Journal of Pharmaceutical Research Vol. 8, No. 2, April 2009 : 89-92.

EVALUATION OF ROSIN AS A CREAM BASE FOR TOPICAL KETOCONAZOLE PREPARATION

Lakshmana Prabu S[1]*, Shirwaikar Arun[2], Shirwaikar Annie[3] and Kumar Aravind[4]
[1]Shasun Chemicals & Drugs Ltd., PIMS Road, Pondicherry – 605 014, India.
[2]Gulf Pharmacy College, Ajman, UAE.
[3]Department of Pharmacognosy, Manipal College of Pharmaceutical Sciences, Manipal – 576 104, India.
[4]Department of Pharmaceutics, Manipal College of Pharmaceutical Sciences, Manipal – 576 104, India.

Received on : 03.11.2008 Revised : 20.04.09 Accepted : 21.04.09

ABSTRACT
The purpose of this investigation was to develop a ketoconazole cream with rosin for both topical and systemic delivery. Creams were prepared by using rosin as one of the components in different proportions with different cream base combinations. The drug excipients interaction studies were carried out and results revealed that there is no interaction between the drug and the excipients used in the formulation. The prepared creams were evaluated for their physicochemical properties, pH, viscosity, particle size, drug content and *in vitro* release studies. The release of the drug, ketoconazole was measured for eight hours and compared with a standard marketed formulation. The formulation (F8) fulfilled all topical formulation parameters; it can be used for the systemic topical drug delivery.

Keywords: *Ketoconazole; In vitro release; Skin permeation; Skin irritation.*

INTRODUCTION

Topical preparations are formulation containing drugs meant to treat disorders on the surface of the skin or within skin. Topical formulations may or may not require intracutaneous penetration and deposition as well. Topical delivery is not an efficient means for systemic drug delivery, since only between 1 percent and 15 percent of a drug in a topical formulation is systemically bioavailable[1].

Natural polymers remain attractive primarily because they are inexpensive, readily available, capable of multitude of chemical modifications and potentially degradable and compatible due to their origin. Rosin and rosin-based polymers have diversified drug delivery applications. Rosin, a natural resin, obtained from pine trees, principally rosin composed of resin acids (abietic and pimaric) and a small amount of non acidic components. Rosin and rosin derivatives have been pharmaceutically evaluated as microencapsulating materials[2-5], anhydrous binding agents in tablets[6,7] , in transdermal drug delivery[8] and as a cream base[9]. Being natural in origin, rosin and its derivatives are expected to be biodegradable *in vivo*[10]. One of the important properties exhibited by rosin biomaterials is their film-forming ability. Based on these data, we have used rosin as one of the components in cream base for ketoconazole topical formulation.

EXPERIMENTAL

Materials

Rosin N grade (Yucca Enterprises, Dombivli, Thane), petroleum jelly and hard paraffin (Loba Chem, Mumbai), liquid paraffin, lanolin, potassium dihydrogen phosphate, sodium hydroxide and hydrochloric acid (S.D. Fine Chemicals, Mumbai), ketoconazole (Micro Labs, Hosur, India), sigma membrane (Sigma chemicals, USA). Distilled water was used when collected fresh.

Preparation of cream

Different formulations were prepared with various ratios of rosin, keeping the amount of ketoconazole (600 mg) constant. The composition of the cream formulation is shown in Table 1. The cream bases were formulated using regular fusion method. The drug was dispersed in water and heated to 70ºC in a glass beaker. Petroleum jelly, hard paraffin, castor oil, lanolin and rosin were melted at 70ºC. To the melted materials the aqueous phase containing drug was added with continuous stirring at 70ºC and mixed for five minutes; the creams were transferred into clean glass bottles and stored.

Drug-excipient interaction studies

Table 1. *Composition of 2% Ketoconazole Cream*

Ingredients for 30 g	F1	F2	F3	F4	F5	F6	F7	F8
Rosin	2.4	2.4	2.4	2.4	5.0	5.0	5.0	5.0
Petroleum Jelly	9.0	4.5	4.5	6.0	9.0	9.0	9.0	6.0
Hard paraffin	-	4.5	4.5	3.0	-	-	-	3.0
Liquid Paraffin	-	-	4.5	9.0	9.0	-	4.5	4.5
Castor oil	9.0	9.0	4.5	-	-	9.0	4.5	4.5
Lanolin	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Ketoconazole	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Conventional methods of accelerated storage stability is time consuming and tedious. DSC provides data as the quantity of heat required to complete the reaction

***Correspondence :** slaxmanvel@gmail.com

between drug and excipient; this is backed by short stress times. Enthalpy change (fusion) due to incompatibility between drug and excipient is measured. Physical mixtures were analyzed by DSC, FTIR and HPTLC to correlate any changes.

Sample preparation and analysis by DSC

The samples were prepared by physical mixture of drug and excipients (1:1) using a clean dried glass mortar and pestle. Samples (5-10 mg) were accurately weighed and hermetically sealed in aluminum pans. Thermograms were obtained using Shimadzu (DSC-60) instrument, heating at a constant rate of 10ºC/min, over a temperature range of 40–300ºC. To maintain an inert atmosphere nitrogen gas was purged at a rate of 20 ml/min.

Sample preparation and analysis by FTIR

FTIR spectra were taken on Shimadzu (FTIR-8300) instrument to find out the chemical stability of the drug with excipients. FTIR spectra of drug, excipients and composition of final formulation were obtained. All the samples were mixed with potassium bromide to get pellets by pressing at 1 ton/unit. Spectral scanning was done in the range of 4000–400 cm^{-1}.

HPTLC studies

Being a non-thermal technique TLC is commonly used for the determination of interaction studies between drug and excipients. Precoated silica gel F_{254} plates was used as stationary phase and composition of n-hexane:chloroform:methanol:diethylamine (50:40:10:1, v/v) was used as mobile phase in HPTLC studies. Chromatograms for drug and the formulation were taken.

Evaluation of Formulations

Physicochemical testing

Topical formulations vary in their organoleptic properties such as viscosity, pearlescence, gloss, smoothness or texture and may feel oily, tacky, wet, slippery or gritty. They also vary in their spreading ability and drying time on the skin.

pH

The pH of 1% of the cream was determined using the pH meter. (Mettler pH meter, USA)

Viscosity

Viscosity measures the flow characteristics of a topical formulation. Brookfield viscometer was used for measuring the viscosity of the formulations.

Particle size and particle size distribution

The particle size of the prepared creams was determined in Lobomed microscope using an eyepiece micrometer attached to a 10X eyepiece and with a high power objective of 40X. The eyepiece micrometer was calibrated using a stage micrometer and determined the average globule size.

Drug content uniformity

One gram of the prepared formulation were taken in a clean 100 ml volumetric flask, 50 ml of the dissolution medium was added and mixed well, and made up to the mark with dissolution medium. Samples were filtered and suitably diluted; analyzed spectrophotometrically and the drug content was determined.

Preparation of the skin membrane

Full thickness abdominal skin was obtained from freshly sacrificed albino rats (Wister strain, male; weight 200–250 g obtained from Central Animal House, Kasturba Medical College, Manipal). Hair from the abdominal region was carefully removed and the dermal side of the skin was washed thoroughly with distilled water to remove any subcutaneous matter and fatty tissues. It was immersed in 20% v/v of methanol in water containing 0.04% v/v of hydrochloric acid at 37 ºC for one hour for equilibration before using for the release studies.

***In vitro* skin permeation studies**

In vitro skin permeation studies were carried out using vertical type diffusion cells having a receptor compartment in 50 ml of receptor medium for all tests[11]. It was placed on a magnetic stirrer with a small magnetic teflon bead placed inside for uniform distribution of the diffusant and maintain the temperature at 37±0.5ºC. Isolated rat skin was placed over a 1 cm^2 orifice of the receptor chamber, weight equivalent amount of ketoconazole, approximately 10 mg, was placed on the rat skin. A sample of 2 ml was withdrawn at 1, 2, 3, 4, 5, 6, 7 and 8 h; filtered and analyzed by using a UV spectrophotometer. The study was performed for eight hours, and cumulative amount of drug permeated was plotted against time.

RESULTS AND DISCUSSION

The demand for the topical drug delivery has been growing during the last decade, particularly for local effect. These dosage forms are applied on the surface of the skin which provides high therapeutic efficacy, low toxicity and to target or enhance delivery of active agents to the skin, thereby resulting in an improved and high therapeutic index. In the present study an attempt was made to formulate ketoconazole cream using rosin, a natural resin as a component of cream base.

Drug-excipient interaction studies

Drug excipient compatibility studies were carried out to check whether any compatibility related problems are associated between drug and excipients used in the formulation. DSC is useful in the investigation of solid-state interactions. The thermograms were generated for pure drug and drug polymer mixture. The DSC thermograms of pure drug and drug polymer mixture results revealed that the physical mixture of

ketoconazole with rosin showed superimposition. But slight preshift was observed at 147.35°C instead of 153.06°C. There is no considerable change observed in melting endotherms of both the drug and drug: rosin mixture and there is no exothermic or endothermic peaks were observed before or after the melting endotherm of the drug (Fig. 1). The principle IR peaks of ketoconazole at wavenumbers 1507, 1640, 1258, 1240, 1221 and 1200 cm^{-1} were present in both pure drug and the physical mixture of ketoconazole and rosin (Fig. 2). Interaction study for the final formulation was carried out by using HPTLC technique and compared with the pure drug. HPTLC studies revealed that the R_f values obtained for the drug and formulation was around 0.64 (Fig. 3). The results of DSC, FTIR and HPTLC studies revealed that there is no interaction between the drug and the excipients used in the formulation.

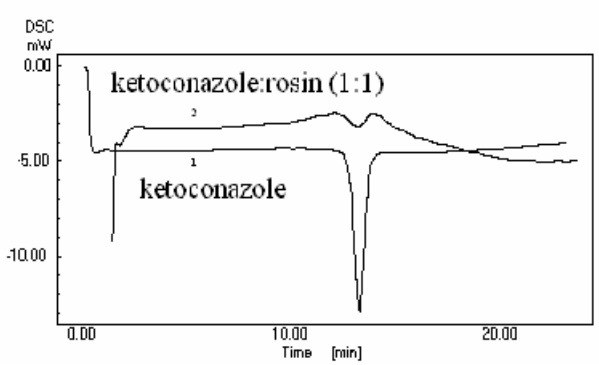

Fig. 1: *DSC thermograms*

Fig. 2: *IR spectra of Ketoconazole and physical mixture*

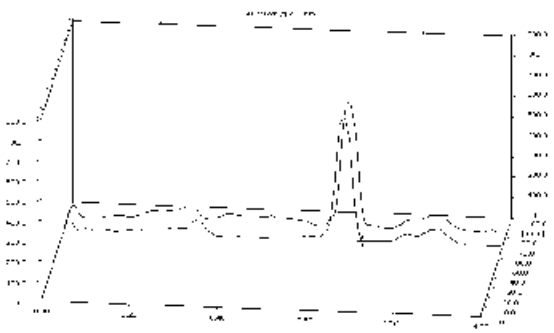

Fig. 3: *Overlain HPTLC chromatogram of ketoconazole and formulation*

Physicochemical characterization

Creams were prepared by using various proportion of rosin as a component in the cream base. Based on their colour, appearance, viscosity and spreading ability, formulation F7 and F8 were taken into consideration for the further studies. The skin has a pH 5-6, and many topical products are designed to be in that pH range. Changes in pH throughout the shelf life of the product may also be indicative of stability problems and should be carefully monitored. The formulated cream having the pH between 5.4 and 5.7, which is the normal pH range of skin.

Viscosity measures the flow characteristics of a topical formulation. The formulated cream having the viscosity between 6100 and 5800 centipoises for formulations F7 and F8 respectively which was comparable to the marketed formulation.

An increase or decrease in the particle size of the drug in a formulation can affect its *in vitro* release and subsequently its bioavailability. For emulsion based products, the particle size of droplets of the internal phase can have an impact on the stability of the emulsion itself. The particle size of the creams was found to be in the range of 5 to 15 µ for both formulations F7 and F8.

Assay and content uniformity should be performed as an integral part of the testing of topical products. The assay provides information on the stability of the drug in the formulation. Ketoconazole content from the formulations (F7 and F8) was found to be in the range of 97.0 to 98.2%. The formulated creams have the drug content within the acceptable limits; indicate that the drug had not undergone any degradation during the preparation.

***In vitro* skin permeation studies**

In vitro release studies are generally employed as a quality control tool for product release and in predicting toxicity of topical formulations. In order to assess the ability of a formulation to deliver a drug to the skin, it is important to determine the drug's release rate from its vehicle. *In vitro* skin permeation studies were carried out in 20% v/v of methanol in water containing 0.04% v/v of hydrochloric acid was used as a receptor medium. The release studies results revealed that formulation F8 showed better release of the drug for the first two hours than the marketed formulation. The overall release was greater for the marketed formulation after two hours. The formulation F8 cream showed release of drugs from 2.49 to 12.36 percent over the period of eight hours. The marketed preparation showed release of the drug from 2.0 to 12.96 percent over the period of eight hours. Thus formulation F8 and marketed formulation showed the similar pattern of release at the end of eight hours, the release study results are shown in Fig.4.

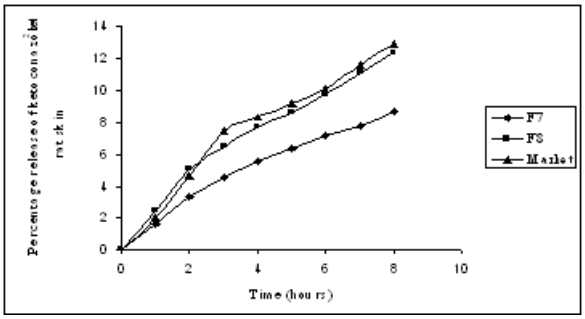

Fig. 4: *Comparative release profile of ketoconazole cream formulations F7, F8 and marketed formulation*

CONCLUSION

In summary, it has been demonstrated that rosin can be used as a component in the cream base for ketoconazole preparation. Formulation F8 skin permeation study was significantly similar to the marketed formulation. Therefore, these observations indicate that rosin can be utilized for topical drug delivery.

REFERENCES

1. Tapash KG. Transdermal and topical delivery systems: An overview and future trends, 1st Edn, CRC Press, Boca Raton, FL, 1997; 1-25.
2. Sheorey DS, et al., J Microencap 1991; 8(1): 79-82.
3. Sheorey DS, et al., J Microencap 1993;10(2): 209-214.
4. Sheorey DS, et al., J Microencap 1994;1(1): 11-17.
5. Shirwaikar AA, et al., Ind J Pharm Sci 2000; 62(4): 308-310.
6. Pathak YV, et al., Drug Dev Ind Pharm 1990; 6(3): 223-227.
7. Ramani CC, et al., Int J Pharm 1996; 1:344-352.
8. Satturwar PM, et al., AAPS PharmSciTech 2005; 6(4): article 81.
9. Dhanorkar VT, et al., J Cosme Sci. 2002; 53: 199-208.
10. Fulzele SV, et al., Eur J Pharm Sci 2003; 20(1): 53-61.
11. Puranjoti P, et al., The J Appl Research 2002: 2. (http://jrnlappliedresearch.com/articles/vol2issipuranjoti.htm)