Original Article

Development of Ketoconazole Shampoo with *Dipterocarpus alatus* Oil as a Permeation Enhancer

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ABSTRACT

Purpose: To develop and evaluate a model ketoconazole shampoo that includes *Dipterocarpus alatus* oil as a natural permeation enhancer. **Methods:** Model shampoos containing ketoconazole, *D. alatus* oil (1-3% v/v), sodium lauryl ether sulfate, sodium lauryl sulfate, lanolin, cocamidopropyl betaine and fragrance were formulated and evaluated for pH, viscosity and appearance. Ketoconazole content was determined by UV spectrophotometry for preliminary stability testing, drug release and permeation studies. A side-by-side diffusion cell incorporating porcine abdominal membrane was used to evaluate ketoconazole permeation. **Results:** All of the model ketoconazole shampoo formulations had a satisfactory appearance, pH and viscosity. The inclusion of 2% *D. alatus* oil in the formulation enhanced the permeation of ketoconazole through porcine abdominal membrane. **Conclusion:** Our model ketoconazole shampoo formulation incorporating *D. alatus* oil showed enhanced permeation of ketoconazole *in vitro*. This method can be simply adapted to study other permeation enhancers and other formulations.

Key words: *Dipterocarpus alatus*, Shampoo, Ketoconazole, Permeability enhancer, Formulation, Membrane.

INTRODUCTION

Ketoconazole shampoo is one kind of formulation used as an antifungal medication to treat fungal infection of the skin and for the treatment of dandruff. However, affected areas of the skin can be a barrier preventing the drug from permeating. This problem should be resolved to improve the effective treatment of fungal infection. Permeation enhancers are one choice that can be added into formulations to help drugs permeate through the skin, which is one long-standing approach for improving transdermal drug delivery.[1-3] Permeation enhancers are also called sorption promoters or accelerants. Numerous compounds have been evaluated for penetration enhancing activity, including sulphoxides (dimethylsulphoxide), azones (laurocapram), pyrrolidones (2-pyrrolidone), alcohols (ethanol), alkanols (decanol), glycols (propylene glycol) and terpenes.[4-5] Many intracellular targets and modes of action have been identified for skin penetration enhancers, such as the intercellular lipid matrix in which the accelerants may disrupt the packing skin membrane layer or intracellular keratin or through increasing drug partitioning into the tissue by acting as a solvent for the permeant within the skin membrane. Other potential modes of action may be come from altering metabolic activity within the skin or by influencing the thermodynamic activity or solubility of the drug. Some natural essential oils are potential permeation enhancers as they contain a large range of chemically acceptable accelerants that help percutaneous drug absorption. Essential oils are also considered safe, with skin toxicity limited to mild irritation.[6-9] *Dipterocarpus alatus* is a plant in the family Dipteroceae, which plays a major role in the economy of many Asian countries. This plant grows naturally in tropical forests of

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Southeast Asia, which means it can be used as a target plant for reforestation planning programs. Natural oil from *D. alatus* is in very high production and supply in many parts of Thailand and is one natural oil that could potentially be included in drug formulations. Previous studies have revealed many kinds of organic chemical compounds, such as terpenes, are found in natural oils and have reviewed the use of natural products, including essential oils, as potential permeation enhancers for transdermal drug delivery.[10-12] Moreover, terpenes have long been used as medicines as well as flavoring and fragrance agents and there is evidence that they can be used as skin permeation enhancers.[13-14] Thus, the aim of this study was to develop a model ketoconazole shampoo incorporating *D. alatus* oil as a permeation enhancer and to evaluate the physico-chemical properties of the formulation.

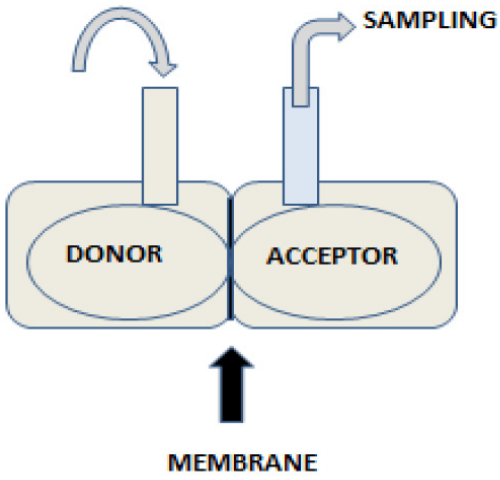

Figure 1: Side-by-side diffusion cell for permeation study.

MATERIALS AND METHODS

Materials and equipment

A side-by-side diffusion cell was used in the permeation study (Figure 1). UV-Visible spectrophotometer was product of Shimadzu®. Ketoconazole was purchased from Sigma-Aldrich®. Sodium dihydrogenphosphate, disodium hydrogenphosphate, dimethyl formamide, sodium hydroxide and octanol were purchased from Merck®. Cellulose nitrate membrane was purchased from Millipore®. *D.alatus* oil was kindly provided by the Yangna research cluster from a single batch and source.

Preparation of drug solutions

The stock standard solution (1mg/ml) of ketoconazole was prepared and dissolved in methanol and then diluted with phosphate buffer to the appropriate concentration for permeation studies. All solutions were freshly prepared daily.

In vitro drug permeation study

The permeation study of ketoconazole shampoo was carried out in a side-by-side diffusion cell. The temperature was controlled at 37 ± 0.5 degree centigrade in water bath. Porcine abdominal membrane was first immersed in phosphate buffer solution for 30 min. The membrane was then clamped in a side-by-side diffusion cell between the donor and receptor compartments. Three milliliters of phosphate buffer solution at pH 7.4 was added into the receptor compartment. The donor compartment received 3 ml of drug solution in phosphate buffer at pH 7.4. Both compartments were magnetically stirred throughout the experiment at 600 rpm. The solution in the receptor compartment was sampled at various time intervals and immediately refilled with the same volume (1 ml) of fresh buffer solution. Samples were analyzed for permeated content by UV-Vis spectrophotometry. The absorbance was measured at its maximum wavelength, which was 222 nm. All experiments were performed in three replicates.

Preparation of model ketoconazole shampoo with *D. alatus* oil

All ingredients including the ketoconazole, *D. alatus* oil, sodium lauryl ether sulfate, sodium lauryl sulfate, lanolin, cocamidopropyl betaine and fragrance were mixed in a volumetric flask and adjusted to volume with water. The resulting shampoo formulations with the percentage of *D. alatus* oil are shown in Table 1.

Evaluation of ketoconazole shampoo with *D. alatus* oil

The amount of ketoconazole that permeated through the porcine abdominal membrane was analyzed by UV spectrophotometry. Physico-chemical properties were determined by visual appraisal. The preliminary stability

Table 1: Ingredients and their content in ketoconazole shampoo formulations.

Ingredients (%w/v)	Content in formulation			
	F1	F2	F3	F4
Ketoconazole	**1**	**1**	**1**	**1**
D.alatus oil	0	1	2	3
Sodium lauryl ether sulfate	3	3	3	3
Sodium lauryl sulfate	3	3	3	3
Lanolin	1	1	1	1
Cocamidopropyl betaine	2	2	2	2
Fragrance	0.3	0.3	0.3	0.3

Table 2: Physico-chemical characteristic of ketoconazole with variation content of *D. alatus* oil.

Physicochemical Characteristic	Formulation			
	F1	F2	F3	F4
Visual estimation	Clear liquid	Yellow-clear liquid	Yellow-clear liquid	Yellow-clear liquid
pH	7.81	7.66	7.53	7.53
Viscosity	low	low	low	low

study was evaluated at two conditions, room temperature and 45 degrees centigrade.

RESULTS

The formulation of model ketoconazole shampoo

A model shampoo was formulated by mixing all the components. Ketoconazole was used as the active ingredient in the formulation for anti-fungal therapeutic use. Sodium lauryl sulfate and sodium lauryl ether sulfate were used as anionic surfactants, which provided dispersing and emulsifying actions in the shampoo formulation. Cocamidopropyl betaine is a non-ionic surfactant, which provided a high foaming property. Lanolin was used as a conditioning agent. *D. alatus* oil was an important additive in this study, as permeation enhancer. Fragrance was added to help the usability of the shampoo formulations. The composition of all of the model ketoconazole shampoos, including the percentage of *D. alatus* oil, are shown in Table 1. The most appropriate formulation was F3, containing 2 percent *D. alatus* oil.

Physico-chemical characteristics of ketoconazole shampoo with *D. alatus* oil

Visual appraisal, pH and viscosity of all shampoo formulations were evaluated and the results are shown in Table 2. From visual inspection, the model shampoo showed an appealing physical appearance, similar to commercial shampoo formulations. A yellow color was observed when *D. alatus* oil was included in the formulation. All shampoo formulations were prepared at neutral or slightly alkaline pH to minimize hair damage and irritation to the eyes and skin. The viscosities of all formulations were low because a viscosity modifier, such as sodium chloride, was not included in the formulations. Thus, other additives might need to be added into the formulations to improve the physical properties.

Preliminary stability study

Samples of the appropriate model product (Formulation F3) were stored at 27±2 degree centigrade (normal room temperature) and in an oven at 45± 2 degree centigrade. The storage conditions were designed for preliminary stability testing and focused on the development of a model shampoo formulation for short time storage under general temperature storage conditions. The model shampoo formulation was not complete, leaving out additives such as viscosity modifiers and preservatives. Thus, only basic stability conditions were tested. After the storage time, the shampoo formulation was analyzed for ketoconazole content (in three replicates) and the results are shown in Figure 2. The absorbance was found to fluctuate slightly when *D. alatus* oil was included in the formulation. This might result from the instability of *D. alatus* oil color. It was noted that the formulation at 45 degree centigrade changed from light to dark yellow, which would increase the absorbance. Thus, some antioxidant should also added into the formulation to stabilize the color.

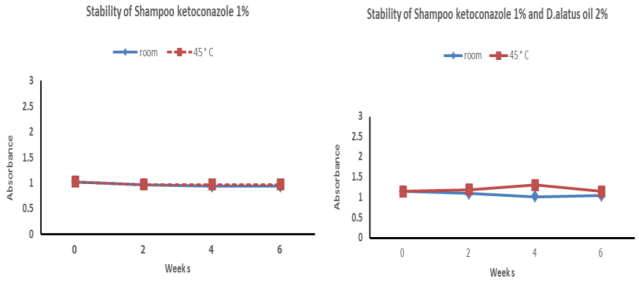

Figure 2: Preliminary stability study of model ketoconazole shampoo with/without *D. alatus* oil.

Permeation of ketoconazole with *D. alatus* oil

The cumulative amount of ketoconazole permeated through porcine abdominal membrane is shown in Figure 3. The formulation containing 2% *D. alatus* oil showed the highest cumulative amount of ketoconazole permeation. The other formulations, containing 1% and 3% *D. alatus* oil, performed showed similar amounts of ketoconazole permeation to the control formulation without *D. alatus* oil. Accumulation of *D. alatus* oil at the surface of the porcine abdominal membrane was observed in the formulation containing 3% *D.alatus* oil, which could obstruct permeation through the membrane. Thus, higher *D. alatus* oil content in the shampoo formulations might not mean increased permeation of ketoconazole.

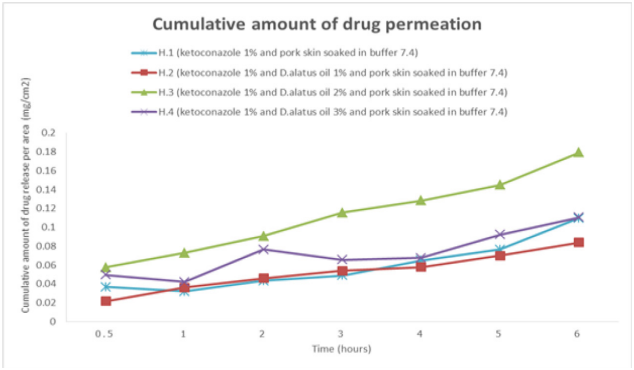

Figure 3: Permeation profile of model ketoconazole shampoo with variation content of *D. alatus* oil.

DISCUSSION

The results of this study reveal an application for *D. alatus* oil as a natural permeation enhancer in drug formulations. Our study confirmed a previous study in which *D. alatus* oil improved the permeation of ibuprofen, ketoconazole and caffeine through newborn pork skin membrane.[15] This study extended this observation, using *D. alatus* oil as a permeation enhancer in a shampoo formulation in which the active ingredient was ketoconazole, an anti-fungal drug and commonly used medication. A similar study using natural oils as permeation enhancers was published by Aggarwal and co-workers in 2012.[6] They investigated the feasibility of transdermal delivery of olanzapine utilizing natural oils as permeation enhancers. They reported the penetration enhancing potential of corn (maize) oil, groundnut oil and jojoba oil on *in vitro* permeation of olanzapine across rat skin. A similar study investigated natural essential oils as permeation enhancers for 5-fluorouracil using excised human skin.[9] Eucalyptus oil and chenopodium oil were found to be very effective (30-fold increase), while Ylang ylang oil was mildly effective (8-fold increase) and anise oil had little activity (3-fold increase).

Here we describe a new application for natural *D. alatus* oil as a permeation enhancing excipient in a model ketoconazole shampoo formulation. Further studies should investigate the other excipients in the formulation such as fragrance, viscosity enhancers and antioxidants to improve the usability and stability of the product.

CONCLUSION

A model ketoconazole shampoo formulation with *D. alatus* oil as permeation enhancer was proposed and developed in this study. Based upon the physicochemical characteristics, this formulation was acceptable for the general basic requirements of appearance, pH and viscosity. This model shampoo formulation could be useful for the further investigation of *D. alatus* oil as a permeation enhancer as well as for evaluating the permeation enhancing properties of other natural oils. This research used a new approach to develop the model formulation that showed *D. alatus* oil as a permeation enhancer and we believe this approach could also be applied to test other formulations.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

UV: Ultraviolet; *D. alatus*: *Dipterocarpus alatus.*

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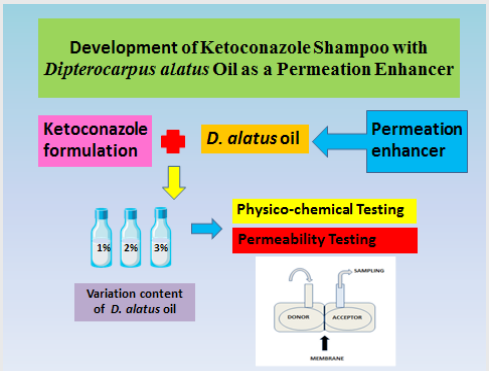
PICTORIAL ABSTRACT



Summary

- A model ketoconazole shampoo formulation with *D. alatus* oil as a permeation enhancer was proposed and developed in this study.
- The developed formulation showed acceptable general basic requirements for appearance, pH and viscosity.
- This research used a new approach and concept for developing the model formulation, which showed *D. alatus* oil is a permeation enhancer.

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