tapering of the upper and lower ends of the glass cell and crimped using rubber bands. Water was circulated in the cell to maintain temperature equivalent to body temperature and also to keep the tissue moist. The bioadhesive tablet was inserted into the tube using a pair of blunt forceps. A preload time of 5 minutes was allowed to help the formulation adhere properly to the vaginal walls.

Simulated vaginal fluid (3 mL/h) was allowed to fall dropwise into the vertically suspended vaginal tube. Expulsion of formulation was recorded from the lower end of the cell.

Measurement of Spreadability of the Tablet

The acid-buffering bioadhesive tablet was allowed to swell in 2 mL of distilled water; the swollen mass was gently transferred to the center of a glass plate and compressed under several glass plates (100 ± 5 g each, every 1 minute) and the spread diameters (Figure 4) recorded each time.[13]

In Vitro Antifungal Studies

In vitro antifungal studies were performed against *Candida albicans* in Sabouraud's agar medium by the cup plate method. The cups cut in the inoculated solidified media were filled with different formulations using sterilized syringes. The marketed tablet was crushed into a powder and dissolved in 2 mL of sterilized water in a sterilized syringe. The marketed gels were applied using the sterilized syringe. The developed acid-buffering bioadhesive tablet was swelled in 2 mL of sterile water applied into the cups. The covered petriplates were incubated at 32°C in the BOD incubator for 40 hours. The zone of inhibition was measured at the end of 40 hours.

Results and Discussion

Characterization of Bioadhesive Tablets

White, round, flat disc-shaped bioadhesive tablets (diameter 16.1 mm, thickness 5.1 mm) were compressed and the results of hardness and bioadhesive strength are presented in Table 3.

Validation of Analytical Method

The recoveries of clotrimazole and metronidazole by the proposed spectrophotometric method were 100.795% ± 0.380% and 99.660% ± 0.310% respectively. The percent precision for clotrimazole was 100.240% ± 0.461% and for metronidazole 99.490% ± 0.429%. LOD/LOQ values (μg/mL)

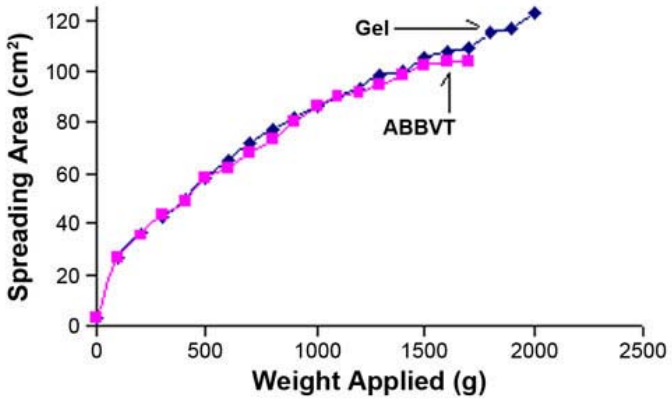

Figure 4. Showing the comparative spreadability of acid-buffering bioadhesive vaginal tablet versus Candid-V gel. ABBVT, acid-buffering bioadhesive vaginal tablet.

Table 3. Bioadhesive strength and hardness of the flat disc tablet formulations

Tablet Formulations	Bioadhesive Strength (N)	Hardness, kg
T-1	0.258	4.4
T-2	0.181	4.8
T-3	0.324	3.6
T-4	0.390	3.8
T-5	0.220	4.0
T-6	0.237	5.0
T-7	0.292	3.8
T-8	0.328	5.2
T-9	0.240	4.6
T-10	0.258	4.8
T-11	0.337	4.4
T-12	0.168	3.8
T-13	0.393	5.4
T-14	0.540	7.0
T-15	0.330	4.2
T-16	0.352	6.6
T-17	0.360	4.2

were found to be 0.14/0.46 (metronidazole) and 0.188/0.590 clotrimazole). The linearity was 1 to 20 µg/mL (metronidazole) and 0.5 to 10.0 µg/mL (clotrimazole).

Release Studies of Bioadhesive Tablets

Table 4 shows the cumulative percent release profiles of tablet formulation T-1 to T-17. Tablets (T-1 to T-10) contained single bioadhesive polymer (6% wt/wt). Tablets T-1, T-2, and T-3 (with different grades of hydroxypropyl methylcellulose [HPMC]) showed sustained release as per individual viscosity grades (100 cp > K4M > K15M). Drugs were completely released within 5 hours (T-4 and T-5). T-4 and T-5 (sodium carboxymethylcellulose [CMC] and hydroxypropyl cellulose [HPC][M] respectively) were more errodable resulting in less prolonged release. The typical T-7 release profile was possibly because of the rigid gel-forming capacity and less errodability of sodium alginate. T-8 (guar gum) swelled rapidly in contact with water and formed rigid gel and resulted in sustained release. T-9 and T-10, containing carbopol and polycarbophil respectively, had less sustained release. Moreover, total drug content (T-9 and T-10) dissolved within 3 hours as tablets disintegrated before polymers could react (or neutralize) with sodium bicarbonate to form the gel. T-11 and T-12 (sodium CMC and HPMC-5cp respectively) swelled rapidly when in contact with water to form gel. This action of sodium CMC and HPMC prevented fast disintegration of the tablet and allowed sufficient time for neutralization of carbopol and formation of prolonged release gel. T-13 exhibited sustained release by the same mechanism as T-11 and T-12 but slow release was due to the presence of the gel structure forming guar gum. T-14 to T-17 swelled in dissolution medium preventing fast disintegration of tablets and provided sufficient time for polycarbophil to gel. The sustained release of T-15 and T-17 was completed in 5 hours while the release profiles of T-14 and T-16 were very slow because of guar and xanthan gums.

Bioadhesive Strength

Bioadhesive strengths of the formulations were determined (Table 3; Figure 2 as representative graph). On the basis of bioadhesive strength and dissolution release studies, T-15 comprising polycarbophil and sodium carboxymethyl cellulose was considered a good candidate for development as an acid-buffering bioadhesive tablet. The good bioadhesion of polycarbophil and fast swelling of sodium CMC provided a good combination of bioadhesive polymers for further development. Fast swellability of sodium CMC prevented the premature disintegration of polycarbophil tablet and polycarbophil prevented the fast erosion of sodium CMC.

Acid-buffering Bioadhesive Vaginal Tablet

The composition of the tablet (Table 2) maintained an acidic pH (4.4), which is a desirable attribute of the formulations used to treat vaginal infections. Sodium monocitrate was used as an acidifying/buffering agent. Lactobacilli were also included to compensate for loss of microflora in vaginal infections or during use of antibiotics. The effervescent composition of sodium monocitrate and sodium bicarbonate along with superdisintegrant helped the tablet to swell and thereafter soften.

The pH of the acid-buffering bioadhesive tablet was found to be acidic (4.40 ± 0.092, $n = 3$), almost similar to the required pH of the tract. The pH of 2 other marketed formulations was also acidic (Infa-V = 5.23 ± 0.246 and Canesten-V $6 = 4.88 \pm 0.085$, $n = 3$ each).

The acid-buffering bioadhesive tablet was optimized on the basis of hardness, release profile, and bioadhesive strength. The cumulative drug release (%) decreased with an increase in the hardness of the tablet. The higher hardness (>5 kg) decreased the swellability of the acid-buffering bioadhesive tablet because water did not penetrate into the tablet and effervescent mixture and superdisintegrant did not act properly. The release of acid-buffering bioadhesive vaginal tablet (hardness 4 to 5 kg) was comparable to Infa-V but the release profile of the bioadhesive tablet (hardness 5 to 6 kg) was slower than that of Infa-V (Table 5). Hardness (4 to 5 kg) was found to be optimum for the acid-buffering bioadhesive tablet. In vitro bioadhesive strength of the acid-buffering bioadhesive vaginal tablet was 0.322 to 0.335 N.

Table 4. Cumulative percent release profiles of tablet formulation T-1 to T-17

		% Release				% Release	
Formulation Code	Time, min	Metro	Clotri	Formulation code	Time, min	Metro	Clotri
T-1	0	0	0	**T-10**	0	0	0
	10	27.9	19.3		10	80.8	60.7
	30	45.7	35.3		30	90.7	83.2
	90	62.0	69.5		90	97.1	90.5
	210	90.1	85.5		210	103	94.1
	300	95.0	101		330	103.6	100
T-2	0	0	0	**T-11**	0	0	0
	10	18.3	16.1		10	5.0	12.8
	30	29.1	25.2		30	9.5	17.5
	90	54.7	52.8		90	16.4	24.5
	210	86.1	79.7		210	35.2	43.7
	300	95.0	97.5		420	94.9	102.6
T-3	0	0	0	**T-12**	0	0	0
	10	35.4	22.2		10	4.7	12.8
	30	50.4	34.7		30	14.8	18.4
	90	79.9	75.0		90	57.7	55.9
	210	91.8	96.8		210	78.8	72.5
	300	93.9	102.0		330	106.4	100
T-4	0	0	0	**T-13**	0	0	0
	10	68.4	53.2		10	4.5	14.0
	30	81.0	90.9		30	11.8	18.2
	90	85.6	96.8		90	14.4	21.0
	210	91.6	107.2		210	23.9	24.6
	300	93.6	102.8		420	43.3	40.9
T-5	0	0	0	**T-14**	0	0	0
	10	28.4	29.0		10	2.9	11.7
	30	57.0	56.1		30	4.1	12.8
	90	92.6	96.6		90	8.7	18.0
	210	96.1	107.2		210	19.0	29.5
	300	101.5	107.2		330	33.3	43.9
T-6	0	0	0	**T-15**	0	0	0
	10	2.8	13.5		10	3.2	12.1
	30	4.8	16.4		30	6.6	16.1
	90	10.0	18.9		90	8.8	31.8
	210	18.4	28.1		210	60.6	74.8
	420	30.9	29.4		330	84.8	102.1
T-7	0	0	0	**T-16**	0	0	0
	10	37.0	25.9		10	2.4	12.1
	30	44.6	40.8		30	3.8	12.7
	90	57.6	54.0		90	4.4	12.7
	210	73.0	70.9		210	9.9	20.8
	300	78.8	81		330	18.4	29.4
T-8	0	0	0	**T-17**	0	0	0
	10	32.3	25.8		10	2.4	14.7
	30	76.8	47.1		30	6.8	20.7
	90	84.9	62.5		90	22.5	36.4
	180	90.7	80.5		210	63.1	81.3
	280	96.9	88.8		300	82.8	94.9
T-9	0	0	0				
	10	8.03	13.6				
	30	30.8	27.7				
	90	87.0	55.5				
	210	100	100.4				
	330	100	99.5				

Metro indicates metronidazole; Clotri, clotrimazole

Ex Vivo Retention Studies on Acid-buffering Bioadhesive Vaginal Tablet

The tablet showed very good retention (> 24 hours) in the ex vivo experiment. The tablet softened inside the vaginal tube after absorbing simulated vaginal fluid and became a swollen structure, helping it to adhere to the vaginal mucosa. Swollen bioadhesive polymers held the solid content of the tablet inside the vagina; at the same time preventing premature leakage. The weight of the tablet (1.2 g) also favored prolonged retention of the tablet inside the tract against gravity. Infa-V disintegrated inside the vagina and its content started leaking after 5 to 8 hours. The spreadability of the acid-buffering bioadhesive vaginal tablet was comparable to Candid-V gel (Figure 4).

Antifungal Studies

The acid-buffering bioadhesive tablet had better antimicrobial activity as compared with the marketed formulations (Infa-V tablet, Canesten 1, and Candid V-gel). The developed vaginal tablet contained clotrimazole, metronidazole, and Lactobacilli along with the acidic buffering agent sodium monocitrate. The composition might have synergized antimicrobial actions of the bioadhesive tablet. Bioadhesive polymers of the tablet had prolonged drug release and provided better contact with the wells cut in the plate, while the Infa-V suspension dried up as water was not available in the wells for prolonged time to allow diffusion of drug molecule(s). The results of antifungal studies are reported in Table 6.

Table 5. Cumulative percent release profiles of ABBV tablets of different hardness and Infa-V

Formulation	Time, min	% Release of Metronidazole, n = 3	% Release of Clotrimazole, n = 3
ABBV tablet of	0	0	0
4–5kg hardness.	10	23.82 ± 1.79	40.72 ± 3.33
	30	56.17 ± 3.25	66.30 ± 2.38
	60	88.54 ± 3.42	86.55 ± 5.56
	90	94.02 ± 1.86	94.25 ± 5.21
ABBV tablet of	0	0	0
5–6kg hardness.	10	10.67 ± 1.98	35.60 ± 2.01
	30	30.99 ± 1.30	48.26 ± 2.11
	60	59.52 ± 2.24	72.16 ± 2.08
	90	74.25 ± 1.80	92.50 ± 1.44
	120	92.93 ± 1.02	98.23 ± 0.90
	150	98.13 ± 1.26	100.62 ± 2.01
Infa-V	0	0	0
	10	46.38 ± 1.94	32.62 ± 1.67
	30	79.12 ± 0.89	46.17 ± 0.86
	60	89.38 ± 1.49	83.18 ± 1.08
	120	92.97 ± 1.13	95.19 ± 1.31
	240	97.52 ± 1.00	97.96 ± 1.06
	360	100.81 ± 1.54	100.38 ± 1.49

Table 6. Antifungal activity of various formulations against *C albicans*

Formulation	Zone of Inhibition, mm, n = 3
ABBV tablet*	42 ± 1.0
Infa-V tablet	31.66 ± 0.57
Canesten 1	25.33 ± 0.57
Candid-V gel	25.33 ± 0.57

*Acid-buffering bioadhesive vaginal tablet.

CONCLUSION

Polycarbophil and sodium carboxymethyl cellulose are the polymers of choice for bioadhesive vaginal tablets. Ex vivo retention studies justified the prolonged retention of the tablet inside the vaginal tract. It can be concluded that the acid-buffering bioadhesive vaginal tablets are more effective as well as having better patient compliance than existing conventional vaginal drug delivery systems.

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