AAD 2007 Poster 809

Comparison of Ketoconazole USP Solubility in 2% Gel and 2% Cream Formulations

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Introduction

- Seborrheic dermatitis is a recurrent, chronic inflammation of the skin, present in 1% to 3% of immunocompetent adults[1,2]
- It occurs on sebum-rich areas such as the face, scalp, and chest and is characterized by red scaly lesions[1]
- Seborrheic dermatitis is believed to have an association with *Malassezia* yeasts that may be due in part to an abnormal or inflammatory immune response[3]
- The azoles represent the largest class of antifungals used in the treatment of seborrheic dermatitis. Some azoles, including ketoconazole, have demonstrated both antifungal properties and antiinflammatory activity, which may be beneficial in alleviating symptoms[3]
- Once-daily Ketoconazole USP 2% gel is an effective, well-tolerated, convenient, and cosmetically acceptable treatment for moderate-to-severe seborrheic dermatitis[4]
- The efficacy is dependent upon the solubility of the ketoconazole, which correlates to its delivery to the affected area for resolution of symptoms

Objectives

- To compare Ketoconazole USP 2% gel, a novel and unique anhydrous gel formulation, with ketoconazole 2% cream, a commercially available cream formulation of the same concentration, using data from microscopic techniques, filtration studies, and an in vitro membrane rate of release study
- To determine qualitatively and quantitatively whether ketoconazole is dissolved or suspended in the cream formulation

Design/Methods: Microscopy

- Laboratory exercises were performed to determine the physical nature of ketoconazole in the gel and cream formulations using optical microscopy at room temperature and hot-stage microscopy at 10X, 20X, and 100X magnification
- Cross polarization of the light source was utilized to determine the crystalline nature of the undissolved ingredients

Design/Methods: HPLC

- Filtration techniques were employed to determine qualitatively whether ketoconazole is dissolved or suspended in the ketoconazole 2% cream formulation, and an HPLC method was developed for quantification of ketoconazole in the cream formulation

- In the filtration studies, the vehicle components were melted at approximately 67°C in a glass syringe, and the molten product was passed through various filters with decreasing pore sizes ranging from 1.6 to 0.1 µm (Table 1). This technique will determine the percentage of ketoconazole that is suspended in the product at about 67°C
- The size of a ketoconazole molecule is ≤0.003 µm and when dissolved in the product, it should pass through the 4 porosities of filters that were evaluated
- Ketoconazole crystals spiked into the cream and dissolved in one of the gel solvents demonstrated the complete recovery of dissolved ketoconazole and the complete filtration of undissolved ketoconazole (Table 2)

Design/Methods: In vitro

- Studies were conducted in accordance with the SUPAC-SS Guidance of the FDA
- The cream and gel formulations were applied to a SPECTRA/MESH membrane in a 2.0 cm^2 Franz diffusion cell at 37°C
- The diffusion of ketoconazole into an alcohol/buffer receptor solution was measured over a 6-hour period

Results

- Microscopy confirmed that ketoconazole was completely dissolved in the gel formulation (Figure 1), but there was a significant amount of undissolved ketoconazole suspended in the cream formulation (Figure 2)

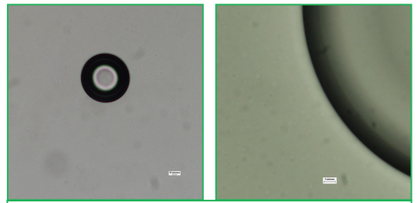

Figure 1. Optical images of Ketoconazole USP 2% gel at different magnifications. The dark circle in the micrograph (left side image, at 10X magnification) shows an air bubble, and the rest of the area is clear without any particles. The micrograph on the right is recorded using a 100X objective, which also shows no particles in the sample.

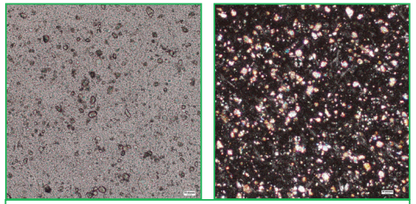

Figure 2. Optical micrographs of Ketoconazole USP 2% cream under normal viewing mode (left side). The undissolved particles turn bright and colorful when viewed with cross polarization (image on the right side), indicating that they are crystalline. Both images are of the same field and recorded using a 20X objective.

- Optical micrographs (Figure 3) of the cream formulation at 65°C (above melting point for nondrug ingredients) showed numerous crystalline particles indicating the presence of ketoconazole (melting point 146°C)

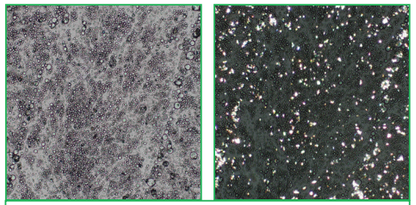

Figure 3. Optical micrograph of Ketoconazole USP 2% cream at 10X magnification at ~65°C. Left: The micrograph shows oil drops, suggesting that the ointment base has melted and dark particles still remained intact. Right: The same area as seen using cross polarization. The bright area or the spots are indicative of crystalline solid material, suggesting that ketoconazole (melting point 146°C) remained solid at 65°C.

- A quantitative analysis of the filtrate from the cream formulation indicates that approximately 20% of the ketoconazole was dissolved, and 80% was suspended as undissolved crystals. Data also demonstrated that the percent of ketoconazole that was recovered from the spiked product vs the unspiked product was approximately the same (Table 2). Therefore, it appears that ketoconazole has been formulated in the cream product as suspended crystals
- When ketoconazole was dissolved in propylene glycol, 99.5% of the ketoconazole passed through the filter. This demonstrated that ketoconazole does not adhere to the filter and that the cream formulation contains crystalline ketoconazole

Table 1. Filtration Studies: Ketoconazole Recoveries From Cream Formulation

Filter	Sample (% Ketoconazole)	% W/W	% Recovery	% Suspended
1.6 µm GF	2% cream	1.37	68.4	31.6
0.45 µm GF	2% cream	0.80	40.0	-
0.2 µm PVDF	2% cream	0.56	28.0	-
1,000 kD MWCO (0.1 µm PES)	2% cream	0.41	20.5	-

Table 2. Filtration Studies: Ketoconazole Recoveries From Spiked Cream Formulation and Propylene Glycol Studies

Filter	Sample (% Ketoconazole)	% W/W	% Recovery
1,000 kD MWCO (0.1 µm PES)	Unspiked cream (2%)	0.41	20.5
1,000 kD MWCO (0.1 µm PES)	Spiked cream (2%)	0.97	24.3
Unfiltered control	Propylene Glycol (2%)	1.96	100
1,000 kD MWCO (0.1 µm PES)	Propylene Glycol (2%)	1.95	99.5

- Data from the in vitro membrane rate of release studies show that the cumulative release of ketoconazole in the gel formulation is more than 4 times greater than that of the cream formulation[5] (Figure 4)

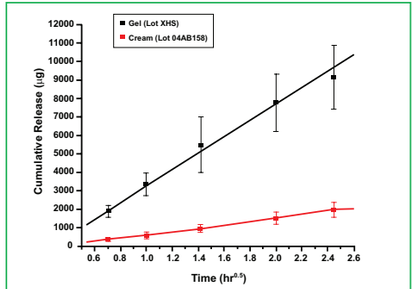

Figure 4. Cumulative release of ketoconazole from the gel and cream formulations (mean ± SD; n=6).

Conclusions

- The efficacy of topical therapy for seborrheic dermatitis is dependent upon the solubility of ketoconazole
- Data from microscopic techniques confirm that ketoconazole is completely dissolved in the 2% gel formulation, while a significant amount of undissolved ketoconazole remains suspended in the cream formulation
- Quantitative analysis using filtration/HPLC shows that 80% of the ketoconazole content is suspended in the cream formulation as undissolved crystals
- Ketoconazole is more soluble in the gel formulation than in the cream formulation and therefore is more readily delivered to the affected area
- The in vitro data demonstrate a fourfold greater rate of release of soluble ketoconazole from the 2% gel formulation than the 2% cream formulation

References

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This poster was sponsored by Barrier Therapeutics.