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A novel ketoconazole bioadhesive effervescent tablet for vaginal delivery: Design, in vitro and 'in vivo' evaluation

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Abstract

Bioadhesive tablet formulations of ketoconazole for vaginal delivery were studied. Carbomer (Carbopol 974P, Carbopol 934P), hydroxypropylmethyl cellulose (HPMC) and hydroxypropyl cellulose (HPC) were used as candidate bioadhesive polymers. Effervescent was incorporated into the formulations as a disintegration agent. The swelling behavior and bioadhesive strength of the drug-free tablets were investigated. Carbopol 934P was selected as biopolymer in combination with HPMC or HPC at different ratios to develop five drug-loaded formulations. The swellings, tackiness and in vitro release were studied on the tablets. A good sustained effect and a moderate bioadhesion were obtained with the tablets. The formulation containing 100 mg of effervescent, with the Carbopol 934P:HPC ratio of 1:9, seemed to be the optimum one for the tablet. In vivo drug residence tests were carried out by administering the preferred formulation to female rats. The results showed that the drug remaining followed a one-order model. Even after 24 h of administration in vagina of rats, 17% of the original employed drug was retained on the vaginal tissue. Our study may provide a potential vaginal tablet formulation of ketoconazole against *Candida albicans*.

Keywords: Ketoconazole; Bioadhesion; Swelling; Vaginal tablets; Effervescent

1. Introduction

In recent years vaginal bioadhesive preparations have been developed as a new type of controlled-release form for the treatment of both topical and systemic diseases. For drugs which are susceptible to gut or hepatic metabolism or which cause GI side effects, vaginal bioadhesive delivery may offer a number of advantages over the other routes of administration. The greatest advantage of such dosage forms is the possibility of maintaining them in the vagina for extended periods of time including daytime and nighttime, thereby enabling lower dosing frequencies (Ahuja et al., 1997). Among various possible bioadhesive polymers, carbopol, hydroxypropylmethyl cellulose (HPMC) and hydroxypropyl cellulose (HPC) are frequently used candidates for bioadhesive preparations due to their characteristics of nontoxic, nonirritant, high bioadhesive strength and easy incorporation with the drugs.

Vaginal candidiasis is a common condition and up to 75% of all women have at least one episode of this infection during their lifetime. About 40–50% of them will suffer a second one, and a small percentage will show a chronic course (Ferrer, 2000; Lanchares and Hernandez, 2000). *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. Ketoconazole (KTZ) is an imdazole derivative antifungal agent developed for the treatment of human mycotic infections and plays an essential role in the antifungal chemotherapy (Karasulu et al., 2004). It is a weak base with limited water solubility (Esclusa-Díaz et al., 1996). In the literature, some additives, such as sodium bicarbonate and citric acid, were added into formulations to improve the disintegration and the dissolution of bioadhesive vaginal tablets because there is rather low moisture content in vagina under normal physiological conditions (Karasulu et al., 2002).

The aim of this study was to prepare a new bioadhesive effervescent vaginal tablet formulation of ketoconazole against *C. albicans*. Effervescent added into the formulations as disintegration agent would be expected to increase the dissolution of KTZ. During the in vitro study, Carbopol 934P, Carbopol

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974P, HPMC and 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 KTZ. 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 in vivo studies and the residence state of the tablet was evaluated.

2. Materials and methods

2.1. Materials

Carbopol 934P, Carbopol 974P (CP 934P, CP 974P, BF Goodrich, USA), hydroxypropylmethyl cellulose (HPMC) (Methocel K4M, Colorcon, Shanghai, China), hydroxypropyl cellulose (HPC) (Klucel HXF, Hercules, USA), ketoconazole (Bai Jingyu, Nanjing, China) were used as received. All other chemicals were of analytical reagent grade.

2.2. Preparation of drug-free tablets

The drug-free tablets were prepared using the mixture of a 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 (MgSt) and 2% silica gel were used as the lubricant and the glidant, respectively. The tablets were compressed on a single punch tablet machine (Fareast, Shanghai, China) with a pressure of 14.3 kN. The tablet mould was especially designed using stainless steel and the tablets formulated had an average weight of 750.7 ± 2.4 mg, 17.2 ± 0.2 mm height, 10.4 ± 0.2 mm width and 3.4 ± 0.3 mm thickness. The compositions of the formulations are shown in Table 1.

2.3. Swelling study

The swelling behavior of tablet described as the water absorbing capacity was determined by gravimetric methods (Kast et al., 2002; Karasulu et al., 2004). In this study, each sample was put into a stainless steel basket with 200 mesh of aperture and weighed. The basket was then placed in 100 ml distilled water, allowing the tablet to swell at 25 °C. The basket was periodically weighed after removing the excess water on the surface with a filter paper:

$$\text{Swelling}\,(\%) = \left[\frac{W_t - W_0}{W_0}\right] \times 100$$

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

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

Polymers	Polymer weight	Effervescent	MCC	MgSt	Silica gel
CP934P	150	0	577.5	7.5	15
	200	0	527.5	7.5	15
	150	50	527.5	7.5	15
	150	100	477.5	7.5	15
CP974P	150	0	577.5	7.5	15
	200	0	527.5	7.5	15
	150	50	527.5	7.5	15
	150	100	477.5	7.5	15
HPMC	150	0	577.5	7.5	15
	200	0	527.5	7.5	15
	150	50	527.5	7.5	15
	150	100	477.5	7.5	15
HPC	150	0	577.5	7.5	15
	200	0	527.5	7.5	15
	150	50	527.5	7.5	15
	150	100	477.5	7.5	15

CP934P: Carbopol 934P; CP974P: Carbopol 974P; HPMC: hydroxypropylmethyl cellulose; HPC: hydroxypropyl cellulose; effervescent: consisted of sodium bicarbonate and citric acid at a molar ratio of 3:1; MCC: microcrystalline cellulose; MgSt: magnesium stearate.

2.4. In vitro bioadhesion study

Several types of mucosa, including rat intestine, pig oral, bovine sublingual, cow vaginal mucosa (Gurny et al., 1984; Gürsoy et al., 1989), have been used as model biological tissues for the evaluation of bioadhesion, which. In this study, mouse peritoneum membrane was preferred. A simple apparatus was devised to measure the minimum detachment force (Fig. 1). A piece of mouse peritoneum membrane (2.0 cm × 1.5 cm) removed from newly sacrificed mouse 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 peritoneum with 20 μl of distilled water, the tablet was brought into contact with the peritoneum by applying 200 g for 2 min. After the initial contact, the tablet was encircled by a firm plastic ring which fastened a light plastic beaker through the crown block. Next, water was dropped into the beaker at a speed of 1.5 ml·min^{-1} until the tablet and peritoneum were pulled apart by the gravity of water. The beaker containing water was weighed and the minimum detachment force was calculated accordingly. The study was approved by the Laboratory Animal Ethics Committee of Shenyang Pharmaceutical University, and the approval document No. was 05-P-144.

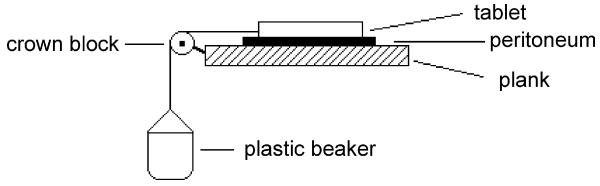

Fig. 1. The scheme of the device used in the bioadhesion studies.

Table 2
Compositions of the KBET formulations (mg)

Formulation codes	Polymer	Polymer weight fraction	Effervescent	MCC	MgSt	silica gel
F1	150	CP934P:HPMC = 1:6	100	77.5	7.5	15
F2	150	CP934P:HPMC = 1:9	100	77.5	7.5	15
F3	150	CP934P:HPC = 1:9	50	127.5	7.5	15
F4	150	CP934P:HPC = 1:9	100	77.5	7.5	15
F5	150	CP934P:HPC = 1:6	50	127.5	7.5	15

2.5. Formulations of KTZ bioadhesive effervescent tablets (KBETs)

Based on swelling behavior and bioadhesive strength of the drug-free tablets, CP934P was selected to mix with HPMC or HPC at different ratios as bioadhesive polymers. KBETs were prepared by direct mixing the polymers, KTZ, effervescent (consisting of sodium bicarbonate and citric acid at the mole ratio of 3:1), MCC, 1% magnesium stearate and 2% silica gel and finally the mixture was compressed to tablets. Each tablet contains 400 mg KTZ and has an approximate weight of 750 mg. The constituents of all formulations are presented in Table 2.

2.6. In vitro KTZ release study

Release studies were carried out using the USP 29 dissolution apparatus II, in 1000 ml phosphate buffer solution (PBS, pH 3.0) as the dissolution medium. The tablet was placed in a settling basket to prevent the tablet from floating. The rate of stirring was 30 rpm. And the medium temperature was maintained at $37 \pm 0.5\,^{\circ}C$. At each sampling interval, 3 ml of the dissolution medium was withdrawn and replaced by an equal volume of fresh PBS. KTZ was determined at 222 nm by using a U-2800 spectrophotometer (Hitachi, Japan).

2.7. Effect of KBETs on pH value of medium

It was reported that the formulations containing Carbopol 934P caused the lowering of pH values in lactate buffer (pH 5), distilled water and phosphate buffer (pH 7) (Baloğlu et al., 2003). In this study, the effects of various KBET formulations on pH values of distilled water and phosphate buffer (pH 4.0) were investigated. The tablet was placed in a 50 ml beaker with 40 ml of medium, and the pH values of medium were measured in 1-h intervals and recorded.

2.8. In vivo residence study

In this study, 21 mature female rats were randomized into seven groups, three in each. Each rat was applied with the formulation coded F4 in its vagina. To make the administration easier, the weight of the tablet was lowered to 25% of the previous design (containing KTZ 100 mg). After the application of the tablet, one group of rats was sacrificed at 2-h intervals and the vagina tissues of rat were dissected. The residual tablet was displaced into a volumetric flask, into which methanol was poured up to scale. After that, the flask was placed in a sonic oscillating water bath till the residual tablet dispersed.

The suspension was filtered and the analysis was performed with a Hitachi HPLC system. A reversed-phase ODS-C18 HPLC column 250 mm × 4.6 mm was utilized at room temperature. The mobile phase was acetonitrile (60%, v/v) and 0.5% triethylamine in water (40%, v/v), with the pH of solution adjusted to pH 7.0 using phosphoric acid. The flow rate was 1 ml/min and the detection was performed at 244 nm. Quantitative analysis was achieved by measuring the peak areas of KTZ and the peak area response was linear in the range of 10.6–84.8 μg/ml.

2.9. Curve fitting

Curve fitting was performed using Microsoft Excel 2003 version. The dissolution data were fitted to the following equation (Eq. (1)) (Kormeyer et al., 1983; Peppas, 1985; Ritger and Peppas, 1987a,b):

$$\frac{M_t}{M_\infty} = kt^n \tag{1}$$

where M_t/M_∞ is the fraction of drug released at time t, k is the kinetic constant of the system, and n is the release exponent indicating the type of drug release mechanism. The release exponent takes various values depending upon different geometries. For the drug release from a cylindrical or a flat swellable polymer, if n approaches to 0.89, the release mechanism could be Case-II transport and if n is close to 0.45, the release mechanism can be Fickian. On the other hand if $0.45 < n < 0.89$, non-Fickian transport could be obtained (Ritger and Peppas, 1987b).

2.10. Statistical analysis

Tests for significant differences between means were performed by Student's t-test or one-way ANOVA by using the software SPSS 12.11. Differences were considered significant at $P < 0.05$ level.

3. Results and discussion

3.1. Swelling study

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. Fig. 2 shows the swelling behavior of the drug-free tablets and the

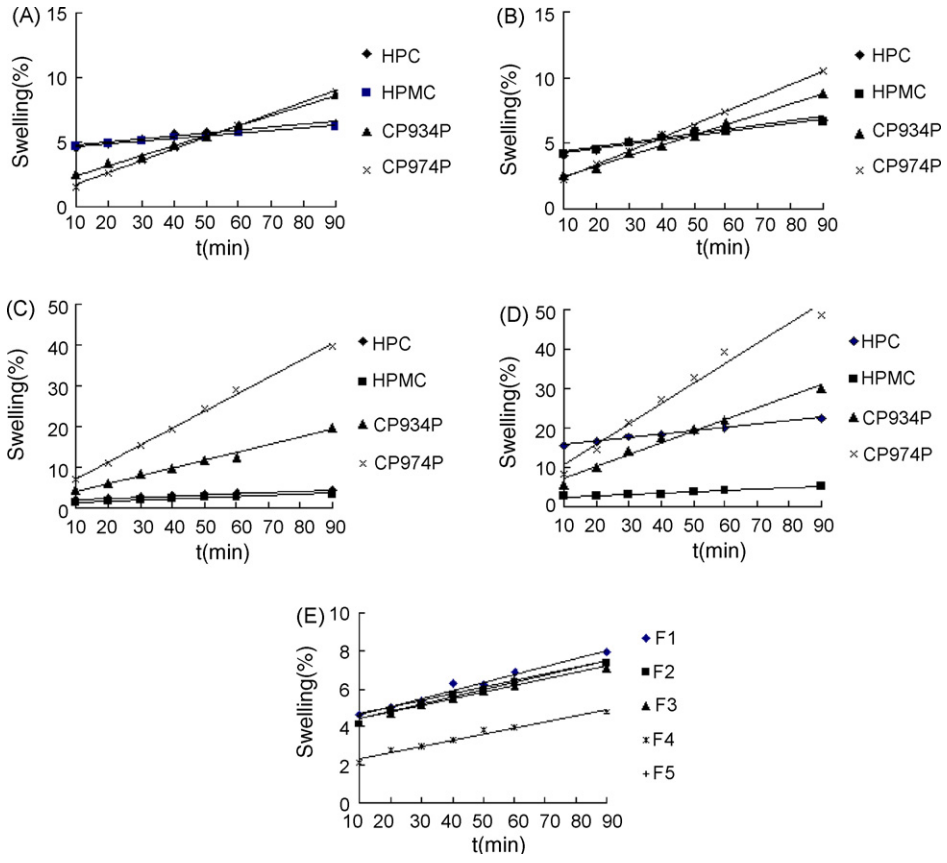

Fig. 2. Swellings of drug-free tablets and KBETs in distilled water ($n = 4$). (A) Drug-free tablets with 150 mg polymers; (B) drug-free tablets with 200 mg polymers; (C) drug-free tablets with 150 mg polymers and 50 mg effervescent; (D) drug-free tablets with 150 mg polymers and 100 mg effervescent; (E) KBETs.

KBETs. It was observed that the order of swelling rate was CP974P > CP934P > HPC = HPMC in drug-free formulations. After increasing the amount of polymers from 150 mg to 200 mg, drug-free tablets provided higher swelling rates except for one employing CP934P. 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 with 50 mg. However, this trend could not be seen in the formulation using HPMC as biopolymer. 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 contacting area between polymer particles and water so that the polymers could be hydrated more easily. Since KTZ is poorly water soluble, the porous channels may contribute to the drug release. Besides, Carbopol performed better swelling property than HPC and HPMC, thus it is considerable to incorporate Carbopol either with HPC or HPMC to achieve suitable bioadhesion and drug release.

As for KBETs, the order of swelling rates for five formulations is F1 = F2 > F3 = F4 = F5. Comparing with drug-free tablets employing the same amount of polymer and effervescent, all KBETs showed lower swelling rates, which is related with the poor solubility of KTZ.

3.2. In vitro bioadhesion study

Fig. 3 shows the detachment forces of the drug-free formulations. According to the results of statistical analysis, for the tablets prepared without effervescent, the order of bioadhesive strength is CP974P = CP934P > HPC = HPMC (Fig. 3A). Although increasing the amount of polymer from 150 mg to 200 mg, the bioadhesion of tablets could not reach a higher level (Fig. 3B). The addition of effervescent in formulations decreased the detachment forces of tablets (Fig. 3C). With tablets containing HPC, the concentration of the effervescent had no effect on bioadhesive properties whereas others were decreased significantly in bioadhesion with increasing effervescent concentration (Fig. 3C and D). The bioadhesion of CP974P showed a more reduction of 13.5% than CP934P's.

In general, the swelling state of polymer contributes to its bioadhesive behavior (Bottenberg et al., 1991). However, they are not quite correlated in this study. It was observed that the swelling rate was developed as effervescent applied to formulation, increased with increasing amount of effervescent; however, the effervescent led to a significant drop in adhesive strength. The influences of effervescent on swelling and bioadhesion were opposite, mainly due to the tiny bubbles created by effervescent. These tiny bubbles depressed the mucosa–polymer interaction, resulting in a decrease in the bioadhesive strength. According to the results obtained in the studies of swelling and bioadhe-

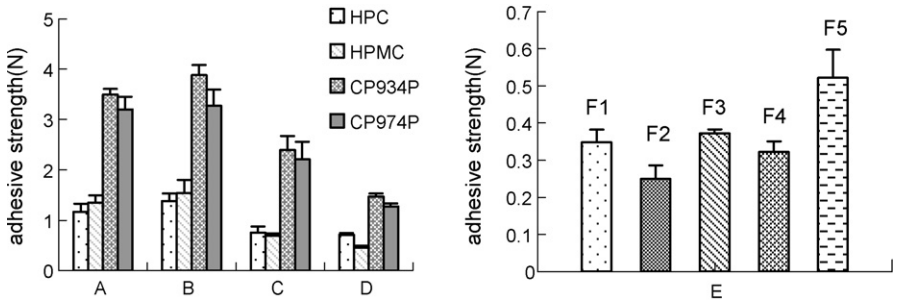

Fig. 3. Comparison of bioadhesive strength of drug-free tablets and KBETs (mean ± S.D., $n = 4$). (A) Drug-free tablets with 150 mg polymers; (B) drug-free tablets with 200 mg polymers; (C) drug-free tablets with 150 mg polymers and 50 mg effervescent; (D) drug-free tablets with 150 mg polymers and 100 mg effervescent; (E) KBETs.

sion, CP934P could serve with HPC or HPMC as biopolymer to prepare KBETs relative to CP974P.

The adhesion strength of formulations containing KTZ followed this order F2 < F1 = F3 = F4 < F5. The minimum adhesion strength was observed in F2, which could be due to the lower ratio of CP934P/HPMC and the higher content of effervescent. On the contrary, with an increase in CP934P/HPC ratio and a reduction of effervescent, the maximum bioadhesive strength (F5) was obtained. The bioadhesion results of KBETs were correlated to the results of the drug-free formulations. In addition, each formulation of KBETs had a lower bioadhesive strength than its corresponding drug-free formulation. This result was partially attributed to the poor solubility and the large amount of KTZ.

3.3. In vitro KTZ release study

The release rate of KTZ from KBETs was described as a function of time as shown in Fig. 4. In all formulations, the burst release of KTZ was observed within the first 2 h, and then gradually increased up to 24 h. About 69%, 67%, 95%, 98%, 93% of the total KTZ loaded in tablets were released within 24 h from formulations coded F1–F5, respectively. The blend of CP934P and HPMC as biopolymer provided a stronger sustained release effect on the drug release (F1 and F2). For the polymer mixture of CP934P and HPC, more drug release could be seen as decreasing CP934P/HPC ratio (F3 > F5). On the other hand, F3 and F4 had the same polymer ratio; the different concentrations of effervescent caused no change in KTZ release. A rational explanation about this phenomenon is that HPC, which is stable at pH 6.0–8.0, might undergo acid hydrolysis at low pH aqueous solutions (Rowe et al., 2003). The effect of sustained release of HPC could be depressed by the hydrolysis. Thus the amounts of effervescent in the two formulations did not influence the in vitro drug release significantly. Nevertheless, among these five formulations, F4 was preferable for subsequent in vivo studies owing to its good drug release, moderate bioadhesion and a higher effervescent concentration, which was expected to present a better disintegration and drug release under normal physiological conditions.

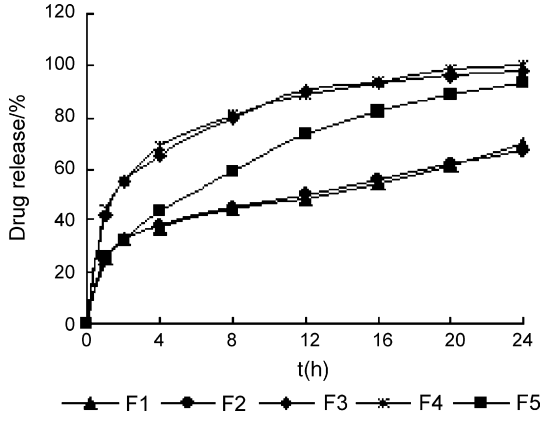

Fig. 4. Release profiles of KTZ from five formulations of KBET ($n = 6$).

The mechanism of release was investigated using Eq. (1). The calculated parameters from this equation are given in Table 3. In all cases the exponent "n" was less than 0.45. It indicated that the drug release did not follow the Fickian diffusion. In general, significant amounts of drug interfere with the macromolecular chain relaxation process, thus leading to a suppression of the relaxational mechanism and observation of only a diffusional mechanism. Consequently, swelling-controlled release systems with large initial amounts of drug loading (usually more than 30 wt%) gave Fickian diffusional release (Lee, 1983). The results presented here are not coincident with those available in the literature. This might be due to the disintegration effect of effervescent which destructed the intact matrix of the tablet. So the diffusion path of drug was shortened and the dissolution mechanism was not observed as Fickian diffusion.

3.4. Effect of KBETs on pH value of medium

It was showed that all formulations of KBETs had an effect on the pH value of the medium (Fig. 5). In distilled water,

Table 3
Fitted equations and correlation coefficients following linear regression of dissolution data of KBETs

Formulations	Fitted equations, M_t/M_∞	Correlation coefficients, r
F1	$25.33\ t^{0.289}$	0.9862
F2	$24.68\ t^{0.302}$	0.9939
F3	$44.19\ t^{0.267}$	0.9906
F4	$45.82\ t^{0.258}$	0.9943
F5	$24.88\ t^{0.423}$	0.9976

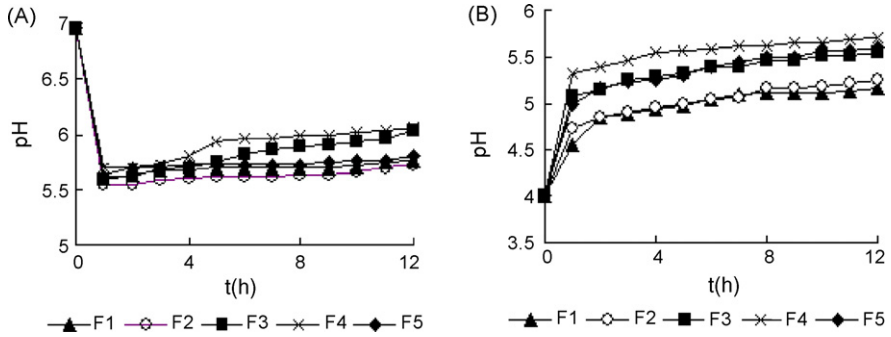

Fig. 5. Effect of KBETs on pH value of medium ($n = 6$). (A) Distilled water and (B) pH 4.0 PBS.

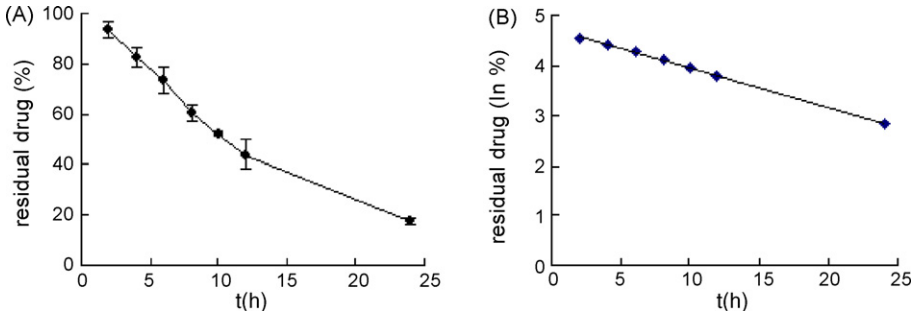

Fig. 6. (A) The residual drug–time curve of KBET coded F4 in vagina of rats (mean ± S.D., $n = 3$); (B) a plot of the recalculated remaining KTZ against the one-order pattern.

KBETs reduced the pH value first and then increased it slowly. The decrease in pH can be explained by the anionic character of CP934P which contains between 56% and 68% carboxylic groups on the dry basis (Ìkinci et al., 2004). As KTZ is a weak base, with the increase of KTZ dissolution, there was an increase in water pH value. In the phosphate buffer, KTZ had a higher dissolution rate and the drug caused a marked increase of pH. The results obtained indicated that the degree of pH increasing was in parallel to the KTZ dissolution.

3.5. *In vivo residence study*

The mean residual KTZ contents obtained in the period following the administration are shown in Fig. 6A. The data were fitted to various equations. It could be concluded from Table 4 that both the exponent equation and the polynomial equation fitted better than others. To simplify the fitted results, the exponent equation was preferred. After recalculating the LN value of the percentages of the remaining drug, a straighter line was plotted for a one-order model (Fig. 6B). The removal of the KBET from vagina tissue was complicated, many factors, including the development of rats, stages of estrus, infection, drug irritation and amount of the mucus in vagina, might affect the state of tablets retaining. In this study, there were 17 percentages of dosage remained in vagina after 24 h, thus the bioadhesive tablet could maintain its effect for at least 24 h.

Table 4
Equations fitted by different functions

Functions	Equations	r^2
Linearity	$Y = -3.4278x + 92.858$	0.9405
Logarithm	$Y = -31.479\ln x + 123.12$	0.9606
Polynomial	$Y = 0.1237x^2 - 6.732x + 107.41$	0.9988
Power	$Y = 196.36x^{-0.6482}$	0.8301
Exponent	$Y = 113.19e^{-0.0782x}$	0.9987

Y: percentage of remaining KTZ; x: time (h).

4. Conclusion

The results of this study reveal that incorporation of effervescent into the bioadhesive tablets leads to the increase in the swellings and the rate of drug release and conversely the tackiness could be decreased. It is shown that with the developed formulations, the KTZ release and bioadhesion properties of bioadhesive tablets can be controlled by changing the polymer type, polymer concentration and effervescent content. The use of KTZ against vaginal candidiasis allowed preparing the tablets by a simple direct compression. The tablet with formulation F4 was selected for in vivo evaluation. The in vivo studies indicate that the profile of KTZ retained in vagina followed a one-order pattern. Bioadhesion of the developed formulations will provide a longer period of residence time, which could result in more available therapy.

References

Ahuja, A., Khar, R.K., Ali, J., 1997. Mucoadhesive drug delivery systems. Drug Dev. Ind. Pharm. 23, 489–515.

Baloğlu, E., Özyazıcı, M., Hızarcıoğlu, S.Y., Karavana, H.A., 2003. An in vitro investigation for vaginal bioadhesive formulations: bioadhesive properties and swelling states of polymer mixtures. Il Farmaco 58, 391–396.

Bottenberg, P., Cleymaet, R., De Muynck, C., Remon, J.P., Coomans, D., Michotte, Y., Slop, D., 1991. Development and testing of bioadhesive, fluoride-containing slow-release tablets for oral use. J. Pharm. Pharmacol. 43, 457–464.

Esclusa-Díaz, M.T., Guimaraens-Méndez, M., Pérez-Marcos, M.B., Vila-Jato, J.L., Torres-Labandeira, J.J., 1996. Characterization and in vitro dissolution behaviour of ketoconazole/β-and 2-hydroxypropyl-β-cyclodextrin inclusion compounds. Int. J. Pharm. 143, 203–210.

Ferrer, J., 2000. Vaginal candidosis: epidemiological and etiological factors. Int. J. Gynecol. Obstet. 71, S21–S27.

Gurny, R., Meyer, J.M., Peppas, N.A., 1984. Bioadhesive intraoral release systems: design, testing and analysis. Biomaterials 5, 336–340.

Gürsoy, A., Sohtorik, I., Uyanik, N., Peppas, N.A., 1989. Bioadhesive controlled release systems for vaginal delivery. STP Pharma. 5, 886–892.

Ìkinci, G., Şenel, S., Wilson, C.G., Şumnu, M., 2004. Development of a buccal bioadhesive nicotine tablet formulation for smoking cessation. Int. J. Pharm. 277, 173–178.

Karasulu, H.Y., Taneri, F., Sanal, E., Güneri, T., Ertan, G., 2002. Sustained release bioadhesive effervescent ketoconazole microcapsules tabletted for vaginal delivery. J. Microencapsul. 19, 357–362.

Karasulu, H.Y., Hilmioğlu, S., Metin, D.Y., Güneri, T., 2004. Efficacy of a new ketoconazole bioadhesive vaginal tablet on *Candida albicans*. Il Farmaco 59, 163–167.

Kast, C.E., Valenta, C., Leopold, M., Bernkop-Schnürch, A., 2002. Design and in vitro evaluation of a noval bioadhesive vaginal drug delivery system for clotrimazole. J. Control. Rel. 81, 347–354.

Kormeyer, R.W., Gurny, R., Doelker, E., Buri, P., Peppas, N.A., 1983. Mechanisms of solute release from porous hydrophilic polymer. Int. J. Pharm. 15, 25–35.

Lanchares, J.L., Hernandez, M.L., 2000. Recurrent vaginal candidiasis changes in etiopathogenical patterns. Int. J. Gynecol. Obstet. 71, S29–S35.

Lee, P.I., 1983. Dimensional changes during drug release from a glassy hydrogel matrix. Polym. Commun. 24, 45–47.

Peppas, N.A., 1985. Analysis of Fickian and non-Fickian drug release from polymers. Pharm. Acta Helv. 60, 110–111.

Ritger, P.L., Peppas, N.A., 1987a. A simple equation for description of solute release. I. Fickian and non-Fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs. J. Control. Rel. 5, 23–36.

Ritger, P.L., Peppas, N.A., 1987b. A simple equation for description of solute release.II. Fickian and anomalous release from swellable devices. J. Control. Rel. 5, 37–42.

Rowe, R.C., Sheskey, P.J., Weller, P.J., 2003. Handbook of Pharmaceutical Excipients, 4th ed. Pharmaceutical Press American Pharmaceutical Association, London Washington, DC, p. 291.