



Research Journal of Pharmaceutical, Biological and Chemical Sciences

Formulation and evaluation of solid dispersion incorporated gel of ketoconazole

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ABSTRACT

The Goal of the present investigation was to design and evaluate gels for topical delivery of water insoluble antifungal agent Ketoconazole with an aim to increase its penetration through skin and thereby its flux. Ketoconazole is a broad spectrum imidazole derivative useful in the treatment of superficial and systemic fungal infections. The solubility of Ketoconazole is increased by complexation with β -cyclodextrin were prepared by solvent evaporation technique with 1:1 and then incorporated into gels. The complex was characterized by infrared spectroscopy. There was no interaction between drug and carrier. Gels have gained more and more importance because the gel-bases formulations are better percutaneously absorbed than creams and ointment bases. Therefore, Ketoconazole gel formulations were made with different polymers like carbopol 940, hydroxy propyl methyl cellulose, methyl cellulose, and sodium carboxymethylcellulose, containing various permeation enhancers namely sodium lauryl sulphate (0.5-1.0%) and dimethyl sulfoxide (5-20%) in different proportions. The formulated gels were evaluated for various physicochemical parameters like, drug content, pH, viscosity, spreadability, extrudability, in-vitro drug release. The in-vitro drug release study were carried out using pH 7.4 phosphate buffer, All the formulated topical preparations showed pH in the range of 6.5 to 7.4, and also showed good spreadability, extrudability. The carbopol 940 with 15% of dimethyl sulfoxide (KCD3) showed best in-vitro drug release 98.07% at the end of 6 hrs.

Keywords: Ketoconazole, Solid dispersion incorporated gels, β -cyclodextrin, and in-vitro drug release.

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INTRODUCTION

In recent years, the development of transdermal dosage form designed to have systemic effects has been attracting increasing attention, due to the several advantages that this administration route offers, such as a better control of blood levels, a reduced incidence of systemic toxicity, an absence of hepatic first-pass metabolism etc. Drug delivery via the skin is not a simple task. The outermost, and least permeable, layer of the skin, the stratum corneum (SC), is a formidable barrier both to water transport out of the body and to inward chemical permeation. In fact, the majority of drugs do not appear to penetrate the skin at a rate sufficiently high for therapeutic efficacy and only the most potent ones with appropriate physicochemical characteristics are valid candidates for transdermal delivery [1]. The most difficult aspect of the transdermal delivery system is to overcome the barrier of stratum corneum against foreign substances. It is well known that the penetration rate of drugs through the stratum corneum can be increased with appropriate vehicles and transdermal penetration enhancers, owing to their ability to increase the solubility of drug and/or enhancers in pharmaceutical formulations and to change the structure of lipophilic and/or keratinized domains in stratum corneum [2].

For skin care, and the topical treatment of dermatological diseases, a wide choice of vehicles ranging from solid to semisolids and liquid preparations, is available to clinicians and patients. Within the major groups of semisolid preparations, the use of transparent gels has expanded, both in cosmetics and pharmaceuticals [3]. Creams, gels, ointments and paste are some of the topical semisolids in use for many decades. Out of various semisolids dosage forms, the gels are becoming more popular due to ease of application and better percutaneous absorption than other semisolid preparations. Effectiveness of topical applications mainly depends upon its rate and extent of drug release from the base [4].

Ketoconazole was used as a model drug, which is an anti-fungal agent with topical and systemic action that can be incorporated into several pharmaceutical forms [5]. It is a recent synthetic triazole antifungal agent used in the treatment of superficial and systemic fungal infections such as, tinea corporis, tinea cruris, tinea manus and tinea pedis caused due to *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Microsporum canis* and for the treatment of seborrheic dermatitis [6].

Hence a study on formulation of Ketoconazole inclusion complex with β -cyclodextrin incorporated gels with different polymers and permeation enhancers at various concentrations was taken up in the present study.

MATERIALS AND METHODS

Materials

Ketoconazole was received as gift sample from FDC Limited, Raigad. β -cyclodextrin, Carbopol 940, Methyl cellulose (Hi-Media Laboratories Pvt. Ltd., Mumbai), Hydroxy propyl methyl cellulose LR, Carboxymethyl cellulose sodium salt (High viscosity) 1100-1900 cps LR, Sodium lauryl sulphate EP, Dimethyl sulphoxide LR, Triethanolamine LR, Methanol LR (sd fine-chem. Limited, Mumbai), Propylene glycol (Loba chem. Pvt. Ltd., Mumbai) were procured from commercial sources. All other chemicals and reagents used in this study were of analytical grade.

Methods

Preparation of inclusion complex of Ketoconazole with β -cyclodextrin

The inclusion complex was prepared 1:1 molar ratio by solvent evaporation technique. The drug and the excipient were dissolved in sufficient volume of methanol with continuous stirring. The solvent was then completely evaporated at 40 - 45°C with continuous stirring to obtain dry granules [7]. The resulting solid dispersion was stored in airtight container till further use [8].

Preparation of gels

Gels were prepared by various polymers as shown in Table- 1. The polymer and purified water I.P. were taken in a mortar and allow soaking for 24 hrs. Solid dispersion containing required amount of drug was dissolved in ethanol and other additives were added. The trituration was continued to get homogenous dispersion of drug in the gel [9].

Permeation Enhancers

The permeation enhancers like sodium lauryl sulphate and dimethyl sulfoxide were incorporated in different concentration (0.25-1.0%) and (5-20%) respectively (Table-2) was added by dissolving in little quantity of distilled water with the selected carbopol 940 formulations.

Table- 1: Formulation of various ketoconazole gels

Ingredients	Carbopol gel	HPMC gel	Methyl cellulose gel	Sodium CMC gel
Ketoconazole	2%	2%	2%	2%
Carbopol 940	1.0%			
HPMC		10%		
Methyl cellulose			5%	
Sodium CMC				3%
Triethanol amine	0.50%	0.50%	0.50%	0.50%
Propylene glycol	10%	10%	10%	10%
Ethanol	2.5%	2.5%	2.5%	2.5%
Water (q.s.)	100ml	100ml	100ml	100ml

Table- 2: formulation of ketoconazole gels with permeation enhancers

Ingredients	KCS ₁	KCS ₂	KCS ₃	KCS ₄	KCD ₁	KCD ₂	KCD ₃	KCD ₄
Ketoconazole	2%	2%	2%	2%	2%	2%	2%	2%
Carbopol 940	1.0%	1.0%	1.0%	1.0%	1.0%	1.0%	1.0%	1.0%
Triethanol amine	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%
Sodium lauryl sulphate(mg)	250	500	750	1000	-	-	-	-
Dimethyl sulfoxide (ml)	-	-	-	-	5	10	15	20
Propylene glycol	10%	10%	10%	10%	10%	10%	10%	10%
Ethanol	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%
Water (ml)	100	100	100	100	100	100	100	100

Evaluation of gels

Prepared gels of Ketoconazole were evaluated for the following parameters:

Physical appearance and homogeneity: Gel formulation containing Ketoconazole were visually inspected for clarity, color, homogeneity, presence of particles and fibers.

Determination of pH: The pH of gels was checked by using a digital Elico pH meter at room temperature. Initially, the pH meter was calibrated using standard buffers of pH 4 and 9.2. Accurately 2.5 gm of gel was weighed and dispersed in 25 ml of purified water and then pH meter was dipped in the dispersion and the pH was noted [10].

Drug content analysis: The drug content of the prepared gels was carried out by dissolving accurately weighed quantity (0.5 g) of gel equivalent to 10 mg of drug was dissolved in 10 ml of methanol, the volume was made up to 100 ml and 5 ml of the above solution was further diluted to 25 ml with methanol. After suitable dilution absorbance of the solution was recorded by using Shimadzu UV/ visible spectrophotometer at 244 nm [3,11].

Viscosity and Rheological studies: The viscosity of gels was determined by using Brookfield (DV-II⁺) viscometer. The gel was placed in the sample holder and the suitable spindle selected was lowered perpendicularly into the sample. The spindle was attached to viscometer and then it was allowed to rotate at a constant optimum speed at room temperature. The readings of viscosity of the formulation were measured after 2 minutes [12].

Spreadability: The spreadability of gel formulations was determined 48 hrs after preparation, by measuring two 20X20 cm glass plates after 1 min. The mass of the upper plate was standardized at 125 g. The spreadability was calculated by using the formula $S = m.L/t$, where S is spreadability, m is the weight tied to the upper slide, L is the length of the glass slide, and t is the time taken [3,13].

Extrudability: In the present study, the method adopted for evaluating gel formulation for extrudability was based upon the quantity in percentage of gel extruded from tube on application of certain load. More the quantity extruded better was extrudability. The formulation under study was filled in a clean, lacquered aluminum collapsible one-ounce tube with a nasal tip of 5 mm opening. It was then placed in between two glass slides and was clamped. Extrudability was determined by weighing the amount of gels extruded through the tip when a constant load of 1 Kg was placed on the slides and gels extruded was collected and weighed. The percentage of gel extruded was calculated and grades were allotted (++ good; + fair) [3,14].

In-Vitro Diffusion Study: The apparatus consists of a glass cylinder with both the ends open, 10 cm in height, 3.7 cm in outer diameter and 3.1 cm in inner diameter was used as a permeation cell. A cellophane membrane soaked in distilled water (24 hours before use) was fixed to the one end of the cylinder with aid of an adhesive. Gels equivalent to 10 mg of Ketoconazole was taken in the cell (donor compartment) and the cell was immersed in a beaker containing 100 ml of phosphate buffer of pH 7.4 (receptor compartment). The whole assembly was fixed in such a way that the lower end of the cell containing gel was just touched (1-2 mm deep) to the diffusion medium, the medium in the compartment was agitated using a magnetic stirrer at the temperature $37 \pm 1^\circ\text{C}$. Aliquots (5 ml) were withdrawn from the receptor compartment periodically (0.5, 1.0, 2.0, 3.0, 4.0, 5.0 and 6 hours) and replaced with 5 ml of fresh buffer. After suitable dilution, the sample was analyzed by using Shimadzu UV visible spectrophotometer at 223 nm [14].

Infrared spectroscopy (IR): FT-IR spectra of KCD3 and pure Ketoconazole, β -cyclodextrin, with its Solid dispersions were obtained by Perkin-Elmer FT-IR spectrophotometer using potassium bromide (KBr) pellets. KBr pellets were prepared by gently mixing the sample with KBr (1:100). The sample was scanned from $4,000$ to 400 cm^{-1} [15].

RESULTS AND DISCUSSION

In-vitro dissolution studies of Ketoconazole and complex

The Ketoconazole complexes with β -cyclodextrin present better dissolution performance over pure drug in an In-vitro test. According to these results, inclusion complexes prepared using with β -cyclodextrin, at 1:1 M ratio showed about 100% drug release in 80 min. shown in Fig. 1.

In-vitro diffusion studies of Ketoconazole Gels

In-vitro diffusion profile of Ketoconazole from gels containing different polymer like Carbopol 940, HPMC, Methyl cellulose and NaCMC are shown in Fig. 2. The total amount of drug released for a fixed period of 6 hr. was observed with Carbopol 940 shown higher release as compared to HPMC, Methyl cellulose and NaCMC.

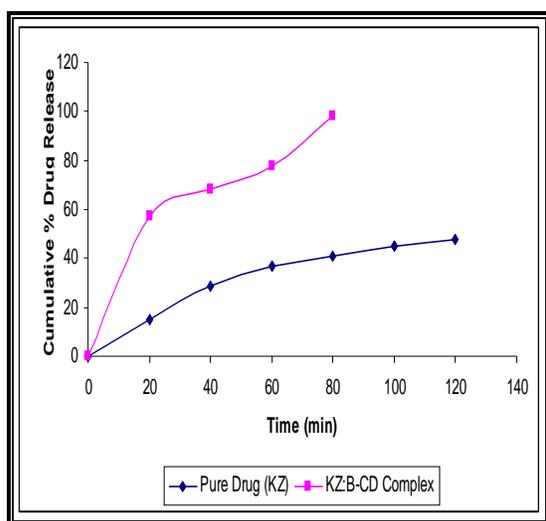


Fig. 1: Dissolution profile of Pure Drug & Ketoconazole: β -cyclodextrin Complex.

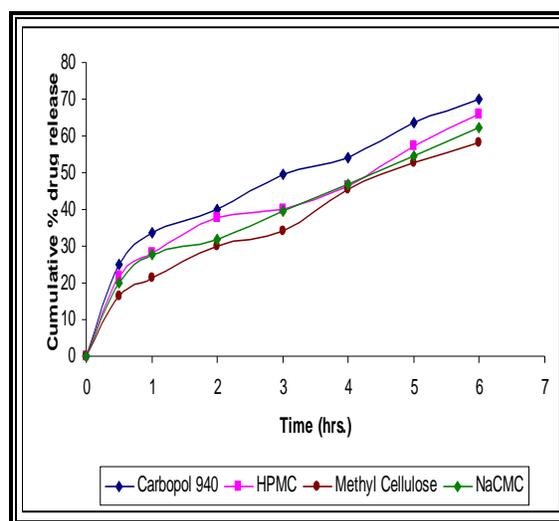


Fig. 2: Diffusion profile of Ketoconazole From various gel formulations.

Composition and physicochemical characteristics of the gel formulation containing carbopol 940 as gelling agent, and different concentration of permeation enhancer viz. SLS and DMSO, are shown in Table- 2. From the result, it is clearly evident that all the gel formulations showed good extrudability, homogeneity, and spreadability.

The drug content was in the range of 92.35% to 99.12%. The formulations viscosity ranged from 2450 to 9775 cps, and pH of all the formulations was between pH 6-7.5, this lies in the normal pH range of the skin. Fig. 3 and Fig. 4 depicts the in-vitro diffusion profile of Ketoconazole from gels containing carbopol 940 and different concentrations of permeation enhancers sodium lauryl sulphate (0.5-1.0%) and dimethyl sulfoxide (5-20%) Sodium lauryl sulphate showed maximum release (94.99%) over a period of 6 hrs. at 0.75% concentration level. Further in SLS concentration to 1% level showed increase in drug release. In fact, the release was found to be slightly decreased. The incorporation of SLS in higher concentration showed the problem of frothing. Fig. 4 depicts that 15% level of Dimethyl sulfoxide released a maximum of 98.07% of Ketoconazole with a period of 6 hrs. Further increase in DMSO concentration to 20% level showed no further increase in drug release. KCD3 is the best formulation.

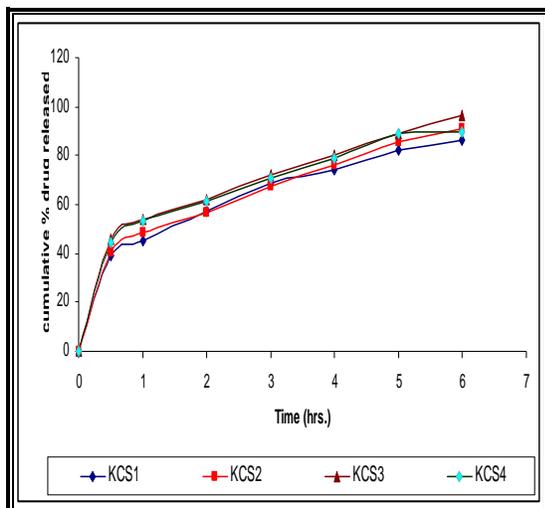


Fig. 3: Diffusion profile of Ketoconazole from various gel formulations.

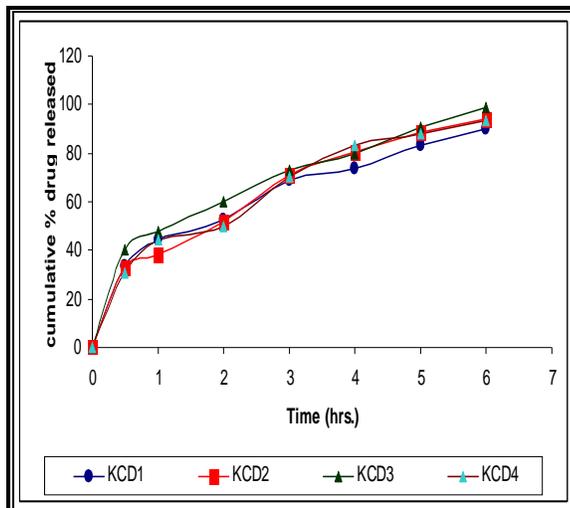


Fig. 4: Diffusion profile of Ketoconazole from various gel formulations.

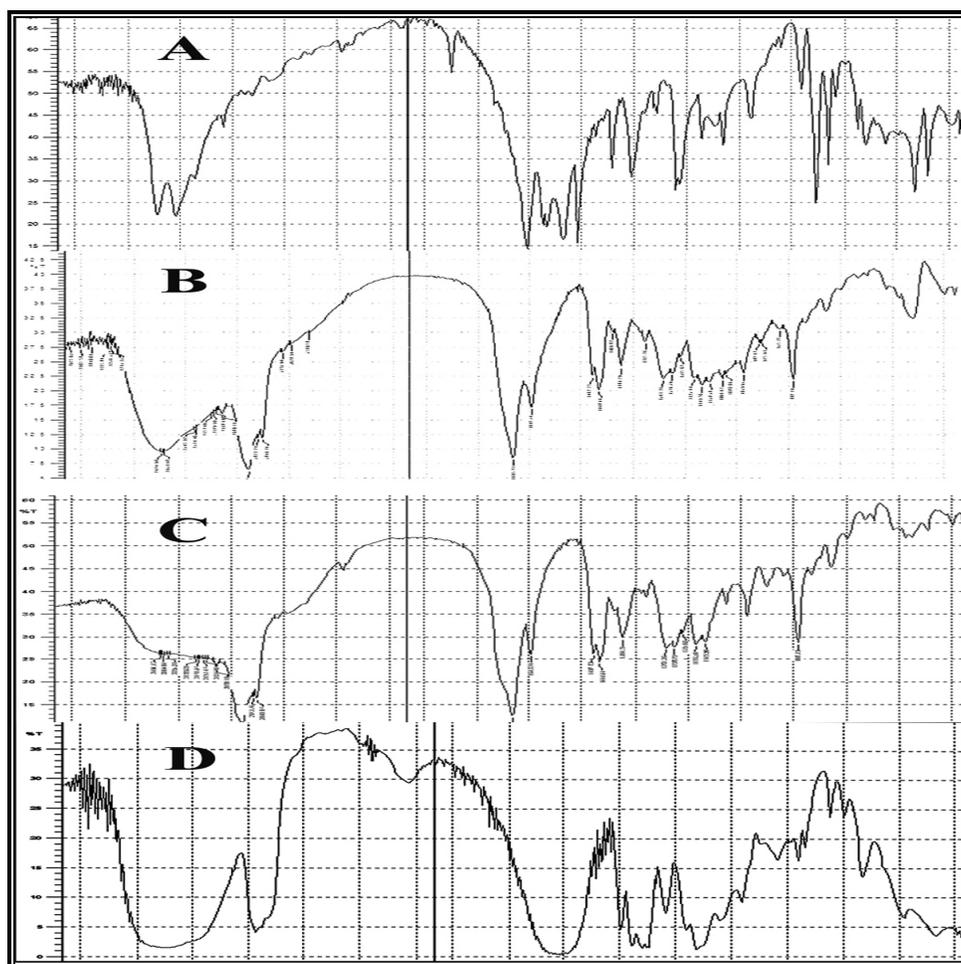


Fig. 5: IR spectra of A = Ketoconazole, B = β -cyclodextrin, C = Ketoconazole: β -cyclodextrin 1:1, solvent evaporation method and D = KCD3

Infrared spectroscopy (IR)

IR spectroscopic studies were conducted to determine possible drug: carrier interactions. IR spectra of KCD3, pure drug Ketoconazole, β -cyclodextrin, and Ketoconazole with its Solid dispersion were obtained which shows all the characteristic peaks of Ketoconazole and carrier was present in the Solid dispersion, thus indicating no significant evidence of chemical interaction between drug and carrier, which confirms the stability of drug with its solid dispersion. The results of IR study are shown in Fig. 5.

CONCLUSION

Based on this study the effect of different polymers like carbopol 940, HPMC, MC, NaCMC and different concentration of permeation enhancers like sodium lauryl sulphate (0.5-1.0%) and dimethyl sulfoxide (5-20%) on Ketoconazole release, an optimum of carbopol 940 with 0.75% SLS and carbopol 940 with 15% DMSO were found to be more suitable to give a better formulation having good drug release characteristics and consistency. Carbopol 940 with 15% DMSO (KCD₃) showed better release of Ketoconazole from gel.

ACKNOWLEDGEMENTS

Authors are thankful to Principal Luqman College of Pharmacy, Gulbarga (India) for providing all the necessary facilities to carry out this research work and also extend thanks to FDC Limited, Raigad (India) for providing gift sample of Ketoconazole.

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