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Development and Evaluation of Mucoadhesive Vaginal Tablet of Sertaconazole for Vaginal Candidiasis

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Abstract: The aim of this study was to prepare mucoadhesive vaginal tablet of sertaconazole using a combination of mucoadhesive polymers like Carbopol 934P, chitosan, carboxymethylcellulose sodium, sodium alginate, methyl cellulose, hydroxypropyl methylcellulose and hydroxypropyl cellulose to enhance its solubility and release characteristics and therefore its feasibility for vaginal delivery for local fungal infections.The tablets were prepared by direct compression method and effervescent was incorporated into formulations to enhance swellabilty of mucoadhesive tablet. For various drug-free formulations, the effect of effervescent on polymers swelling characteristics was investigated. Swelling, mucoadhesive property and drug release study of the tablets with different proportions of mucoadhesive polymer in formulations were conducted. A good sustained effect and moderate bioadhesion were obtained with tablets containing 100 mg of effervescent, with Chitosan: HPMC K4M (1:1) seemed to be the optimum for the tablet. From the ex vivo retention study it was found that the mucoadhesive polymers hold the tablet for more than 24 hours inside the vaginal tube. The results of these studies demonstrated the applicability of a sertaconazole for local controlled delivery of the antifungal to the vagina. Our study may provide a potential vaginal tablet formulation of sertaconazole against *Candida albicans*.
***Keywords*:** mucoadhesion, mucoadhesive polymers, vaginal infections, effervescent mucoadhesive tablet.

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] Sertaconazole is an imidazole derivative antifungal agent developed for treatment of human mycotic infections and plays an essential role in antifungal chemotherapy.[2] It is lipophilic with limited water solubility except at low pH.[3] For treatment of vulvovaginal candidiasis local antifungal has been favored due to numerous side effects, toxicity and teratogenic potential of systemically applied drug. Sertaconazole generally given by oral route but one of limitation of conventional dosage form in vaginal therapy is the relatively short residence time of drug at site of application. To achieve desirable therapeutic effect vaginal delivery system for sertaconazole need to reside at the site of infection for prolong period. Hence there is need to develop effective drug delivery system that should prolong the contact of drug with vaginal mucosal surface. Traditional vaginal drug delivery systems include solutions, suspensions, gels, foams and tablets.[4] 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. Foam producing dosage forms are preferred as excessive lubrication and leakage from the vagina are minimal and the foam adheres to the vaginal walls. Thus vaginal tablets appear to be useful dosage forms as they are easy to apply, portable and the user knows how many units remain.[5,6]

Therefore present work was aimed to develop effervescent mucoadhesive tablet of sertaconazole capable to efficiently deliver drug during extended period of time against *C. albicans*. Effervescent added into the formulations to enhance swellabilty bioadhesive tablet. During the in vitro study, Carbopol 934P, chitosan, carboxymethylcellulose sodium (sodium CMC), sodium alginate, methyl cellulose (MC), hydroxypropyl methylcellulose (HPMC) and hydroxypropyl cellulose (HPC) were chosen as bioadhesive polymers. The performances of these bioadhesive polymers were evaluated by two parameters, the swelling behavior and the bioadhesive strength. For the various drug-free formulations, the effect of effervescent on polymers' bioadhesive characteristics was investigated. On the basis of these data, suitable polymers were selected to prepare the bioadhesive effervescent vaginal tablets of sertaconazole. Swellings, bioadhesive properties and drug release of the tablets with different proportions of bioadhesive polymer and effervescent in formulations were conducted. One ideal formulation was selected for the subsequent ex vivo mucoadhesion time of the tablet and in vitro antifungal study.

EXPERIMENTAL

Materials

Sertaconazole was gifted by (Cipla Ltd., Mumbai, India). Carbopol 934P(Corel pharmaceutical Ltd., Ahmedabad, India), Chitosan(Troikka Pharmaceuticals Ltd., Ahmedabad, India) , sodium alginate and methyl cellulose (MC)(S.D. Fine Chemicals Ltd., Mumbai, India), carboxymethylcellulose sodium (sodium CMC), hydroxypropyl methylcellulose (HPMC) and hydroxypropyl cellulose (HPC) (Zydus-Cadila Healthcare Ltd., Ahmedabad, India), were used as received. All other chemicals were of analytical reagent grade.

Formulation of drug-free tablets

The drug-free tablets were prepared using the mixture of polymer and microcrystalline cellulose (MCC) with or without effervescent. In the case of tablets loaded with effervescent, the effervescent agent consisted of sodium bicarbonate and citric acid at a mole ratio of 3:1. One percentage magnesium stearate (Mg. Stearate) and 2% talc were used as the lubricant and the glidant, respectively. All the powders were passed through 80 mesh sieve, finally the mixture was compressed to tablets using Cadmack single punch tablet compression machine. Average weight of tablet is 1000mg. The compositions of the drug-free tablet formulations are shown in (**Table 1).**

Swelling study of drug free tablet formulation using different polymer with and without effervescent mixture[7, 8]

The swelling behavior of tablet described as the water absorbing capacity. Drug-free tablets were weighed individually (W_0) and placed separately in 2% agar gel plates and incubated at 37 ± 1°C. At regular 0.5 hour time intervals until 4 hours, the tablet was removed from the Petridish and excess surface water was removed carefully using filter paper. The swollen tablet was then reweighed (Wt) and the % swelling were calculated using the following formula:

$$\% \text{ Swelling} = \{(Wt - W_0)/ W_0\} \times 100$$

Where Wt is the weight of the tablet at time t and W_0 is the initial weight of tablet. The swelling was calculated and then plotted as a function of time. The slope of the linear plots was taken as the swelling rate.

Figure 1 The scheme of the device used in the mucoadhesion studies

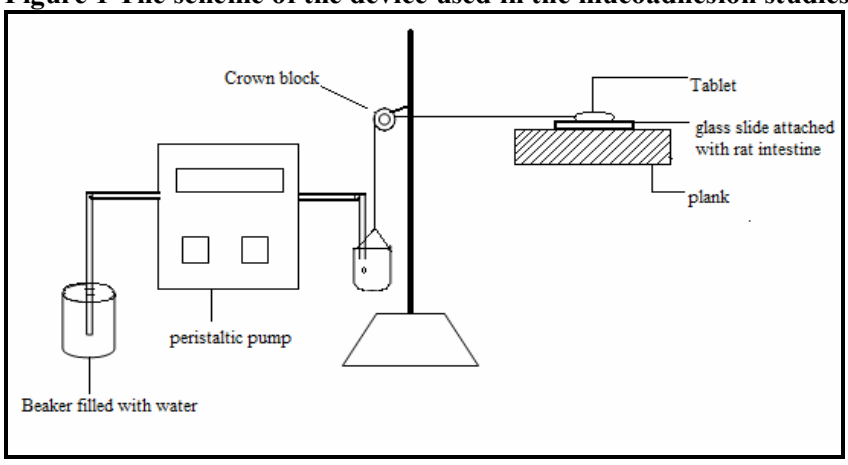


Table-1: Compositions of the drug-free tablet formulations (mg)

Code	Polymers	Polymer weight	Effervescent Mixture	MCC	Mg. Stearate	Talc
S1	Carbopol 934P	150	0	827.5	7.5	15
S1'	Carbopol 934P	150	100	727.5	7.5	15
S2	Chitosan	150	0	827.5	7.5	15
S2'	Chitosan	150	100	727.5	7.5	15
S3	Sodium CMC	150	0	827.5	7.5	15
S3'	Sodium CMC	150	100	727.5	7.5	15
S4	HPMC K4M	150	0	827.5	7.5	15
S4'	HPMC K4M	150	100	727.5	7.5	15
S5	CP +Sod.CMC	75+75	0	827.5	7.5	15
S5'	CP +Sod.CMC	75+75	100	727.5	7.5	15
S6	Chitosan+ HPMC K4M	75+75	0	827.5	7.5	15
S6'	Chitosan+ HPMC K4M	75+75	100	727.5	7.5	15
S7	Sod.CMC+ HPMC K4M	75+75	0	827.5	7.5	15
S7'	Sod. CMC+ HPMC K4M	75+75	100	727.5	7.5	15

Effervescent: consisted of sodium bicarbonate and citric acid at a molar ratio of 3:1

Formulation of sertaconazole effervescent mucoadhesive vaginal tablet

Different tablets formulations were prepared by direct compression technique. All the powders were passed through 80 mesh sieve. Sertaconazole effervescent mucoadhesive vaginal tablet were prepared by direct mixing the required quantity of polymers, sertaconazole, effervescent (consisting of sodium bicarbonate and citric acid at the mole ratio of 3:1), MCC, 1% magnesium stearate and 2% talc and finally the mixture was compressed to tablets using Cadmack single punch tablet compression machine. Talc and magnesium stearate were added as glidant and lubricant respectively. Each tablet contained 500mg of sertaconazole and has an approximate weight of 1000mg. Other pharmaceutical ingredients as listed in (Table 2) and (Table 3).

Table-2: Formulation of sertaconazole effervescent mucoadhesive vaginal tablet

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8
Sertaconazole	500	500	500	500	500	500	500	500
Carbopol 934P	150	-	-	-	-	-	-	-
HPMC K4M	-	150	-	-	-	-	-	-
HPMC K15M	-	-	150	-	-	-	-	-
HPC	-	-	-	150	-	-	-	-
Sod. CMC	-	-	-	-	150	-	-	-
Sod. Alginate	-	-	-	-	-	150	-	-
MC	-	-	-	-	-	-	150	-
Chitosan	-	-	-	-	-	-	-	150
MCC	227.5	227.5	227.5	227.5	227.5	227.5	227.5	227.5
Sod.bicabonate	75	75	75	75	75	75	75	75
Citric Acid	25	25	25	25	25	25	25	25

Each formulation of Table II contains 7.5 mg of magnesium stearate and 15 mg Talc

Table-3: Formulation of sertaconazole effervescent mucoadhesive vaginal tablet

Ingredients(mg)	F9	F10	F11	F12	F13	F14	F15	F16
Sertaconazole	500	500	500	500	500	500	500	500
Carbopol 934P	75	-	-	-	-	75	60	-
HPMC K4M	75	75	75	75	-	-	60	60
Chitosan	-	75	-	-	-	-	-	-
MC	-	-	75	-	-	-	-	-
Sod. CMC	-	-	-	75	75	75	-	60
HPC	-	-	-	-	75	-	-	-
MCC	227.5	227.5	227.5	227.5	227.5	227.5	257.5	257.5
Sod.bicabonate	75	75	75	75	75	75	75	75
Citric Acid	25	25	25	25	25	25	25	25

Each formulation of Table III contains 7.5 mg of magnesium stearate and 15 mg Talc.

Evaluation of mucoadhesive tablets

The formulated tablets (10 tablets) of each batch were evaluated for hardness using the Monsanto hardness tester (Tab Machines, India). Friability was determined according to the procedure mentioned in USP .[9] Mass variations of the formulated tablets (20 tablets) was tested in accordance with the procedures given in Indian Pharmacopoeia.[10] The swelling rate of mucoadhesive tablets was evaluated by using a 2% agar gel plate at 37 ± 1ºC.

In vitro mucoadhesion study

Several types of mucosa, including rat intestine, pig oral, bovine sublingual, cow vaginal mucosa[11, 12] have been used as model biological tissues for the evaluation of bioadhesion, which. In this study, rat intestine was preferred. A simple apparatus was devised to measure the minimum detachment force shown in (Figure 1). A piece of rat intestine (2.0 cm×1.0 cm) removed from newly sacrificed rat was adhered to a piece of glass, which was fixed on a plank and the plank was assembled with a little crown block. After hydrating the rat intestine with distilled water, the tablet was brought into contact with the rat intestine by applying little force for minute. After the initial contact, the tablet was encircled by a thread which fastened a light plastic beaker through the crown block. Next, water was dropped into the beaker at a speed of 3.0 ml/minute using peristaltic pump until the tablet and rat intestine were pulled apart by the gravity of water. The beaker containing water was weighed and the minimum detachment force was calculated accordingly. The experiments were performed in triplicate and average values with standard deviation (SD) were reported.

Ex-vivo mucoadhesion time

The ex-vivo mucoadhesion time was examined after application of the vaginal tablet on freshly cut rat intestine. The fresh rat intestine was tied on the glass slide, and a mucoadhesive tablet was wetted with 1 drop of phosphate buffer and pasted to the rat intestine by applying a light force with a fingertip for 30 seconds. The glass slide was then tied on paddle of dissolution apparatus, put in dissolution bowl, which was filled with 250 ml of the phosphate buffer and kept at 37 ± 1°C. After 2 minutes, a slow stirring rate was applied to simulate the vaginal cavity environment, and tablet adhesion was monitored for 24 hours. The time for the tablet to detach from the rat intestine was recorded as the mucoadhesion time.

In Vitro sertaconazole release study

The release rate of sertaconazole effervescent mucoadhesive vaginal tablet (n=3) was determined using *The United States Pharmacopoeia* (USP) XXIV dissolution testing apparatus I (basket method) in 500ml of phosphate buffer pH 4.0 as the dissolution medium.. The tablet was placed in a settling basket to prevent the tablet from floating. [13] The rate of stirring was 30 rpm (revolution per minute). And the medium temperature was maintained at 37 ± 0.5 ºC. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. The samples were filtered through a filter and diluted to a suitable concentration with phosphate buffer pH 4.0. Absorbance of these solutions was measured at 260 nm using a Shimadzu UV-1800 UV/Vis double beam spectrophotometer. Cumulative percentage of drug release was calculated using the equation obtained from a standard curve.

In vitro antifungal studies [14]

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 (Candid®-V_3 tablet) was crushed into a powder and dissolved in 2 ml of sterilized water in a sterilized syringe. The marketed gel (Candid®-V gel) was applied using the sterilized syringe. The developed sertaconazole effervescent mucoadhesive vaginal tablet was swelled in 2 ml of sterile water applied into the cups. The covered Petri plates were incubated at 22°C in the BOD incubator for 48 hours. The zone of inhibition was measured at the end of 48 hours.

Table-4: Characterization of various mucoadhesive vaginal tablet

Batch	Swelling Index	Drug content (%)	Mucoadhesive strength(N)
F1	15.30±1.3	98.5±2.5	0.385±0.29
F2	23.47±1.73	97.5±4.5	0.205±0.08
F3	22.32±3.04	99.2±2.0	0.219±0.34
F4	23.58±2.72	99.0±2.5	0.173±0.07
F5	18.83±3.41	97.8±3.0	0.301±0.28
F6	22.98±3.53	99.1±3.0	0.212±0.06
F7	22.14±2.04	96.2±1.5	0.227±0.08
F8	18.34±2.01	98.4±3.5	0.316±0.24
F9	20.02±5.08	98.6±4.5	0.254±0.35
F10	21.13±3.11	97.3±1.5	0.250±0.09
F11	22.74±1.87	98.1±2.5	0.215±0.23
F12	21.38±2.43	99.2±1.5	0.239±0.07
F13	24.28±3.76	97.6±2.0	0.166±0.31
F14	19.32±3.24	96.8±3.0	0.272±0.08
F15	21.65±2.09	98.2±2.5	0.232±0.24
F16	25.51±1.41	97.4±1.5	0.160±0.09

Each value represents mean ± SD: n=3

Table-5: Antifungal activity of various formulations against C. albicans

Formulation	Zone of Inhibition(mm)
Sertaconazole effervescent mucoadhesive vaginal tablet	22.33±1.52
Candid®-V3 tablet	16.66 ±1.52
Candid®-V gel	14.33 ±2.08

Each value represents mean ± SD: n=3

Figure 2 Swelling study of drug free tablet formulation using different polymer without effervescent mixture

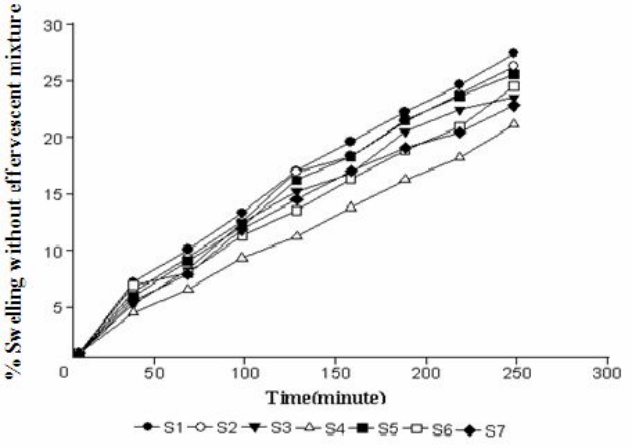


Figure 3 Swelling study of drug free tablet formulation using different polymer with effervescent mixture

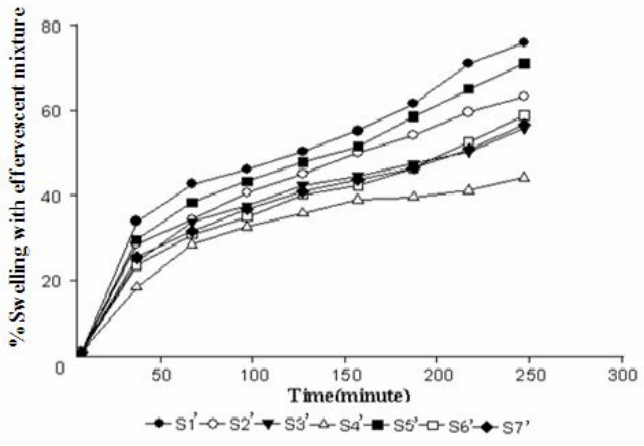


Figure 4 Release profile of sertaconazole from sertaconazole effervescent mucoadhesive vaginal tablet (F1-F8). Each point denotes mean±SD, *n* = 3.

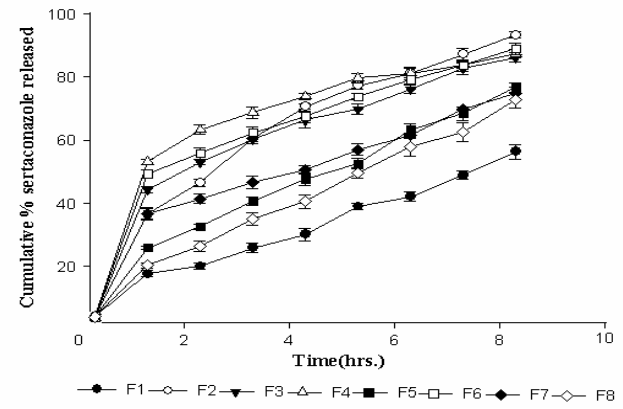
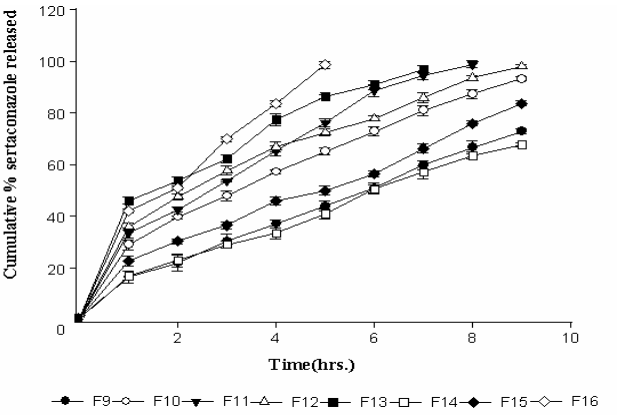


Figure 5 Release profile of sertaconazole from sertaconazole effervescent mucoadhesive vaginal tablet (F9-F16). Each point denotes mean±SD, *n* = 3.



RESULTS AND DISCUSSION

The tablet mould was especially designed (capsule shape) using stainless steel and the average mass of vaginal tablets was found to range from 975 to 995 mg exhibiting a mass of 998.67±7.02mg (mean ± SD), 20.8mm height, 8.5mm width and 6.17±0.057mm thickness. Hardness of the prepared tablets was observed within the range of 4.5-6 kg/cm^2. Tablets of all batches complied with the mass variation requirement of *Indian Pharmacopoeia* [10]; tablets of no batch varied more than 5% of the average mass. Average hardness of tablets belonging to various batches indicated good strength. Sufficient strength of all tablets was also evident since the friability was less than 1%, indicating compliance with the requirements of *USP 28*.[9] The total amount of sertaconazole present in each tablet was found to be in the range of 96.2 % to 99.2%.

Swelling study of drug free tablet formulation using different polymer

Swelling is important for the assessment of adhesion. Shortly after swelling, adhesion does occur, but with a weak bond formed. To develop maximum adhesion strength, an optimum water concentration was needed for polymer particles.[13]

(Figure 2) and (Figure 3) show the swelling behavior of the drug free tablet formulation without and with effervescent using different polymer respectively. It was observed that the order of swelling rate was Carbopol 934P > Chitosan > Sod.CMC > HPMC K4M in drug free formulations. According to the comparison of the corresponding swelling profiles of formulations with/without effervescent, it could be seen that the effervescent resulted in a marked increase in swelling rate.

Furthermore, most tablets with 100 mg effervescent showed a higher swelling capacity than tablets without effervescent. It was observed that the swelling rate was developed as effervescent applied to formulation, increased with increasing amount of effervescent. The phenomenon of swelling increasing could be explained by the good disintegration effect of effervescent, which made tablets increase in volume and construct porous channels on surface and inside of tablets. The porous channels increased the area of contacting between polymer particles and water so that the polymers could be hydrated more easily.

In vitro dissolution study sertaconazole effervescent mucoadhesive vaginal tablet

The dissolution of tablets were carried out in phophate buffer pH 4.0. (**Figure 4) and (Figure 5**) shows the effect of the polymer type and ratio on the dissolution of sertaconazole from mucoadhesive vaginal tablets. In all the formulation, the burst release of sertaconazole was observed within first 2 hrs. and gradually increasing upto 8-10 hrs. Formulations F1 to F8 contained single mucoadhesive polymer. F1 (carbopol 934P) and F2 (chitosan) swelled rapidly with aqueous fluid and formed rigid structure and provided a stronger sustained release effect on the drug release. F2, F3, F4 and F6 containing HPMC K4M, HPMC K15M, HPC and sod.alginate respectively were more erodible resulting in less prolong release. F5(sod. CMC) and F7(MC) swelled rapidly when in contact with aqueous fluid to form gel which prevent fast disintegration of the tablet and formation of prolong release gel(Figure 4). F9 and F14 containing carbopol 934P led to gradual swelling. The drug release was in a controlled manner for more than 8 hours. The percentage drug release after 8 hours was 72.36% and 67.11 % respectively which was not satisfactory to achieve 100% drug release. F11(containing HPMC K4M and MC), F13 (containing sod. CMC and HPC) and F16 (containing sod. CMC and HPMC K4M) shows rapid disintegration , more erodibility and complete drug release within 5-7 hours. Here percentage drug release was observed faster than the requirment. F10 and F12 shows good drug release profile compare to other formulations and exactly fit in the criteria for drug release(Figure 5). (Tablet should release more than 90% of drug within 8-10 hours. to avoid vaginal irritation).

In vitro mucoadhesion study of sertaconazole effervescent mucoadhesive vaginal tablet

Mucoadhesive strength of formulation F1 to F16 was determined using self developed force detachment method and observed within the range of 0.160 to 0.385 N. Based on results obtained from dissolution study F10 and F12 both show good release profile. Furthermore, F10 (0.250N) show slight more adhesion property compare to F12 (0.239N). So on the basis of mucoadhesive strength and dissolution release studies, F10 (containing chitosan and HPMC K4M) was considered a good candidate for development of a sertaconazole effervescent mucoadhesive vaginal tablet.

F10 was considered optimize formulation because of its good drug release and moderate mucoadhesion. As observed chitosan having better swelling property than HPMC K4M so chitosan was used to achieve suitable mucoadhesion and drug release because more mucoadhesion strength leads to local irritation in vagina. The % swelling and drug content of mucoadhesive vaginal tablet of sertaconazole shown in (Table 4).

Ex-vivo mucoadhesion time

The time for the tablet to detach from the rat intestine was recorded as the mucoadhesion time. The formulation F1, F5, F8, F9, F10 and F14 containing carbopol 934P, Sodium CMC, chitosan, Carbopol 934P and HPMC K4M, Chitosan and HPMC K4M and Carbopol941 and Sodium CMC showed higher mucoadhesion time (more than 10 hours) compare to other formulation. F10 (HPMC K4M and Chitosan) showed mucoadhesion time 12 hours. Ex-vivo retention studies justified the prolong retention of the tablet inside the vaginal tract. Consequently, the mucoadhesive form of the drug would increase the time of contact with the vaginal mucosa and thus its therapeutic effect. In addition, the soft and rubbery nature of mucoadhesive polymers will minimize mechanical and frictional irritation to the surrounding tissue.

Anti fungal study

As a result of mucoadhesive strength and dissolution release studies, F10 (containing chitosan and HPMC K4M) was considered a good candidate for development of a sertaconazole effervescent mucoadhesive vaginal tablet and has been selected for antifungal study. The antimicrobial activity of effervescent mucoadhesive vaginal tablet F10 had compared with the marketed formulations (Candid V_3®- tablet and Candid V®-gel). Mucoadhesive polymers of the tablet had prolonged drug release and provided better contact with the wells cut in the plate, while the Candid V_3 suspension dried up as water was not available in the wells for prolonged time to allow diffusion of drug molecules. The zone of inhibition was measured at the end of 48 hours. The results of antifungal studies are reported in (Table 5).

CONCLUSION

The results of this study reveal that incorporation of effervescent into the mucoadhesive tablets leads to the increase in the swellings and the rate of drug release and conversely the adhesion could be decreased. It was observed that with the developed formulations, the sertaconazole release and mucoadhesion properties of mucoadhesive vaginal tablets can be controlled by changing the polymer type, polymer concentration and effervescent content.

ABBREVIATIONS

%	- Percentage
°C	- Degree centigrade
USP	- United State pharmacopoeia
HPMC K4M	- Hydroxypropylmethyl cellulose
Sod. CMC	- Sodium carboxymethyl cellulose
MCC	- Microcrystalline cellulose;
Mg stearate	- Magnesium stearate.
HPC	- Hydroxypropyl cellulose
gm	- Gram
kg	- Kilograms
mg	- Milligram
ml	- Milliliter
mm	- Millimeter
cm	- Centimeter
nm	- Nanometer
SD	- Standard Deviation
N	- Newton.

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