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Formulation of terconazole loaded transferosomal gel for topical delivery

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ABSTRACT

The present study aimed to formulate the transferosomal gel formulation of antifungal drug Terconazole for prolonged drug release. Terconazole is an anti-fungal drug mainly used to treat vaginal yeast infections (or vaginal candidiasis). Terconazole-loaded transferosomes were prepared by modified handshaking thin-film method using a varied ratio of Soya phosphatidylcholine: Tween 80, Soya phosphatidylcholine: Span 80, Soya lecithin: Tween 80 and Soya lecithin: Span 80. FT-IR study was carried out to check any possible interactions between the drug and excipients. To quantify the drug concentration in the in-vitro samples, UV spectrophotometric studies were selected. Terconazole transferosomal gel was successfully prepared which can be useful in the treatment of fungal infection.

Key words: Terconazole, Vaginal candidiasis, Transferosomes, lipophilic.

INTRODUCTION

Drug delivery systems are technological tools for the delivery and/or controlled release of therapeutic agents in a targeted manner. Various drug delivery and drug targeting systems are currently under development to reduce drug degradation and loss, to prevent harmful side effects, and to increase drug bioavailability and the fraction of the drug accumulated in the appropriate region. Soluble polymers, microparticles made of insoluble or biodegradable organic and synthetic polymers, microcapsules, cells, cell ghosts, lipoproteins, liposomes, and micelles can be named among the drug carriers. Terconazole is an antifungal medicine used to treat the infection of vaginal yeast. It comes as a lotion or suppository and disrupts the yeast cell's biosynthesis of fats. Compared to azole compounds, but not triazole compounds, it has a relatively wide spectrum. For those suffering from chronic vulvovaginal candidiasis, clinical evidence suggests that it is an effective prophylaxis compound.

Structure of Terconazole

ChemicalName:1-(4-{[(2R,4S)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3- dioxolan-4-yl]methoxy}phenyl)-4-(propan-2-yl)piperazine.
Melting point: 126.3°C
Solubility: It is insoluble in water; sparingly soluble in ethanol, and soluble in butanol.

Via disrupting normal fungal cell membrane permeability, terconazole can exert its antifungal activity. In susceptible fungi, terconazole and other triazole antifungal agents inhibit cytochrome P450 14-alpha-demethylase, leading to the accumulation of lanosterol and other methylated sterols and a drop in the concentration of ergosterol. Ergosterol depletion in the membrane disrupts the fungal cell's structure and function, leading to a decrease or inhibition of fungal growth.

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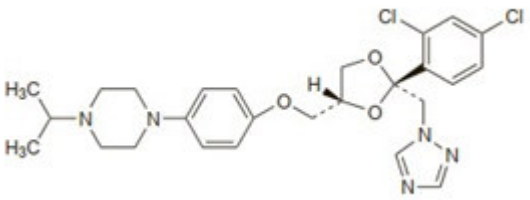

Terconazole belongs to a recent chemical class of antifungal agents, the triazoles. To be more active than the imidazoles, it was formulated and synthesized. Terconazole's fundamental mechanism of action, the inhibition of fungal cytochrome P-450, is similar to that of imidazole. The present study aimed to formulate the transferosomal gel formulation of antifungal drug Terconazole for prolonged drug release[1,2].

Experimental Methods

Pre-formulation studies

Melting Point

Melting point determination of the obtained drug sample was done as it is the first indication of the purity of the sample. The presence of a relatively small amount of impurity can be detected by a lowering as well as widening in the melting point range. The melting point of Terconazole was measured by Thiele's tube apparatus.

Preparation of phosphate buffer 7.4

Take accurate amount i.e. 27.2 gm of potassium dihydrogen orthophosphate (KH_2PO_4) and dissolved in 1000mL water. And 8 gm sodium hydroxide pellets were dissolved in 1000 mL of the beaker. 50 mL of 0.2 M potassium dihydrogen phosphate and 39.1 mL of 0.2 M NaOH were taken in 200 mL volumetric flask and the volume was made up to the mark with distilled water. The pH is adjusted using NaOH or dilute HCl solution.

Determination of λmax

Standard Terconazole of 10mg was accurately weighed and transferred to 10ml volumetric flask. It was dissolved properly and diluted to mark with 0.1N HCl to obtain a concentration of 1mg/ml. As a stock solution, this solution was used. The working standard solution and sufficient dilutions were prepared[3].

Standard Curve for Terconazole

100mg of Terconazole was accurately weighed and dissolved 50 ml of 0.1 N HCl. The solution was sonicated for 5 min, and the final volume was adjusted to 100 mL to give stock solution-I (1000 µg/ml concentration). 10 mL of stock solution-I was placed in 100 mL volumetric flask and volume were adjusted with methanol to give stock solution-II of 100µg/mL concentration. Stock solution-II was further diluted with methanol to get working standard solution of 5, 10, 15, 20 and 25 µg/mL of 0.1 N HCl to construct Beer's law plot for the pure drug. The absorbance of the solutions was measured at 227 nm using UV-visible spectrophotometer. A graph of concentration Vs absorbance was plotted[3].

Compatibility study using FT-IR

Using a Thermo Nicolet FTIR, infrared spectroscopy was performed and the spectrum was registered in the 4000 to 400 cm-1 regions. The treatment consisted of sample dispersion (drug and drug-excipient combination, 1:1 ratio) in KBr (200-400 mg) and compression into discs by applying a hydraulic pressing pressure of 5 tonnes for 5 minutes. All spectra were collected as an average of three scans at a resolution of 2 cm^{-1}. The interaction between drug-excipients was observed from IR Spectral studies by observing any shift in peaks of the drug in the spectrum of a physical mixture of the drug[4].

Formulation Design

1. Preparation of Transferosomes by modified handshaking thin-film method

Twelve transferosome formulations were prepared by modified handshaking lipid film hydration method using Terconazole, Soya lecithin, Soya phosphatidylcholine and different surfactants (Tween-80, Span-80). The amount of drug is kept constant (100mg) for all the formulations. Soya lecithin, Soya phosphatidylcholine, surfactants and the drug are dissolved in 5mL of the organic solvent (Chloroform: ethanol; 3:1) and then placed in a clean, dry bottom flask. The organic solvent was carefully evaporated under reduced pressure above the lipid transition temperature by rotary evaporation to form a lipid film on the flask wall and lipid film was hydrated with a phosphate buffer solution (pH 7.4) by rotation for 1hr at room temperature at 60 rpm. The resulting vesicles are swollen for 2 hrs at room temperature. The multilamellar lipid vesicles (MLV) are then sonicated using a sonicator for 30 minutes[5,6].

Table 1: Composition of different formulation of Terconazole Transferosomes

Formulation Code	Drug (mg)	SL (mg)	Soya Phosphatidyl Choline (mg)	Tw 80 (mg)	Sp 80 (mg)	Chloroform/ ethanol
F1	100	90	-	10	-	2:1
F2	100	85	-	15	-	2:1

F3	100	80	-	20	-	2:1
F4	100	90	-	-	10	2:1
F5	100	85	-	-	15	2:1
F6	100	80	-	-	20	2:1
F7	100	-	90	10	-	2:1
F8	100	-	85	15	-	2:1
F9	100	-	80	20	-	2:1
F10	100	-	90	-	10	2:1
F11	100	-	85	-	15	2:1
F12	100	-	80	-	20	2:1

Drug – Terconazole SL – Soya Lecithin SPC – Soya Phosphatidyl Choline Tw 80 – Tween 80 Sp – Span 80

2. Preparation of topical transferosomal gel

Carbopol gels were prepared to be used as a vehicle for the incorporation of transferosomes for topical delivery. For the topical gel formulation, the aqueous dispersion of transferosomes was used. Gel polymer was used to prepare transferosomal gel, such as carbopol 940. 2 g of carbopol 940 powder was dispersed into distilled water (taking care to avoid the formation of dispersible lumps) and allowed to hydrate for 24 hours by vigorously stirring (stirred by the magnetic stirrer Remi 5MLH). The dispersion was neutralized with triethanolamine to adjust the pH [7.4] by using a pH meter[5].

RESULTS

Melting point determination

The melting point of the drug was determined by using a melting point apparatus (Thiele's tube). This was compared with the literature melting point value of the drug. The melting point of the pure drug Terconazole was found to be at 126 ± 0.5^{O}C.

Analytical method determination of Terconazole

The ultra-violet spectrophotometry technique is one of the most widely used in pharmaceutical research. This includes calculating the quantity of ultraviolet (190-380 nm) or visible (380-800 nm) radiation absorbed by the solution material.

Determination of λmax

UV method was employed to determine the λmax of pure drug Terconazole. The λmax of the Terconazole was found to be 227 nm in 0.1N HCl and the same wavelength was used for further studies.

Determination of calibration curve

The absorbance of Terconazole was measured in a UV spectrophotometer at 227 nm against 0.1N HCl. The absorbance therefore obtained was tabulated, and the graph was obtained by plotting absorbance Vs concentration (Figure 1).

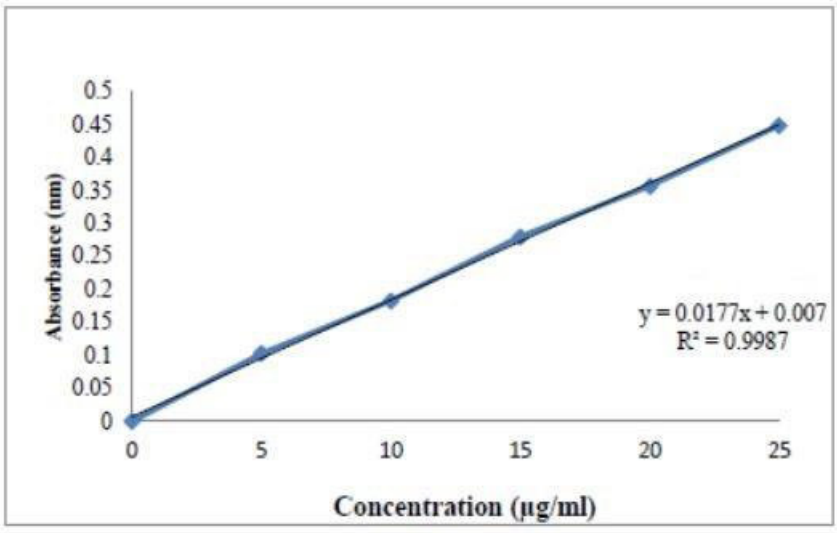

Figure 1: Calibration curve of Terconazole in 0.1N HCl Drug Excipients Interaction Study

While designing any drug delivery system, it is imperative to consider the compatibility of drug and polymer used within the system. Therefore, it is necessary to confirm that the drug is not interacting with the polymer under experimental conditions and shelf life. The interaction studies can be done based on Assay, UV, Infra-red and TLC analysis. In this study drug, excipients interaction study was done by FTIR study.

Compatibility studies using FTIR

Infra-red spectrum of drug, polymers and mixture of

both was determined by KBr disks method. Samples were prepared in KBr disks utilizing a hydrostatic press at 5 tons pressure for 5 min and obtained spectra are shown in Figure 2-5. All of Terconazole's characteristic peaks were found in the drug and polymer mixture range, suggesting compatibility between the drug and the polymer. The spectrum indicated that the chemical integrity of the drug had not substantially altered. There is no change in functional group peaks [C=O(s), C=C (s), C-H (b), C-N(s), C-O (s), =C-H (b)] of Terconazole in all the IR-spectra.

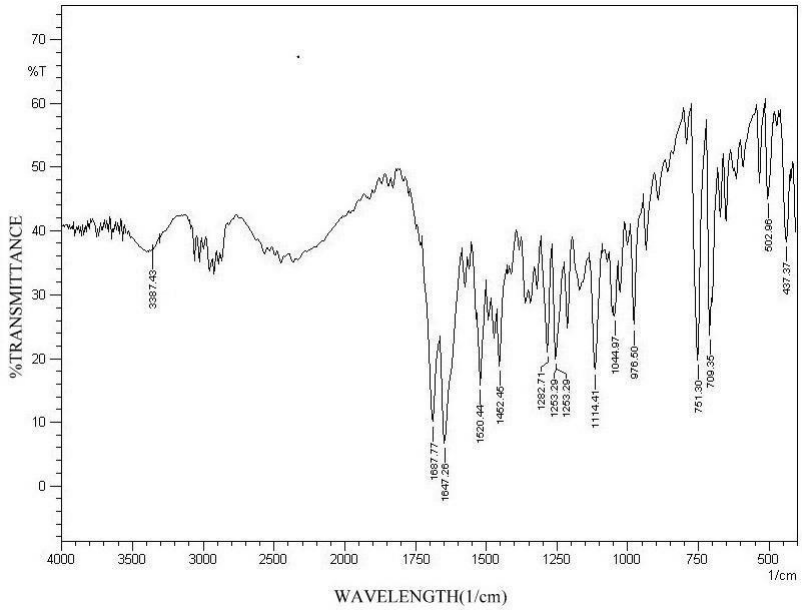

Figure 2: FT-IR spectrum of the pure drug (Terconazole).

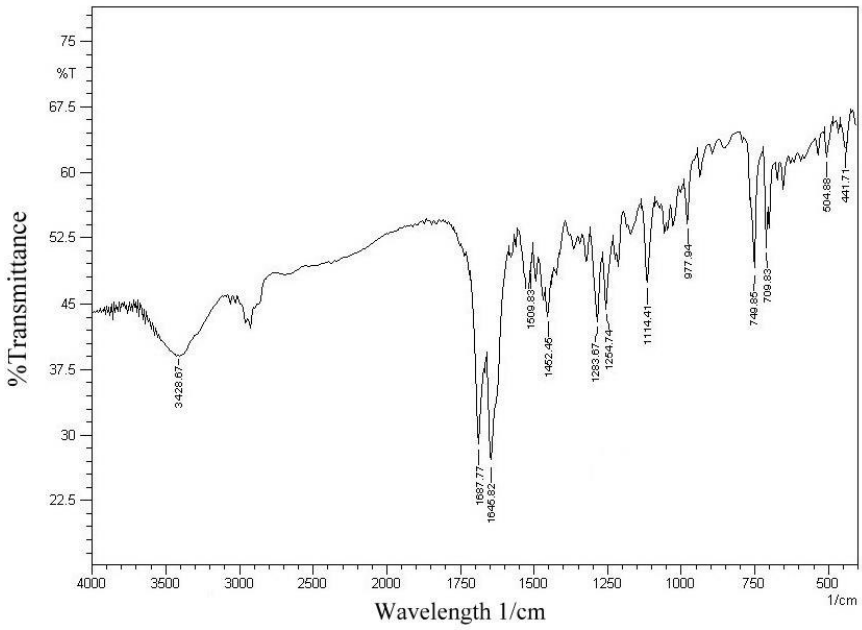

Figure 3: FT-IR spectrum of drug+ Tween 80.

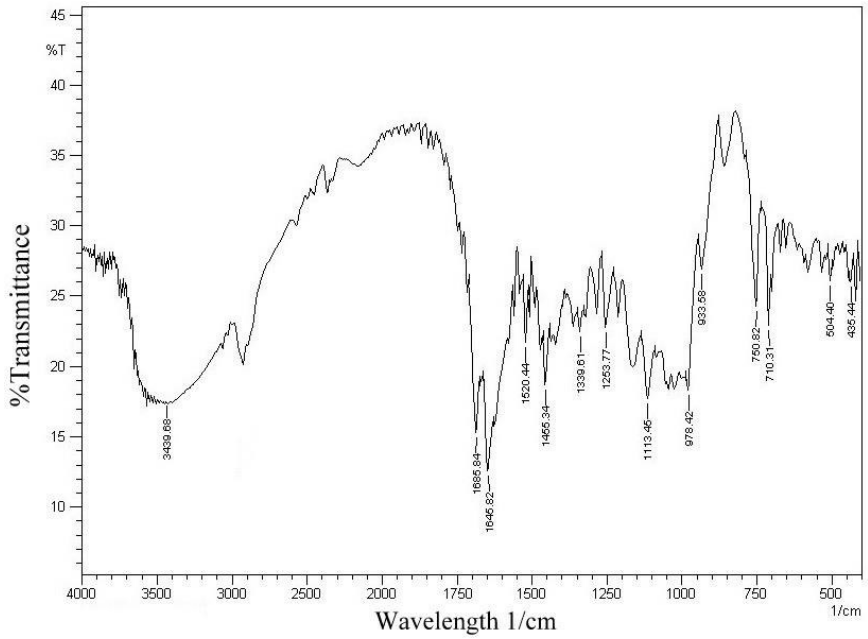

Figure 4: FT-IR spectrum of drug + Span 80.

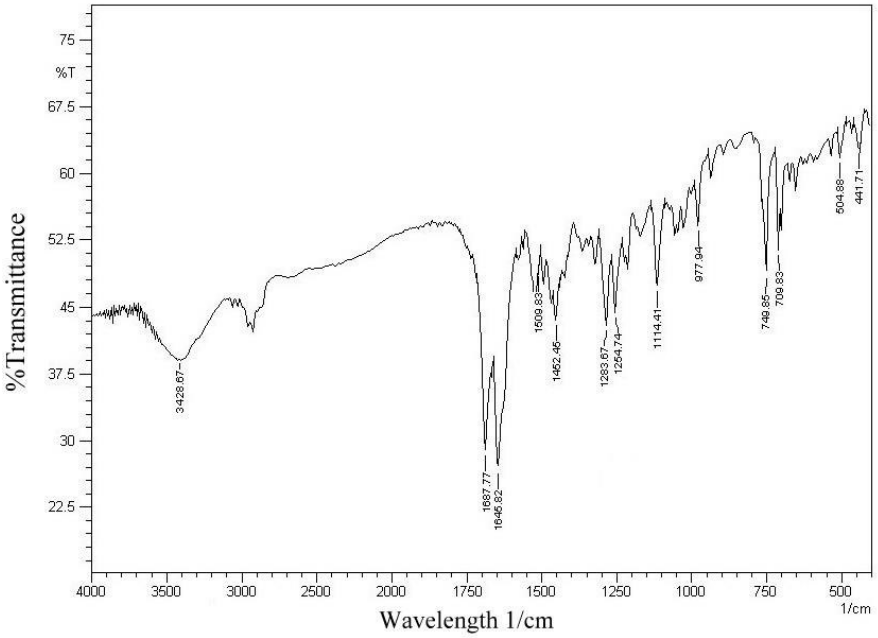

Figure 5: FT-IR spectrum of drug + physical mixtures.

CONCLUSION

Terconazole-loaded transferosomes were prepared by the modified hand shaking thin film method using varied ratio of Soya phosphatidyl choline: Tween 80, Soya phosphatidyl choline: Span 80, Soya lecithin: Tween 80 and Soya lecithin: span 80. A total of 12 batches of transferosomes were prepared using varying ratio of lipids and non-ionic surfactants. FT-IR study was carried out to check any possible interactions between the drug and excipients. Pure drug was mixed with 1:1 ratio of excipients and checked for interaction if any. The major FT- IR peaks of drug were retained in the FTIR physical mixtures. The study results revealed that no major interaction between the selected drug and excipients. To quantify the drug concentration in the in-vitro samples, UV spectrophotometric studies were selected. Puredrug was dissolved in 0.1N HCl and λmax was found to be 227 nm in same solvents. The standard solutions were prepared using methanol as mobile phase. Standard curve obtained with slope value 0.998 was used for the estimation of unknown samples.

CONFLICT OF INTEREST

The authors hereby declare that there is no conflict of interest involved.

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