Original Article

Development of Fluconazole Suppositories for the Treatment of Candida Infection of Genitourinary Tract

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ABSTRACT

Background: Vulvovaginal candidiasis is a communal problem in virtually all the women which is caused by *Candida albicans.* **Objective:** Aim of the present study was to prepare and characterize vaginal suppositories of fluconazole for the treatment of vulvovaginal candidiasis. **Methods:** Fluconazole suppositories were prepared using water soluble and fatty bases. Bases and their proportions used were selected in such a way that they have flexibility in storage conditions unlike conventional suppositories. Suppositories were prepared and examined for physical characteristics and *in vitro* release studies. **Results:** Present study showed ultimate results with respect to the physical characteristics of suppositories and *in vitro* drug release studies. *In vitro* drug release from the prepared suppositories was in the following order FVS 3 (100.00 ± 3.7% in 1.0 h) > FVS 1 (86.29 ± 4.9% in 12.0 h) > FVS 2 (80.47 ± 2.4% in 12.0 h) > FVS 5 (22.51 ± 0.42% in 24.0 h) > FVS 4 (18.09 ± 1.31% in 24.0 h). These drug release results are supported by the disintegration time of suppositories. Lesser the disintegration time faster the drug release. **Conclusion:** Study concludes that it may be fruitful to explore the *in vivo* activities of suppositories prepared with the combination of agar and HPMC as it showed around 80% drug release over 12.0 h. Represented combination may also be more effective for the treatment of vulvovaginal candidiasis.

Key words: Vulvovaginal candidiasis, *Candida albicans*, Fluconazole, Fluconazole suppositories, Vaginal suppositories, Vaginal infection, Agar, Hydroxypropyl methylcellulose, Glycerol-gelatin, Cocoa butter, Bees wax.

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INTRODUCTION

Vulvovaginal candidiasis (VVC) is a very common problem in almost all the women and caused by *Candida albicans* in vagina.[1] It has been reported that around 75% of the women of reproductive age experiences vulvovaginal candidiasis infection at least once in their lifetime.[2-3] VVC is associated with the very embarrassing condition in the women with the symptoms of irritation, itching, white to pale white vaginal discharge.[3-5] *Candida albicans* account for around 85% to 95% of VVC[2,6]. The most commonly used agents for the treatment of VVC infection are azole derivatives.[3,7-8] Fluconazole (FLZ) is one of the azole derivative which is used for this treatment and is also available as oral tablets and suspensions. But, oral therapy of azoles should be avoided in the pregnant women especially after first trimester as it may cause birth defects in the new born babies.[9] Oral delivery of fluconazole has dose-dependent teratogenicity. But, the azoles can be delivered to the pregnant women as a topical delivery.[10-13] Hence, the vaginal drug delivery of FLZ is considered to be effective for the treatment of VVC due to its targeting to the specific site and safety in pregnant women.[9,14]

Few formulations of FLZ for the vaginal drug delivery have also been prepared to

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solve the above mentioned problems such as vaginal films[5,8] vaginal gels[15-18] vaginal tablets,[19] etc. But, the main problems with vaginal films and vaginal gels are their low drug content, wetting and leakage.[20-22] Similarly, vaginal tablets cause irritation, hypertonic and discomfort as it takes more time for disintegration. Hence, there is a need to explore an intermediate product for the treatment of this infection which exist between gels/films and tablets.

Vaginal suppositories of FLZ which may be useful for the treatment of VVC due to its highest concentration of drug in the vagina, safe in pregnant women, site specific delivery, helps to conserve the privacy, etc. FLZ also have mild side effects such as nausea and dizziness which can also be taken care by the help of FLZ vaginal suppositories.[23]

The aim of the present study was to prepare and characterize the vaginal suppositories of FLZ for the treatment of VVC. In this study, the prepared vaginal suppositories of FLZ were characterized with respect to the hardness of suppositories, weight variation, content homogeneity, *in vitro* drug release studies, etc.

MATERIALS AND METHODS

Materials

Fluconazole was received as a gift sample from Ipca Laboratories, Mumbai. Agar was purchased from HiMedia® Lab., Mumbai, India. HPMC K 100 was procured from Loba Chemie Pvt. Ltd., Mumbai, India. Propylene Glycol was bought from Spectrochem Pvt. Ltd., Mumbai, India. Glycerin was obtained from Merck Life Science Pvt. Ltd., Mumbai, India. Gelatin was acquired from Sigma Aldrich® Co, St. Louis Missouri, US. Cocoa butter was purchased from Yarrow Chem Products, Mumbai, India. Bees wax was procured from SD Fine-Chem Limited, Mumbai, India. Distilled water was prepared freshly in our Pharmaceutics research lab.

Instrumentation and Apparatus

Electronic weighing scale (Essae-Teraoka Pvt. Ltd., Mangalore, Karnataka, India), Fourier transform Infrared spectrophotometer (FTIR-8300, Shimadzu Corporation, Kyoto, Japan) with IR solution v.1.30, Disintegration apparatus (ED-2L, Electrolab India Pvt. Ltd., Mumbai, India), Dissolution apparatus (TDT-08L, Electrolab India Pvt. Ltd., Mumbai, India), Hardness tester (EH-01, Electrolab India Pvt. Ltd., Mumbai, India), Screw gauge (Mitutoyo Corporation, Japan), UV visible spectrophotometer (UV-1601PC, Shimadzu Corporation, Kyoto, Japan).

Table 1: Composition of fluconazole vaginal suppositories.

Ingredients	Composition (%w/w)				
	FVS1	FVS2	FVS3	FVS4	FVS5
Fluconazole	10.00	10.00	10.00	10.00	10.00
Agar	9.00	9.00	-----	-----	-----
HPMC	1.50	0.50	-----	-----	-----
Propylene glycol	9.00	9.00	-----	-----	-----
Gelatin	-----	-----	18.00	-----	-----
Glycerin	-----	-----	63.00	-----	-----
Cocoa butter	-----	-----	-----	45.00	68.00
Bees wax	-----	-----	-----	45.00	22.00
Water q.s. to	100.00	100.00	100.00	-----	-----

Drug-excipient Compatibility Studies

Drug and excipient compatibility was confirmed using FTIR in the physical mixtures (1:1 ratio of drug: excipient). The FTIR study was performed by using KBr pellet method and the spectra was recorded in the range 4000 to 450 cm^{-1}. Physical mixture results were compared with pure drug results.

Preparation of Fluconazole Vaginal Suppositories

FLZ vaginal suppositories were prepared with different suppository bases using different methods. Composition of prepared vaginal suppositories is shown in Table 1.

Preparation of Suppositories using Agar and HPMC K 100

Required weight of agar and HPMC K 100 was dissolved in purified hot water. Propylene glycol was added in the above mixture and was stirred until homogenous mixture was achieved. Then the drug was dissolved in the above mixture, was transferred into the suppository molds (1.0 g) and was cooled using ice bath. The prepared suppositories were de-molded and each suppository was wrapped separately in a butter paper. The wrapped suppositories were packed in wide mouth container and was stored at cool and dry place till further use.

Preparation of Suppositories using Glycerol-gelatin Base

Accurately weighed amount of gelatin and drug were dissolved in purified water in a beaker. Measured volume of glycerin was taken in another beaker and heated at 120°C. Then the gelatin mixture was transferred into the glycerin containing beaker and heating was continued until the homogeneous mixture was produced. Finally, the mixture was poured into the pre-cleaned suppository molds (1.0 g) followed by cooling in ice bath. The prepared suppositories were collected and stored at cool

and dry place in wide mouth containers after wrapping in butter paper.

Preparation of Suppositories using Cocoa Butter and Bees Wax

Cocoa butter and bees wax were weighed and melted in a china dish in a water bath then FLZ was added to the molten mixture. The above molten mixture was poured into the pre-cleaned suppository molds (1.0 g) followed by cooling in ice bath. The suppositories were then separated from the molds and were stored at a cool and dry place in wide mouth containers after wrapping in butter paper.

Physical Appearance of Suppositories

The color and shape of prepared FLZ vaginal suppositories were observed with naked eyes and the observations were recorded in an observation sheet.[24]

Dimensions of Suppositories

Three suppositories from each batch were taken randomly and length and width of the prepared suppositories were measured.[25]

Homogeneity Test

Three suppositories from each batch were cut longitudinally and drug distribution pattern (rough or dryness) in prepared vaginal suppositories was recorded.[25-26]

Weight Variation

Twenty FLZ vaginal suppositories were taken randomly from each batch and the weight of each suppository was recorded. Obtained results of weight variation studies were compared with the official limits.[24-25,27-28]

Hardness

Hardness of FLZ vaginal suppositories from each batch was determined using hardness tester at room temperature. Three vaginal suppositories from each batch was taken and the hardness was measured.[27-29]

Content Uniformity

Suppository was taken in a volumetric flask (100 mL) and was dissolved in methanol (10 mL) with the slight heating. Then the final volume was made up to the mark with acetate buffer pH 4.6. The final solution was filtered through membrane filter (pore size 0.45 μ) and the presence of drug was determined using UV visible spectrophotometer after suitable dilutions with acetate buffer at 261 nm wavelength.[8,28] Three suppositories were taken from each batch for this study.

Disintegration Time

Six FLZ vaginal suppositories (from each batch) were taken in cylindrical glass containers of USP tablet disintegration apparatus. Suppositories containing cylindrical glass containers were immersed in 900 mL of acetate buffer pH 4.6. The glass containers were allowed to move up and down in acetate buffer. The time taken by the suppository to completely vanish from the perforated ends of glass container was recorded.[28]

In vitro Drug Release Studies

In vitro drug release of prepared FLZ vaginal suppositories was determined using USP Type II apparatus (Paddle Type). Speed of the paddle was maintained at 25 rpm in 500 mL of acetate buffer pH 4.6. The experiment temperature of the medium was maintained at 37 ± 0.5°C for the entire study. Sink conditions were maintained by collecting 2.0 mL of sample and by replacing the same volume with blank acetate buffer at predetermined time intervals. Presence of drug in the samples was determined with the help of UV visible spectrophotometer at 261 nm wavelength. *In vitro* drug release studies was performed on three suppositories of each batch.[8]

RESULTS AND DISCUSSION

FTIR spectra of drug; drug, agar and HPMC physical mixture; drug and gelatin physical mixture; drug and bees wax physical mixture; and drug and cocoa butter physical mixture are shown in Figure 1(A); 1(B); 1(C); 1(D) and 1(E), respectively.

Figure 1(A) represents FLZ had characteristics absorbance bands at 1139.93 cm^{-1} for C-F stretching, 1361.74 cm^{-1} for O-H def. band, 1510.26 cm^{-1} for C=C and C-N stretching, 1616.35 cm^{-1} for C=C group and 3155.54 cm^{-1} for O-H stretching. The results of these spectra are also confirmed from the literature[8]. Figure 1(B) shows the FTIR spectra of FLZ, agar and HPMC physical mixture displayed the absorbance bands at 1139.93 cm^{-1} for C-F stretching, 1363.67 cm^{-1} for O-H def. band, 1512.19 cm^{-1} for C=C and C-N stretching, 1616.35 cm^{-1} for C=C group and 3180.62 cm^{-1} for O-H stretching. Figure 1(C) represents the FTIR spectra of FLZ and gelatin physical mixture demonstrated the absorbance bands at 1139.93 cm^{-1} for C-F stretching, 1361.74 cm^{-1} for O-H def. band, 1510.26 cm^{-1} for C=C and C-N stretching, 1616.35 cm^{-1} for C=C group and 3182.55 cm^{-1} for O-H stretching. Figure 1(D) signifies the FTIR spectra of FLZ and bees wax physical mixture revealed the absorbance bands at 1141.86 cm^{-1} for C-F stretching, 1367.53 cm^{-1} for O-H def. band, 1510.26 cm^{-1} for C=C

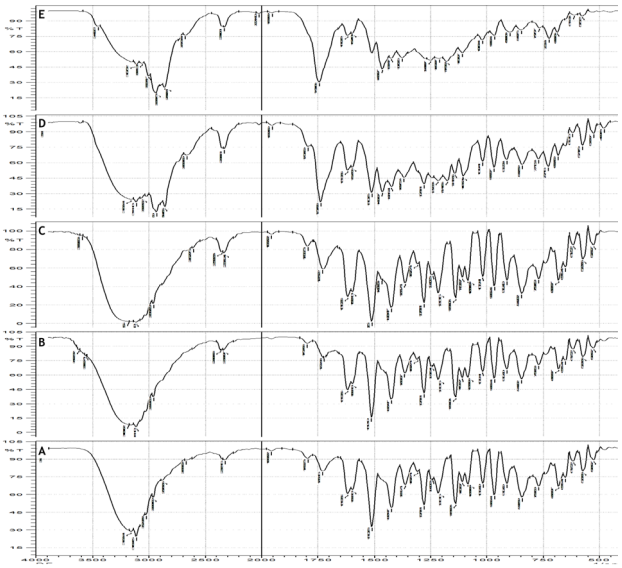

Figure 1: FTIR Spectra: (A) FLZ; (B) FLZ, agar and HPMC physical mixture; (C) FLZ and gelatin physical mixture; (D) FLZ and bees wax physical mixture; and (E) FLZ and cocoa butter physical mixture.

and C-N stretching, 1616.35 cm^{-1} for C=C group and 3155.54 cm^{-1} for O-H stretching. Figure 1(E) illustrates the FTIR spectra of FLZ and cocoa butter physical mixture exhibited the absorbance bands at 1375.25 cm^{-1} for O-H def. band, 1512.19 cm^{-1} for C=C and C-N stretching and 1618.28 cm^{-1} for C=C group. In a physical mixture of FLZ and cocoa butter the two important peaks were absent i.e. C-F stretching and O-H stretching. The absence of these two peaks may be due to the encapsulation of FLZ in cocoa butter. FTIR study confirmed the absence of interaction between the FLZ and excipients.

Prepared FLZ vaginal suppositories were characterized with respect to the color, shape, dimensions, homogeneity, weight variation, hardness and content uniformity. The results of the physical characteristics studies are reported in Table 2. There were notable differences in the color and opacity between prepared suppositories. Suppositories made of agar and HPMC base were slightly brownish in color and were translucent and soft to touch. Suppositories made of gelatin and glycerin were slightly yellowish in color and were transparent. Suppositories made of cocoa butter and bees wax were transparent in molten state and turned off-white in color and opaque when cooled. All the suppositories were of almost equal dimensions and were in conical shape without any breakage except FVS3. FVS3 suppositories were having the slightly less dimensions i.e. 22.0 × 6.0 mm^2 which may be due to its more softness and jelly nature.

The results of parameter like weight variation and content uniformity were within the limits. There were major variations in hardness and disintegration time. Suppositories with cocoa butter and bees wax took more time to disintegrate as they were made up of fatty bases. Whereas, glycero-gelatin suppositories and suppositories made of agar and HPMC were disintegrated within 45 min. As shown in Table 2, order of disintegration was FVS 4 >FVS 5 >FVS 1 >FVS 2 >FVS 3. It was observed that glycero-gelatin suppositories took less time to disintegrate. It was also noticed that FVS 1 suppositories had more disintegration time in comparison of FVS 2 which may be due to the higher proportion of HPMC in FVS 1 suppositories as HPMC has some viscoelastic nature.

Even though FVS 3 suppositories were softer than the other suppositories, but the hardness was found to be greater than the other suppositories which may be due to their jelling nature. It was observed that the bees wax

Table 2: Physical characteristics of fluconazole vaginal suppositories.

Physical characteristics	Formulation Batch				
	FVS1	FVS2	FVS3	FVS4	FVS5
Color and opacity*	Slight brownish and translucent	Slight brownish and translucent	Slight yellowish and transparent	Off white and opaque	Off white and opaque
Shape*	Conical	Conical	Conical	Conical	Conical
Dimensions (mm^2)*	25.0 × 7.62	25.2 × 7.9	22.0 × 6.0	24.0 × 7.0	24.2 × 7.2
Homogeneity*	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous
Weight variation (mg)$	0.96 ± 0.02	0.96 ± 0.02	1.12 ± 0.06	0.79 ± 0.02	0.83 ± 0.01
Hardness (kg/cm^3)*	0.41 ± 0.02	0.44 ± 0.03	2.56 ± 0.20	1.43 ± 0.22	0.46 ± 0.04
Content uniformity (%)*	93.40 ± 2.36	97.20 ± 0.55	96.10 ± 3.10	94.70 ± 2.50	96.60 ± 0.95
Disintegration (min)#	41.33 ± 1.15	27.66 ± 0.58	11.61 ± 0.33	> 60.00	> 60.00

*Results represented as Mean ± SD, n = 3; $Results represented as Mean ± SD, n = 20; and #Results represented as Mean ± SD, n = 6.

also contributes to enhance the hardness of suppositories as hardness of FVS 4 was found to be greater than the hardness of FVS5, because FVS 4 contained more bees wax compare to FVS 5. The hardness of FVS 1, FVS 2 and FVS 5 was found to be almost same and showed lesser value than the hardness of FVS 3 and FVS 4. It was noticed that the suppositories prepared using the glycerol-gelatin base shows almost the same hardness, weight variation and disintegration time than the suppositories prepared using the Witepsol, grade H15.[14]

The drug release obtained from the prepared FLZ vaginal suppositories is shown in Figure 2. It was observed that the glycero-gelatin suppositories (FVS 3) released full amount of drug within 60.0 min of dissolution. This may be due to the water soluble bases. The suppositories prepared with agar and HPMC released more than 80.0% of drug within 12.0 h. The drug release from FVS 1 was greater than the FVS 2 which may be due to the swelling nature of HPMC as the concentration of HPMC is more in FVS 1. But, the suppositories prepared with cocoa butter and bees wax didn't release even 25.0% of drug in 24.0 h. These drug release results are supported by the disintegration time of suppositories. Lesser the disintegration time, faster the release of drug from the suppositories. These results shows that the FLZ suppositories formulated using hydrophilic bases gives fast drug release when compared to the suppositories formulated using hydrophobic bases. These findings are also supported by the earlier research on FLZ suppositories using other suppository bases.[30]

Based on the release pattern obtained from *in vitro* drug release studies, it was observed that glycero-gelatin suppositories can be used for immediate drug release as it released 100% drug within 1.0 h. The suppositories made up of agar and HPMC combination i.e., FVS 1 and FVS 2 provided the best release pattern over 12.0 h as these suppositories released 86.29 and 80.47% drug, respectively whereas the suppositories made up of cocoa butter and bees wax combinations showed a maximum release of 22.0% over a period of 24.0 h. The present study indicates that agar and HPMC can be used to prepare the sustained release suppositories.

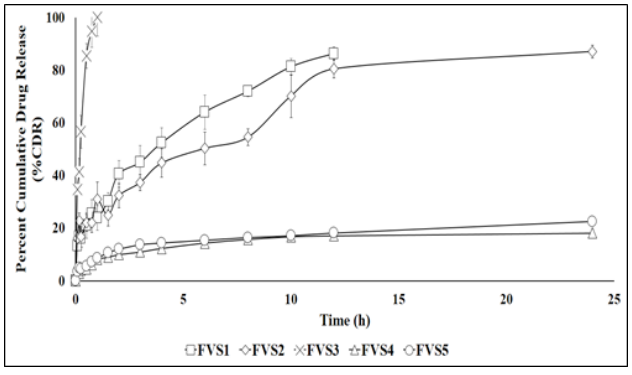

Figure 2: *In vitro* drug release studies of fluconazole vaginal suppositories. Results represented as Mean ± SD, n = 3.

CONCLUSION

The study was planned for the vaginal delivery of FLZ for the treatment of VVC by preparing its vaginal suppositories. In the present study, three different combination of polymers and/or suppository bases were studied such as agar and HPMC combination, glycerol-gelatin base, and cocoa butter and bees wax bases combination. This study showed ultimate results with respect to the physical characteristics of suppositories (especially hardness and disintegration time) and *in vitro* drug release studies. *In vitro* drug release study concludes that it may be fruitful to explore the *in vivo* activities of suppositories prepared with the combination of agar and HPMC as it showed around 80% drug release over 12.0 h. The obtained results suggested that the agar and HPMC combination may be helpful for the treatment of VVC.

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CONFLICT OF INTEREST

There are no conflicts of interest.

ABBREVIATIONS

FLZ: Fluconazole; **FTIR:** Fourier Transform Infrared Spectrophotometer; **FVS:** Fluconazole Vaginal Suppositories; **HPMC:** Hydroxy Propyl Methylcellulose; **KBr:** Potassium Bromide; **SD:** Standard Deviation; **USP:** United States Pharmacopoeia; **UV:** Ultra Violet; **VVC:** Vulvovaginal candidiasis.

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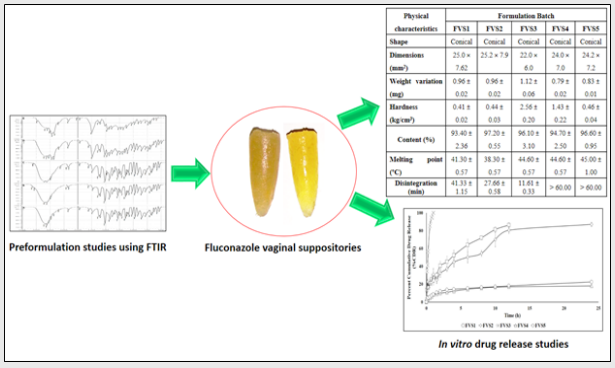
PICTORIAL ABSTRACT



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SUMMARY

- Drug-excipient compatibility studies.
- Preparation of fluconazole vaginal suppositories.
- Physical characterizations of prepared vaginal suppositories.
- *In vitro* drug release studies of prepared vaginal suppositories.
- Fluconazole vaginal suppositories showed ultimate results with respect to the physical characteristics of suppositories especially hardness and disintegration time.
- In vitro drug release study also concludes that it may be fruitful to explore the *in vivo* activities of suppositories prepared with the combination of agar and HPMC as it showed around 80% drug release over 12.0 h.
- The obtained results evidenced that the agar and HPMC combination may be helpful for the treatment of VVC.

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