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Evaluation of formulation properties and skin penetration in the same additive-containing formulation

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ABSTRACT

The aim of this study is to examine the physicochemical properties of the external preparation, the effect on the skin permeability and the human senses. Miconazole nitrate cream formulation (MCZ-A: bland name and MCZ-B, −C, −D: generics) to measure the physicochemical properties, was performed by the skin permeation test and human sensory test. The flattening, viscoelasticity, and water content of each cream were measured and each cream was subjected to near-infrared (NIR) absorption spectroscopy and human sensory testing. The yield value was calculated based on measured flattening and was 734.8 dynes/cm^2 for MCZ-A, 1198.9 dynes/cm^2 for MCZ-B, 461.3 dynes/cm^2 for MCZ-C and 3112.3 dynes/cm^2 for MCZ-D. Measurement of viscoelasticity and viscosity revealed that MCZ-C had a smaller tanδ than the other 3 creams at 25 °C. NIR absorption spectroscopy revealed that MCZ-A had the highest absorption peak due to hydroxyl groups, followed by MCZ-C, −B, and then −D. Measurement of water content revealed that MCZ-A had a water content of 65.9%, MCZ-B, −C, and −D had a water content of around 56.3%. Human sensory testing revealed differences between MCZ-A and MCZ-C and between MCZ-B and MCZ-D in terms of spreadability and feel. These findings indicate that differences in water and oil content and emulsification resulted in the creams having different physical properties, such as flattening, internal structure, and dynamic viscoelasticity. NIR absorption spectroscopy, which allows non-destructive measurement of a sample's physicochemical properties, and measurement of viscoelasticity and viscosity, which allows measurement of a sample's dynamic viscoelasticity, revealed differences in the physical properties of creams. The skin permeation test, skin MCZ amount was 7.48 μg/cm^2 for MCZ-A, 5.11 μg/cm^2 for MCZ-B, 12.08 μg/cm^2 for MCZ-C and 3.75 μg/cm^2 for MCZ-D. In addition, since the drug spread is good about the skin migration, spreadability is affecting the potential dermal transfer.

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1. Introduction

Providing safe and effective drugs to individual patients is an important responsibility of pharmacists. Medical costs borne by the Japanese public have soared over the past few years. Those costs need to be reduced, and use of generic drugs (generics) is recommended as one way to achieve that goal. Generics are cheaper than brand-name drugs but have the same quality. However, generics have gained little traction in Japan despite accounting for half of the drug market in the US and UK [1]. Testing to assess generics in Japan includes dissolution tests and bioequivalence tests. Only a few types of testing are used to assess some forms of preparations, there is a lack of information on the clinical efficacy and safety of these forms, and many experts feel that information on these forms is inadequate [2,3]. Types and ratios of additives are not necessarily the same for different external preparations, and many pharmacists question their quality [4]. In addition, information differences in the additives, method of manufacture, and properties of each preparation must be gathered when preparations are used even if they have the same ingredients [5]. Unlike drugs that are taken orally, external preparations like those applied to the skin are visible to the patient (during application, for example), so characteristics like ease of application and hardness are important.

Ergosterol is a component of the fungal cell membrane that is associated with its permeability. At low concentrations, miconazole (MCZ), an imidazole antifungal agent, primarily exhibits antifungal action by inhibiting the synthesis of ergosterol. This in turn inhibits the transport of substances across the fungal cell membrane, it interferes with the permeability barrier of those cells, it inhibits the synthesis of high-molecular-weight substances, and it inhibits the respiration of those cells. At high concentrations, MCZ causes necrotic

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changes in cells and it has fungicidal action. MCZ is typically used because of its activity against *Trichophyton*, *Microsporum*, and *Epidermophyton*, which cause ringworm, and against *Candida*, which causes candidiasis, although MCZ also has potent antifungal activity against other species, such as *Aspergillus* spp. and *Cryptococcus neoformans*. However, there are generic forms of MCZ, and differences in additive content and how those additives were manufactured may affect how MCZ creams feel to patients when used in a clinical setting. The Laboratory of Drug Safety Management has previously studied acyclovir (ACV), an antiviral, as well as triamcinolone acetonide (TA), a corticosteroid. These studies indicated that the physicochemical properties of preparations affect how they feel to patients [6,7]. Examining viscous characteristics, which are associated with feel, can provide useful information on the clinical use of preparations. Thus, ascertaining a preparation's physicochemical properties and examining their association with its feel provides indicators of what use of the preparation will be like in clinical settings. Assessment of dynamic viscosity in particular is an important component of the association between physicochemical properties and feel.

In addition, creams consist mainly of additives, so a preparation can be greatly affected by additives. In studies of ACV and TA, this Laboratory compared preparations with different additives. However, no studies have compared the characteristics of preparations with the same types of additives, and no studies have examined physical properties and feel.

In Tulobuterol percutaneous absorption formulation, it is reported for the reason of the difference in additives to contain that it is easy to separate. But also in clinical, it has been reported that complained of "easy to come off" is, one after another by switching to generic drugs from the original drug [8]. Moreover, even if additives contained in formulation is the same, it is reported that release behavior of an active ingredient is different depending on the manufacture methods. It has been reported that there is a possibility that the release time is different in a controlled release formulation [5]. The reason why composition and the production method of the additive agent of each tablet have a difference, the physical properties of cream preparation may be affected. As a result, it is expected that a difference arises in the cutaneous permeability of cream preparation.

The current study assessed the physicochemical properties of MCZ creams with the same additives. It carried out about the cutaneous permeability examination and human sensory testing in each formulation. As reported here, findings provided information that allows selection of a preparation in accordance with a patient's preferences and the intent of the prescribing physician without requiring use of the preparation in a clinical setting beforehand.

2. Materials and methods

2.1. Materials

Four MCZ creams (MCZ-A, MCZ-B, MCZ-C, and MCZ-D) were used in the current study (Table 1). MCZ crystals were purchased from Wako Pure Chemical Industries. Other reagents were special commercial grade (from Wako Pure Chemical Industries or Tokyo Chemical Industry).

Table 1
Additives of MCZ creams.

Formulation	Additives
MCZ-A, −B, −C, −D	Polyoxyethylene Cetylether, Liquidparaffin, Glycerylstearate (SE), Propylparaben, Methylparaben, Isopropyl myristate, Cetanol

2.2. Methods

2.2.1. Calculation of yield values

Flattening was measured with a spread meter (Rigo). Flattening was measured at a temperature of 25 °C with a glass plate weight of 114.2 g. Spread diameter was measured after 5, 10, 30, 60, 120, and 180 s. The yield value was calculated with the following formula using the spread diameter after 120 s.

$F = 47,040 \times G \times G \times V/\pi^2 \times D^5$

F: yield value (dynes/cm^2)
G: glass plate weight (114.2 g)
V: sample size (cm^3)
D: diameter (mm) when sample spreading stopped

2.2.2. Measurement of dynamic viscosity

Dynamic viscosity was measured using a type-E rotational viscometer (Toki Sangyo). The dynamic viscosity of 1 mL of each cream was measured for 600 s at 25 °C using the viscometer with a 1°34′ × R24 cone rotor. Dynamic viscosity was measured at 1 rpm and was read after rotation for 180 s.

2.2.3. Measurement of viscosity and viscoelasticity

Viscosity and viscoelasticity were measured with a rheometer (Haake Mars, Thermo Scientific) with a 1° × R35 cone rotor. The viscosity (Epa (Pa s)), stress (Tau (Pa)), and loss tangent (tan δ) were measured each second. The conditions for measurement of viscosity were a sample amount of 0.2 mL and a gap of 0.051 mm. Recovery of viscosity was measured with a shear rate of 0–500 s^{-1}(90 min) → 500–0 s^{-1}(90 min). The conditions for measurement of viscoelasticity were a sample amount of 2 mL, a gap of 1 mm, and stress of 1 Pa → 10 Pa.

2.2.4. Light microscopy

Microscopy was done using a light microscope (Olympus). Samples were applied to microscope slides and then held in place with a cover slip for viewing.

2.2.5. Measurement of water content

Water content was measured using a Karl-Fisher moisture content meter (CA-06, Mitsubishi Chemical Corporation). AQUAMICRON®AX (Mitsubishi Chemical Corporation) served as the catholyte and AQUAMICRON®CNU (Mitsubishi Chemical Corporation) served as the anolyte. Water content in 0.01 g of each sample was measured 3 times at room temperature.

2.2.6. Near-infrared absorption spectroscopy

Near-infrared absorption spectra were recorded using a Fourier-transform near-infrared analyzer (Buchi NIRFlex N-500). Spectroscopy was done with a wavelength range of 1000–2500 nm and a wavenumber range of 10,000–4000 cm^{-1}; spectra were recorded for 8 s at a temperature of 25 °C. Each sample was poured into a sample cup and spectroscopy was performed.

2.2.7. Assay

An assay was performed using a high-performance liquid chromatograph (HPLC) (Waters). Assay conditions were an inertsilODS-3 column (4.6 × 250 mm^2, φ5 μm), a column temperature of 40 °C, a mobile phase of acetic acid buffer (pH 5.0) and methanol (1:5), detection wavelength of 250 nm, and xanthone (1 → 10,000) as the internal standard. About 0.2 g of each cream was weighed accurately and dissolved by adding 10 mL of diluent (chloroform: methanol = 7: 3). The mixture was shaken for

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