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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.

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

15 min and then filtered with a 0.45-μm filter. Five mL of the filtrate was weighed accurately, 1 mL of the internal standard was added, and the solution was shaken. The resulting solution served as the sample solution. A calibration curve was prepared using MCZ crystals. Calibrations were done so that the retention time for MCZ could be determined in 8 min.

2.2.8. Human sensory testing[9]

Sensory testing was done using single-blinding. Each sample was randomly designated A, B, C, or D. Before testing, testers washed their hands with tap water and dried them with paper towels for 5 min. Afterwards, testers selected cream A, B, C, or D. Testers were given a 0.1-g dollop of cream (measured beforehand), which they gently rubbed onto the back of their hand with their index finger. This rubbing was done 10 times in a circular motion. Testers left each cream on for 5 min and they used an assessment sheet to assess aspects of the cream. Afterwards, they used tap water to rinse off the area where cream had been applied. Testers subsequently applied and assessed each of the remaining creams. The sensory test in this study was approved by the Ethics Review Committee for Life Sciences Research of Josai University. The sensory test was fully explained to each tester, and 38 testers consented in writing to participate in this testing. Each cream was assessed in terms of 5 aspects rated on a 4-point scale (1: poor, 2: somewhat poor, 3: somewhat good, 4: good). The assessment sheet featured a comment area where testers wrote their impressions of each cream.

2.2.9. Skin permeation test [10]

The experiments using (Yucatán MicroPig (YMP), female) skin YMP resected was performed using Franz diffusion cells having an effective diffusion area of 0.38 cm^2. YMP skin were prepared as described by Takeuchi, et al. [11]. The full-thickness pig skin which is stored in a freezer at −80 °C advance, thawed slowly at about 4 °C, subcutaneous fat was removed using scissors. After removal of the subcutaneous fat, and smelt cut to about 2.5 × 2.5 cm^2 to YMP skin. In addition, those samples stripping the stratum corneum by 30 times in the tape stripping tape. The skins are then placed in the upper epidermal side on a paper towel soaked in saline, and stored for 12 h at 4 °C, was used in the test.

Skin permeation test was performed using Franz diffusion cell (diffusion area: about 0.95 cm^2). The skin samples were mounted in the upper epidermal side diffusion cells and the receptor cells were filled with a solution prepared by dissolving 3% albumin in saline receiver phase. The receptor cell was kept at 32 °C and stirred using a stirrer at a constant speed of 150 rpm. The test was started with about 0.5 g of each formulation applied on the skin. Sample was the YMP skin after 24 h and the receiver solution of 1, 3, 6, 9, 24 h after application of each drug. Samples were deproteinized with methanol and was determined by HPLC after centrifugation (10 min 4 °C, 3600 × *g*). YMP skin were deproteinized with methanol after the homogenate and was determined by HPLC after centrifugation.

2.2.10. Statistical testing

Statistical indices were assessed using a Tukey test.

3. Results

3.1. Measurement of flattening

Flattening was measured and yield values were calculated as an indicator of a cream's viscosity (Figs. 1 and 2). After 120 s, the spread of creams plateaued. The diameter of that spread was 32.7 mm for MCZ-A, 29.9 mm for MCZ-B, 35.6 mm for MCZ-C, and 24.5 mm for MCZ-D. The yield value serves as an indicator of hardness. MCZ-A had a yield value of 734.8 dynes/cm^2, MCZ-B had a yield value of 1198.9 dynes/cm^2, MCZ-C had a yield value of 461.3 dynes/cm^2, and MCZ-D had a yield value of 3112.3 dynes/cm^2. MCZ-D had a higher yield value than the other 3 creams ($p < 0.001$) and MCZ-B had a higher yield value than MCZ-C ($p < 0.005$).

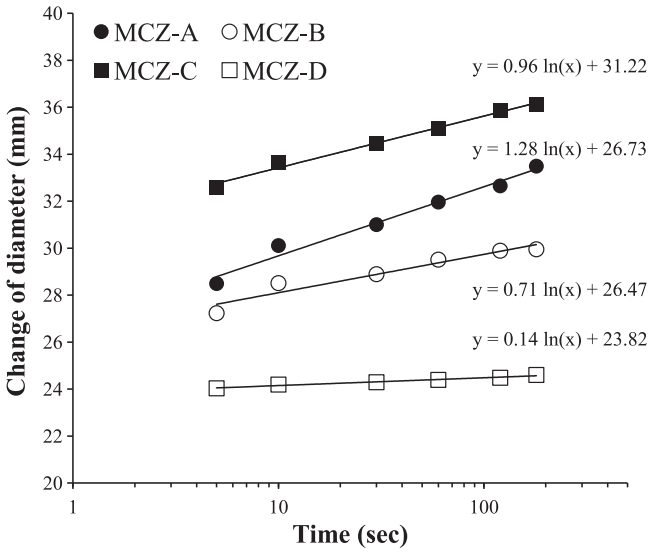

Fig. 1. Spreadability of MCZ creams at 25 °C.

3.2. Measurement of dynamic viscosity

Measurements of the dynamic viscosity of each cream are shown in Fig. 3. After 180 s, MCZ-A had a dynamic viscosity of 1790 Pa s, MCZ-B had a dynamic viscosity of 418 Pa s, MCZ-C had a dynamic viscosity of 229 Pa s, and MCZ-D had a dynamic viscosity of 377 Pa s. When dynamic viscosity was measured for 900 s, MCZ-A originally had a high dynamic viscosity that gradually decreased. MCZ-A continued to have a higher dynamic viscosity than then other 3 creams.

3.3. Measurement of viscosity and viscoelasticity

The viscosity of each cream was determined (Fig. 4). At 25 °C, MCZ-A and MCZ-B had a similar flow curve area. MCZ-C had a smaller flow curve area than the other 3 creams. MCZ-D had a large flow curve area than the other 3 creams. MCZ-D had the greatest tolerance to stress, followed by MCZ-B, MCZ-A, and then

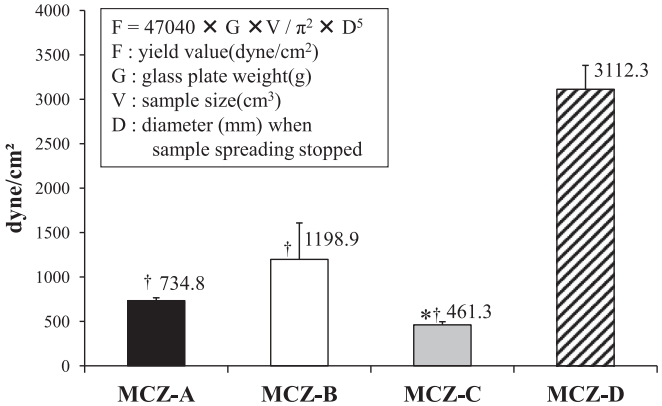

Fig. 2. Yield value on the MCZ creams at 25 °C.*: $p < 0.05$ vs MCZ-B, †: $p < 0.01$ vs MCZ-D, Tukey test (mean ± S.D. $n = 4$).

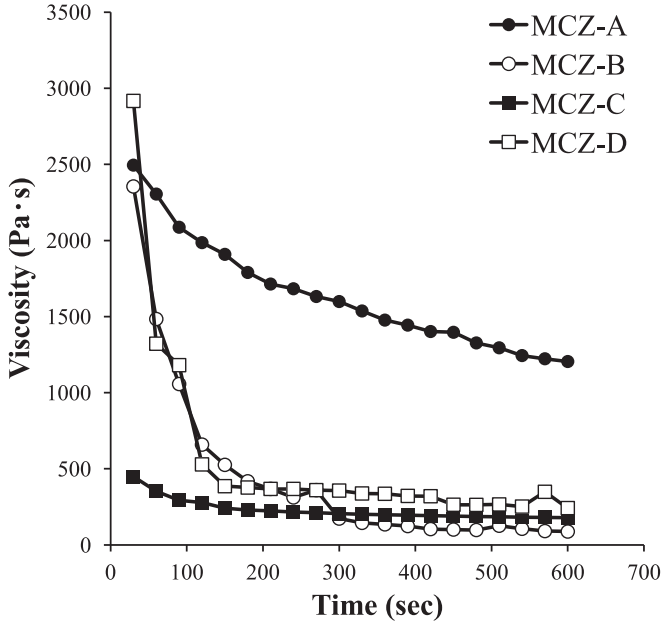

Fig. 3. Viscosity curves of MCZ creams at 25 °C.

MCZ-C. Comparison of the flow curve area and tolerance to stress of 25 °C and 35 °C revealed that MCZ-A and MCZ-C had similar results. However, MCZ-B and MCZ-D exhibited less stress at 35 °C than at 25 °C, and MCZ-B and MCZ-D were found to have a smaller flow curve area at 35 °C than at 25 °C.

The loss tangent tanδ (Fig. 5) was determined with a rheometer in order to compare the viscoelasticity of the creams. Measurement revealed that MCZ-C had a smaller tanδ than the other 3 creams at 25 °C, so MCZ-C had a small viscosity component. In contrast, MCZ-A, MCZ-B, and MCZ-D had a similar tanδ, so they may have similar tackiness. At 35 °C, all 4 creams had a similar tan δ.

3.4. Light microscopy

Light microscopy was performed, and creams were checked for the presence of crystals and dispersibility (Fig. 6). Results revealed that MCZ-C was highly emulsified and that MCZ crystals were evenly and uniformly dispersed overall. In contrast, crystals were noted in the other 3 creams.

3.5. Measurement of water content

The water content in each cream was determined to compare the water content in the creams. Water content was 65.9 ± 2.0% for MCZ-A, 56.3 ± 1.7% for MCZ-B, 56.6 ± 1.9% for MCZ-C, and 56.9 ± 0.9% for MCZ-D. A Tukey test revealed that MCZ-A had a high water content. In addition, there were no significant differences in the water content of MCZ-B, MCZ-C, and MCZ-D.

3.6. Near-infrared absorption spectroscopy

NIR absorption spectroscopy was performed (Fig. 7) to reveal differences in the oil and water content of the creams. Spectra resulting from olefin (-CH_2) groups from oleaginous bases have been observed [12] in the vicinity of 4300 and 5800 cm^{-1} and spectra resulting from hydroxyl (-OH) groups from water [13] have been observed in the vicinity of 5200 cm^{-1}. Based on second-derivative NIR absorption spectra, MCZ-B, MCZ-C, and MCZ-D had similar spectra in the vicinity of 4300 cm^{-1} while MCZ-A had a lower spectrum than the other 3 creams. MCZ-A and MCZ-C had higher spectra in the vicinity of 5200 cm^{-1} while MCZ-B and MCZ-D had lower spectra.

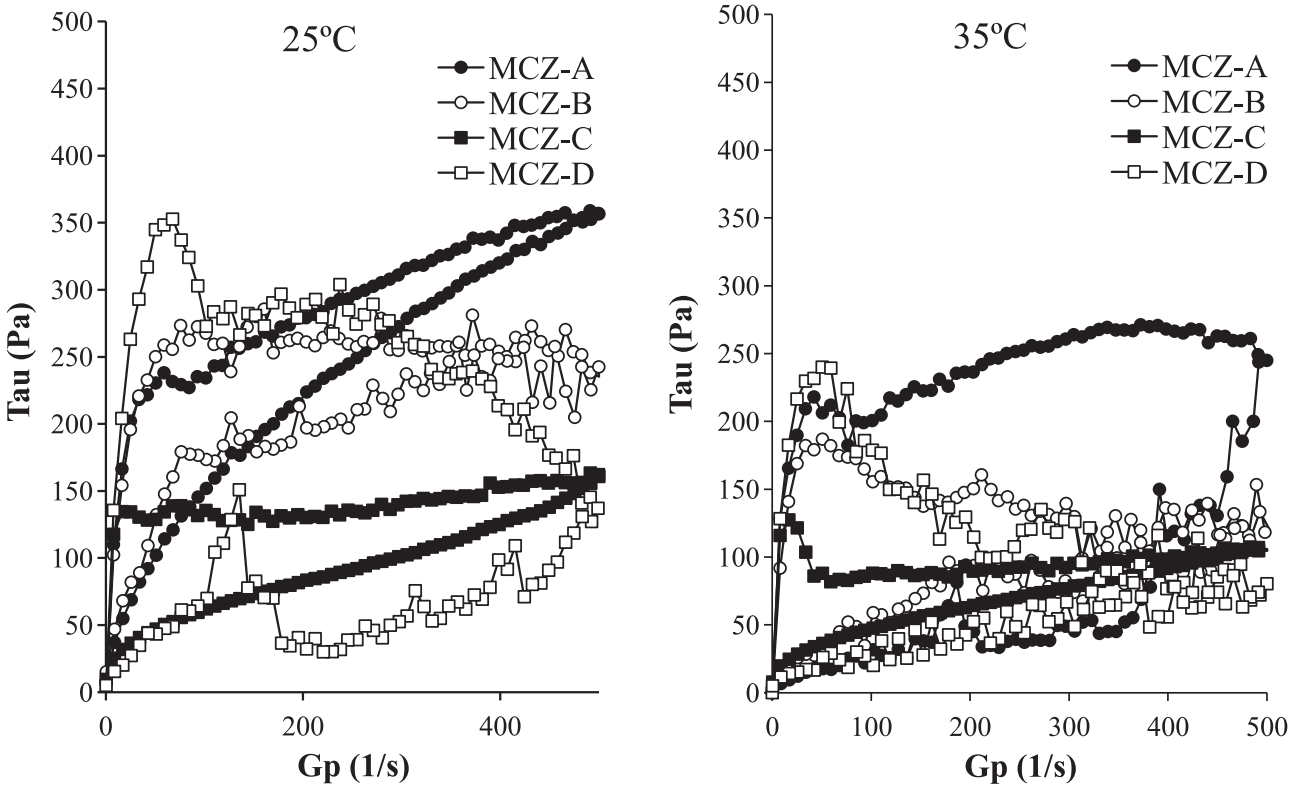

Fig. 4. Shear stress vs shear speed curves of MCZ creams.

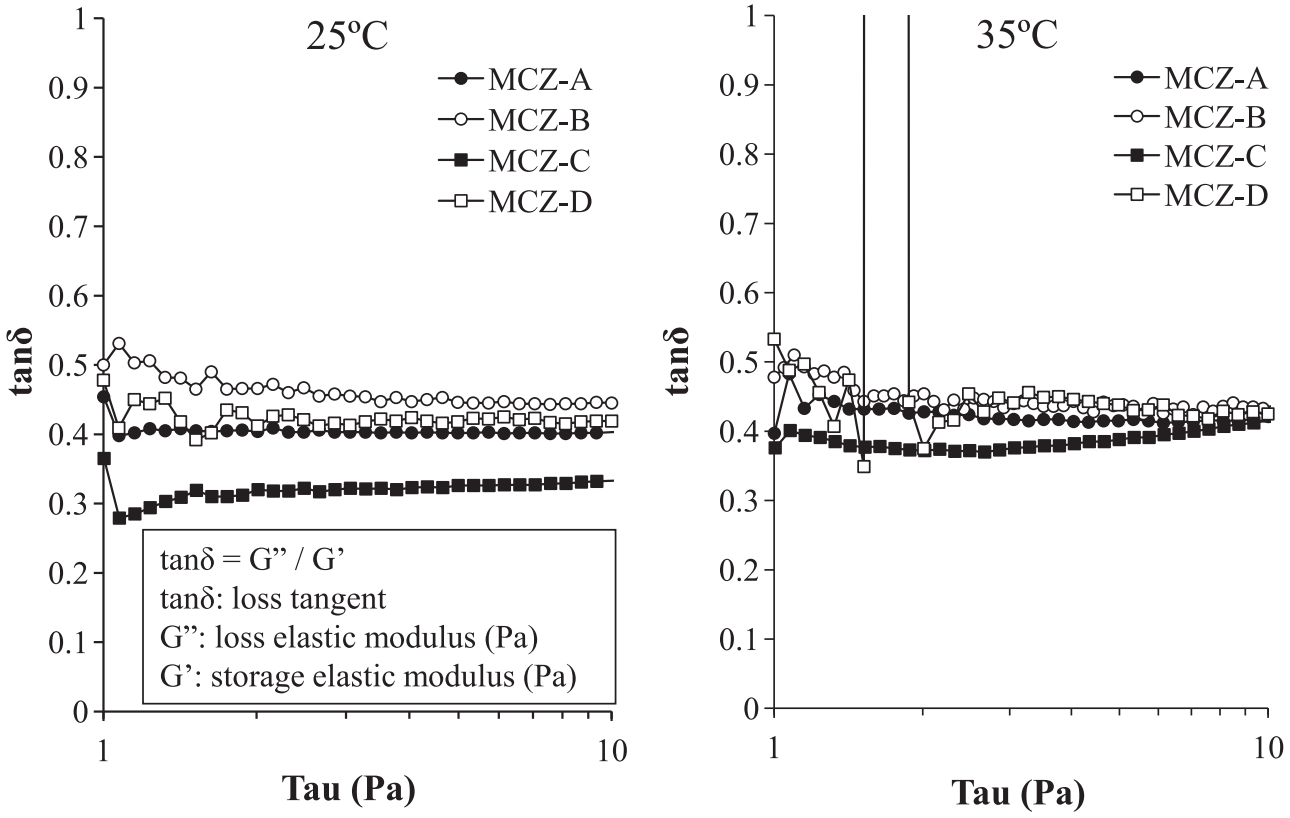

Fig. 5. tan δ versus Tau for MCZ creams.

3.7. Content uniformity test

An assay using HPLC was performed to determine the MCZ content in each cream. This assay revealed that MCZ-A had an MCZ content of $100.6 \pm 1.5\%$, MCZ-B had an MCZ content of $100.3 \pm 1.4\%$, MCZ-C had an MCZ content of $99.6 \pm 2.9\%$, and MCZ-D had an MCZ content of $101.1 \pm 1.6\%$. All of the creams were found to have an MCZ content of 95% or higher.

3.8. Human sensory testing

Human sensory testing with regard to 4 attributes (texture, extensibility, cohesiveness, and availability) was conducted (Fig. 8) in order to determine the correlation between the physical properties and feel of each cream. Testing indicated that MCZ-B and MCZ-D had similar attributes. The MCZ-A, significance has been confirmed in the evaluation item of spreadability with MCZ-D. Moreover, the MCZ-A, significant differences has been confirmed in the evaluation item of availability with MCZ-D and MCZ-B ($p < 0.05$). MCZ-C had a significantly better spreadability than MCZ-B and MCZ-D ($p < 0.05$).

3.9. Skin permeation test

The skin permeation test was performed to potential dermal transfer of each of the formulations and to examine the skin permeability (Fig. 9). Results, MCZ was detected in the skin, but could not be detected at all measurement time in the receiver solution. Skin MCZ amount, calculated by the skin per area. MCZ amount is 7.4 μg/cm^2 for MCZ-A, 5.11 μg/cm^2 for MCZ-B, 12.08 μg/cm^2 for MCZ-C, 3.75 μg/cm^2 for MCZ-D. MCZ-C had migrated into the skin significantly from MCZ-D and MCZ-B ($p < 0.05$).

4. Discussion

In order to determine the physicochemical properties of each cream, flattening, dynamic viscosity, viscoelasticity, viscosity, and water content were measured and microscopy and NIR absorption spectroscopy were performed. Differences in physical properties were noted. In order to determine the effects of differences in physical properties on feel to humans, a sensory test was conducted. Findings indicated that physicochemical properties are associated with feel to humans. Analytical instruments that measure physical properties could presumably help to assess feel to humans.

MCZ-C spread more readily than MCZ-B and MCZ-D and MCZ-A spread more readily than MCZ-D. Calculation of the rate of spread revealed differences in that rate. MCZ-A and MCZ-C spread at a faster rate than MCZ-B and MCZ-D.

Dynamic viscosity typically changes over time. If a certain amount of force is applied and a substance's yield value is exceeded, then its structure will be disrupted and its dynamic viscosity will decrease. Despite the application of force, the structure of MCZ-A was less susceptible to destruction than that of the other 3 creams, so the dynamic viscosity of MCZ-A was less likely to decrease. MCZ-B and MCZ-D had the same level of dynamic viscosity in the 30 s just after measurement of dynamic viscosity began, but after 120 s their dynamic viscosity decreased to the same level of dynamic viscosity as MCZ-C had. Thus, creams MCZ-B and MCZ-D were similarly affected when force was applied. As force continued to be applied, the internal state of MCZ-B and MCZ-D gradually began to resemble that of MCZ-C, i.e. the structure of the creams was presumably disrupted. Thirty sec after measurement of dynamic viscosity began, MCZ-C had a lower dynamic viscosity than the other 3 creams. The fact that this dynamic viscosity remained low indicates that MCZ-C had the lowest dynamic viscosity of the 4 creams.

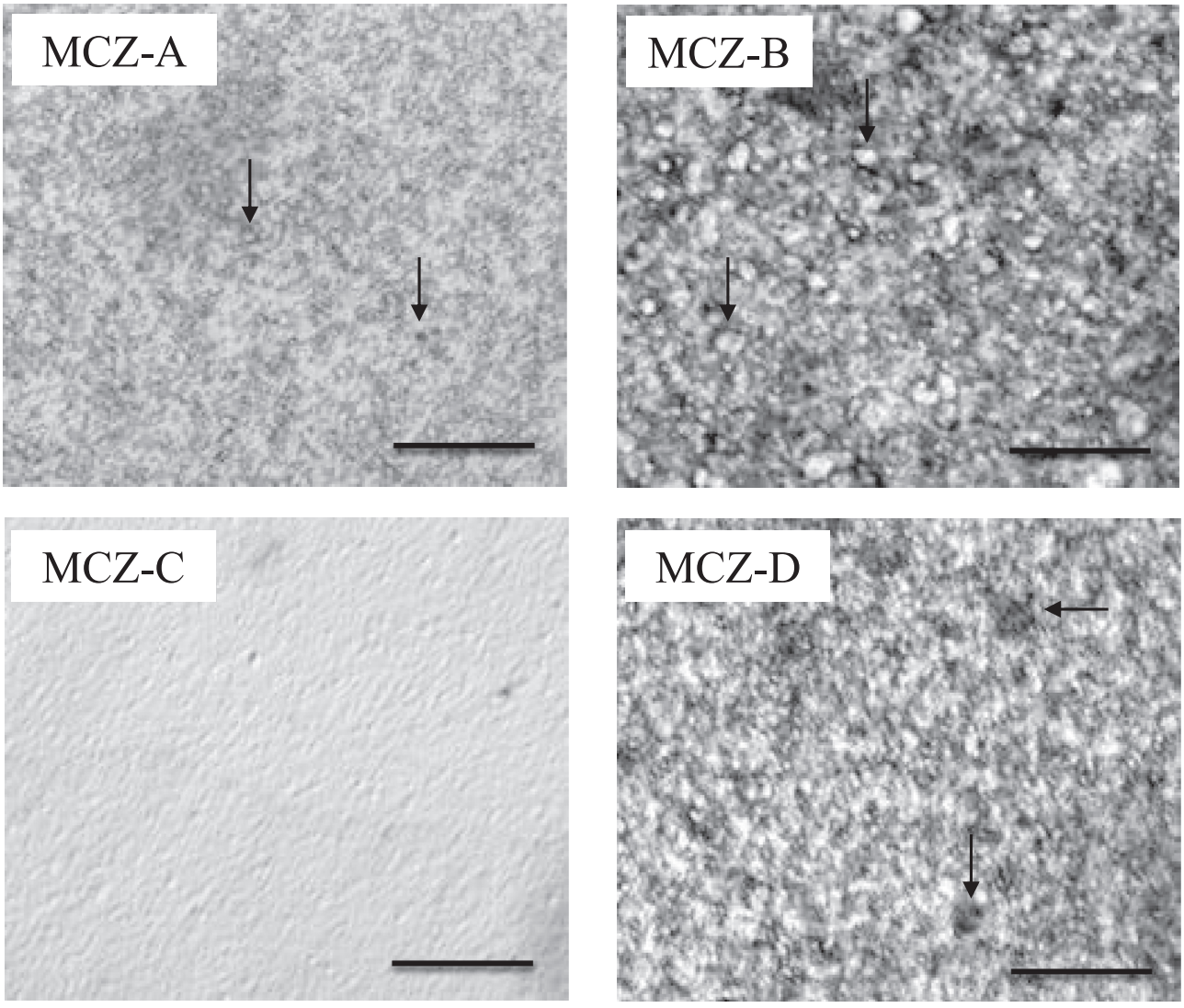

Fig. 6. Light microscopy of MCZ creams. Scale bars represent 100 μm.

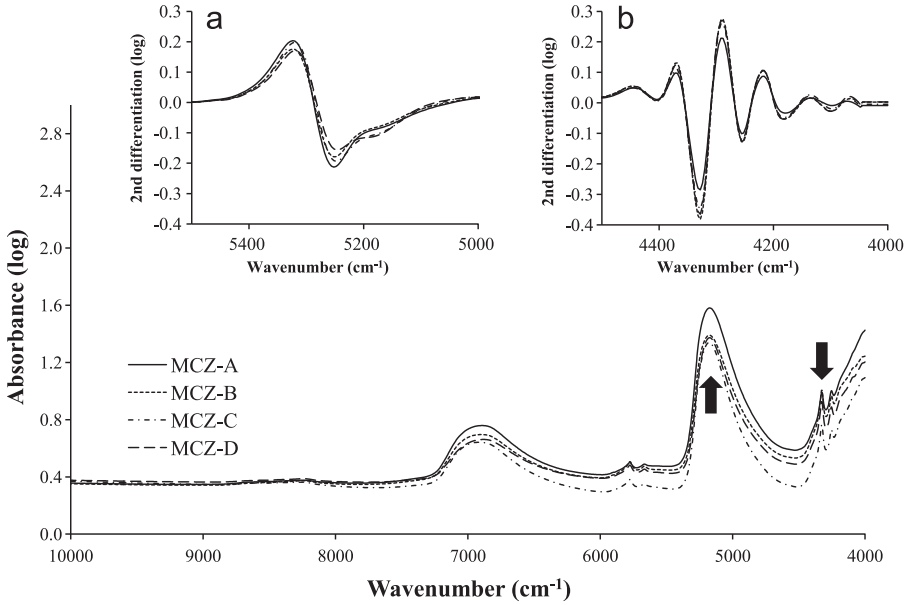

Fig. 7. Near-infrared absorption spectra of MCZ creams. Observed to 4000–10,000 cm^{-1}. (a) 2nd differential near-infrared absorption spectra of MCZ creams. Observed to 5000–5500 cm^{-1}. (b) 2nd differential near-infrared absorption spectra of MCZ creams. Observed to 4000–4500 cm^{-1}.

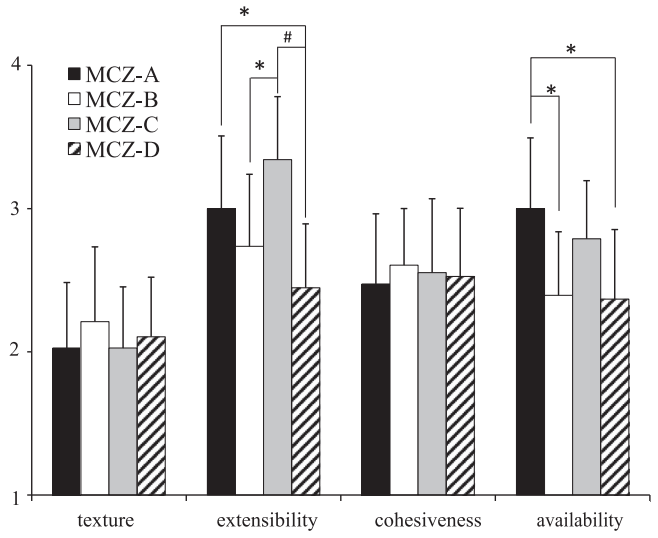

Fig. 8. Sensory test of MCZ creams $^{*}p < 0.05$, $^{\#}p < 0.001$, Tukey test (mean ± S.D. $n = 38$)

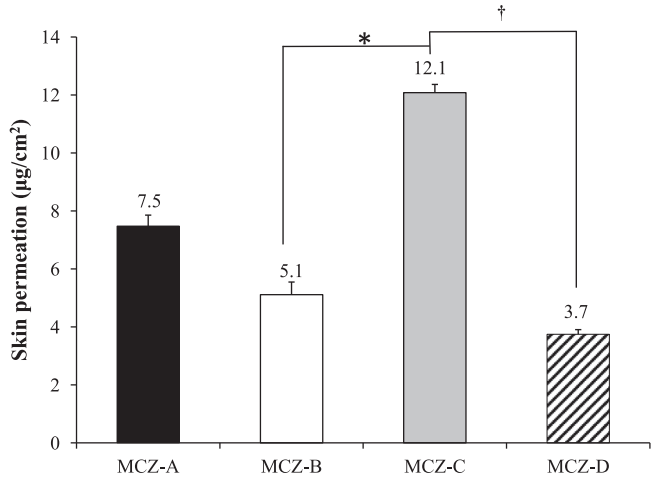

Fig. 9. Skin permeation test of MCZ creams *: $p < 0.05$, $^{\dagger}p < 0.01$, Tukey test (mean ± S.D. $n = 5$)

Viscosity measurements provide flow curves when the shear rate increases and when it decreases. Differences in the flow curve area in turn allow determination of a substance's thixotropic nature, i.e. the robustness of its internal structure. At 25 °C, MCZ-A and MCZ-B had a similar flow curve area, so their internal structures had similar levels of robustness. In addition, MCZ-C had a smaller flow curve area than the other 3 creams, so it had a weaker internal structure than the other 3 creams. MCZ-D had a large flow curve area than the other 3 creams, so it had a more robust internal structure than the other 3 creams. In addition, MCZ-D had the greatest tolerance to stress, followed by MCZ-B, MCZ-A, and then MCZ-C. MCZ-C had the lowest tolerance to stress and the smallest flow curve area, so presumably its internal structure is readily disrupted. Comparison of the flow curve area and tolerance to stress of 25 °C and 35 °C revealed that MCZ-C had similar results. These creams might be affected little by a rise in temperature. However, Influence of the temperature rise is large MCZ-D and MCZ-B, the internal structure is not maintained by soluble additives with a low melting point. Therefore, the shear stress is low from shear rate of early rise, flow curve area becomes smaller. However, the effect on the temperature rise is small compared to MCZ-D and MCZ-B in MCZ-A, there is no difference between the 25 °C the shear stress of the shear rate increased early. Then, to increase the shear rate, the internal structure is destroyed in the vicinity of 500Gp, consider shear stress is low recovery behavior.

As the temperature rose, oils in the creams and additives with a low melting point eluted from MCZ-B and MCZ-D, so their internal structure may have been more susceptible to disruption. Typically, human skin temperature is about 32 °C. When heat of friction is produced by rubbing, that temperature increases further. Measurement at 35 °C in the current study is assumed to indicate the state of a cream's internal structure when the cream is used. In other words, a cream that has hardened in its container gradually softens when it is rubbed in (when it is applied). The cream will have an internal structure akin to that of MCZ-C, which is highly emulsified. There may be a correlation between the flow curve area and tolerance to stress and measurements of dynamic viscosity.

tanδ is a ratio of the loss modulus G'', which represents the viscosity component, and the storage modulus G', which represents the elasticity component, and is expressed as G''/G'. tan δ is considered to be associated with the pastiness and stickiness of foods [14,15] and is associated with tackiness when talking about creams. The fact that the 4 creams had a differing tanδ at 25 °C but a similar tanδ at 35 °C indicates that the creams had differing levels of sensitivity to temperature at 25 °C and 35 °C. Like the measured flow curves, this finding indicates that a rise in temperature results in creams eluting oils or additives with a low melting point. The 4 creams had a similar internal state, which may be why their tackiness did not differ.

Measurement of flattening, dynamic viscosity, and viscosity revealed differences in the physicochemical properties of the creams. Those differences may have been the result of the structural characteristics of the creams. These 3 creams had crystals that were irregularly dispersed, the creams were slightly emulsified, and the dispersibility of the creams differed. These differences may have been the result of different techniques used to manufacture the creams.

Spectroscopy revealed differences in water content and oil content. Although creams had the same additives, differences in additive content presumably led to differences in water and oil content.

Light microscopy revealed differences in structural characteristics while measurement of water content and NIR spectroscopy revealed differences in composition. These differences resulted in MCZ-C being highly emulsified and MCZ-A have high water content. MCZ-C and MCZ-A spread better than the other creams. This finding indicates that factors related to a cream's spread reflect differences in water and oil content and emulsification. Additionally, MCZ-A and MCZ-C had higher spectra in the vicinity of 5200 cm^{-1} while MCZ-B and MCZ-D had lower spectra. Therefore, we consider that there is a possibility that the spectrum that are considered to be derived from a hydroxyl group in the near-infrared spectrum is to contribute to the spreadability.

Sensory testing revealed an association between assessed spreadability and the measured extensibility of each cream. Spread as was indicated by measuring extensibility was correlated with significant differences in assessments according to the sensory test, and yield values were also correlated with significant differences in assessments according to the sensory test. A cream's physical property of softening and spreading may be linked to how well it spreads when it is actually applied to human skin. cohesiveness was associated with the viscoelasticity of each cream at 35 °C. Creams had similar levels of viscoelasticity at 35 °C, and no differences in viscoelasticity were evident in the sensory test, so viscoelasticity presumably indicates how tacky a cream feels to humans. The assessed feel was associated with the measured

extensibility and the assessed spreadability. Humans may view a cream as having a good feel when it is soft and it spreads well when first applied. How well or poorly a cream spreads when applied and changes in its softness as its internal structure is disrupted do not affect its feel. Additionally, in general, High water content formulation is not tacky, and the formulation has good extensibility. In humans, not sticky and good extensibility Formulation, is easy to be evaluated feeling is good.

It is considered that the results of the skin permeability test, MCZ was not detected in the receiver solution, the MCZ cream is a local formulation does not migrate systemically, and not pass through the skin. On the other hand, skin remaining amount was confirmed a significant difference between formulations at 4 creams. It is believed that the water / oil content and emulsified state of the drug has affected extensibility, have an effect on skin permeability, reason for extensibility good skin permeability as good formulation. Formulation high moisture content and emulsified state good formulation is likely to enter into the cell gap and pores familiar well on the skin. It is believed that skin permeability is good for that. It is believed that the physicochemical properties to affect the skin migration of the formulation. Moreover, it was confirmed that this is not a crystal of the MCZ bulk powder from polarization observation (undated). Therefore, the dissolution of the crystal does not affect the skin penetration by the skin temperature.

5. Conclusion

This study noted differences in the physicochemical properties and assessments (via a sensory test) of MCZ creams. In our laboratory, we have conducted a similar study using the anti-viral drugs and antibiotics in the past. Formulation which has been used was the preparation of different additives. The MCZ formulation physicochemical properties are different, however MCZ's additives is the same.

This finding indicates that differences in the oil and water content and the emulsification technique used affective physicochemical properties. In addition, differences in physicochemical properties due to oil and water content and emulsification are evident in differences in the feel of a cream in a clinical setting. NIR absorption spectroscopy is a non-destructive method of analysis that allows measurement of physicochemical properties without altering emulsification. Measurement of viscosity allows the fluidity of a cream to be gauged when it is actually applied by humans. These 2 techniques are a useful way to identify differences in forms of preparations [16]. The current findings suggested a correlation between assessment of physical properties and results of a sensory test, so determining a preparation's physicochemical properties is a useful indicator of how the preparation will feel to humans [17]. Patients apply creams directly, so differences in a cream's feel directly affect compliance [18,19]. If a preparation suited to individual preferences could be chosen based on assessment of its physicochemical properties, then this could lead to improved adherence and compliance. In addition, differences in types and ratios of additives are reported to affect skin penetration [20]. Also in the cream formulation, the difference in physicochemical properties can affect the skin permeation of the formulation. Therefore, it has been suggested that there is a possibility that also influence the effect of the drug differences in physicochemical properties. Studying the physicochemical properties of preparations is an important way for pharmacists to obtain drug information and can provide useful information when selecting a cream.

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