



Relationship between the usability and physicochemical properties of triamcinolone acetonide ointments[☆]

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ABSTRACT

The purpose of this study was to examine the physicochemical properties of TA ointments and conduct a human sensory test to assess the properties of those ointments. Physicochemical assessment was done via near-infrared (NIR) absorption spectroscopy, measurement of water content, microscopy, and measurement of viscoelasticity. The human sensory test examined 5 aspects (texture, cohesiveness, spreadability, smell, and feel). Three TA ointments were used: TA-A, a brand-name preparation, and TA-B and TA-C, two generics. The sensory test revealed significant differences between TA-A and TA-B and TA-C in terms of cohesiveness and spreadability. Significant differences between TA-A and TA-C and between TA-B and TA-C in terms of feel were noted. Microscopic examination revealed that TA-C had good dispersibility while TA-A and TA-B produced crystallization. NIR spectroscopy revealed differences in absorption spectra attributed to oil and water content in TAA, TA-B, and TA-C. Measurement of water content indicated water content of $0.06 \pm 0.02\%$ for TA-A, $0.08 \pm 0.08\%$ for TA-B, and $36.7 \pm 1.19\%$ for TA-C. Assessment of viscoelasticity indicated that stress decreased for all 3 ointments at 35°C compared to that at 25°C . TA-A and TA-B were found to have a higher percent decrease in stress than was TA-C. These findings indicate that differences in the types and content of additives caused differences in the physicochemical properties of individual ointments. In addition, differences in physicochemical properties presumably resulted in the close correlation between cohesiveness and spreadability in the sensory test.

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1. Introduction

Generic drugs contain the same active ingredients as brand-name drugs and are less expensive than their brand-name counterparts, but they are considered to have equivalent quality. Since generics and their brand-name counterparts have different additives such as preservatives and coloring agents, the quality of generics is often questioned by physicians and pharmacists [1]. Studies have questioned the equivalence of some generics to their brand-name counterparts in terms of clinical efficacy and safety, and there is a lack of clinical information and data on the clinical efficacy and safety of generics [2,3].

Drugs applied to the skin consist of transdermal preparations, in which drugs act by traveling throughout the body, and topical preparations, in which drugs are applied externally to a certain place on the skin. The latter are most often semisolid preparations in the form of ointments, creams, and gels, liquids such as lotions, and adhesive

preparations such as cataplasms/gel patches and tapes. Bases differ vastly among brand-name topical preparations and their generic counterparts, and the characteristics of these bases may differ. Ointments are drugs largely consisting of additives such as thickening agents and pH adjusters. Clinical efficacy, adverse reactions, and feel may differ due to factors such as bases and additives and the site of use despite drugs having the same principal agent [4]. If the method and conditions of manufacture differ, then brand-name drugs may have different properties despite having the same content of active ingredients and the same additives. Sustained-release preparations that have the same components but different manufacturers must be viewed as clinically different drugs [5]. One example would be differences in the additives in brand-name and generic tulobuterol patches; these differences are reportedly a factor that affects drug release [6]. Thus, information such as differences in the types and ratios of additives, method of manufacture, and properties is needed regardless of whether drugs are brand name or generic.

Topical steroids are used clinically to treat various dermatoses such as eczema and dermatitis. Topical steroids are used as the principal treatment for inflammatory dermatoses and pruritus, such as atopic dermatitis [7]. These drugs are often prescribed by dermatology departments because of their anticipated anti-inflammatory action. However, local adverse reactions to topical steroids include skin atrophy, thinning skin, vasoconstriction, and skin infections due

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Table 1
Additives list for TA ointments.

Formulation	Additives
TA-A	Vaseline (PJ), methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, purified lanolin
TA-B	Vaseline (PJ), crotamiton
TA-C	Crotamiton, propylene glycol, disodium edetate hydrate, carboxyvinyl polymer, acidity regulator

to compromised immunity. Caution regarding these adverse reactions is required, and prolonged use of these steroids is discouraged. Moreover, abrupt cessation of topical steroids produces a rebound phenomenon accompanying withdrawal, possibly causing a skin condition to temporarily worsen. Ceasing use of topical steroids is difficult, and there are instances when patients will resume using topical steroids because of their worsening skin condition due to the rebound phenomenon and anxiety. The potency of topical steroids is ranked in 7 groups based on the intensity of vasoconstriction [8]. Depending on the site of application, topical steroids must be appropriately selected and used based on their ranked potency.

Clinical study of topical steroids began with use of cortisone acetate to treat dermatoses by Goldman et al. in [9]. Numerous studies of their pharmacology and therapeutic efficacy [9–11] have been conducted. 16α -Hydroxycorticoids were developed when 16α -hydroxycortisol was synthesized by introducing a hydroxyl group at the C-16 position of the steroid nucleus. This compound had potent glucocorticoid activity and anti-inflammatory activity but did not cause Na retention. Later, triamcinolone, an analog of 9α -fluoroprednisolone with a 16α -OH, was successfully synthesized. Triamcinolone acetonide (TA) was developed by suspending triamcinolone in acetone to yield a drug with greater bioactivity than 9α -fluoroprednisolone. TA preparations are commercially available as ointments, creams, and injectables, and their usage differs depending on the patient's condition.

Researchers at the Laboratory of Drug Safety Management previously reported a correlation between the physicochemical properties and feel of antimicrobial and antiviral creams [12]. TA ointments are drugs with a “medium” ranking as a steroid. Brand-name and generic preparations are commercially available, but the additives in preparations differ, so differences in the physicochemical properties of individual TA ointments are expected. These differences in physicochemical properties are presumed to affect the feel of these ointments to humans, but these physicochemical properties and feel have not been studied.

Results of the current study should provide information on future drug selection and use in clinical practice. Thus, the current study physically assessed brand-name and generic TA ointments and it compared the properties of those ointments in conjunction with a sensory test with humans.

2. Materials and methods

2.1. Materials

Three different 0.1% TA ointments were used in the present study: the original product, TA-A (AlfresaPharma Co., Ltd., Japan), and two generic products, TA-B (Yoshindou Co., Ltd., Japan) and TA-C (Kaken Pharmaceutical Co., Ltd., Japan). The three products were randomly named TA-A, TA-B, or TA-C. Additives list of each formulation in Table 1. All other reagents were of special reagent grade.

2.2. Methods

2.2.1. Sensory test

The sensory test was carried out by the single-blind method and each sample (A, B, and C) was distributed at random. For assessment, four aspects—texture, spreadability, cohesiveness (3: yes, 2: slightly, 1: very few, and 0: no) were evaluated in four steps. And usability (3: good, 2: slightly good, 1: slightly worse, and 0: worse)—was evaluated in four steps. Moreover, we prepared a general opinion column on the assessment sheet. The test was conducted as follows: first, the subjects washed their hands, then wiped them with a paper towel and let them air-dry for 5 min. Thereafter each subject chose one 50 mg sample of ointment A, B, or C. The ointment was rubbed onto the back of a hand using a finger and a circular motion (10 times). Each aspect indicated on the assessment sheet was evaluated within 5 min, and the next assessment was done 5 min later. Subsequent ointments were similarly applied. Ointments were not applied to the same part and a different finger was used each time. The subjects avoided applying hand ointment to the tested area an hour prior to the test. The subjects were 34 healthy adult volunteers with an average age of 23.5 ± 3.51 years (22–58 years). The male-female ratio of the subjects was 16:18. The average age of the male was 26.5 ± 9.4 years (22–58 years) with an average age of women at the age of 23.7 ± 0.7 years (22–24 years). Those who had medical histories of allergies or side effects to these medicines were excluded as candidates. The evaluation obtained was changed into an evaluation with a score of 0–3. A statistical test was then performed using Turkey's test. In addition, the sensory test in this study was conducted with the approval of Josai University's Life Science Research Ethics Screening Committee after the study was fully explained to the test subjects and their written consent was obtained.

2.2.2. Microscopy

Polarization microscopy was performed using a KEYENCE model VHX-1000 microscope.

2.2.3. Near infrared (NIR) absorption spectrometry

Each sample was analyzed using a Fourier transform near-infrared absorption spectrometer, an NIRFlex N-500 analyzer (Buchi Labortechnik AG, Switzerland), 10,000–4000 cm^{-1} measurement frequency, at 4 cm^{-1} intervals. Measurement conditions were an optical path of 1 nm at 25 °C.

2.2.4. Water content measurement

The titrimetric determination of water content was performed at room temperature using a CA-06 Karl-Fischer moisture content meter (Mitsubishi Chemical Co., Ltd., Japan) equipped with a coulometric titration system ($n = 3$). The Karl-Fischer reagents, AQUAMICRON[®] AX RS as the catholyte and AQUAMICRON[®] CXU as the anolyte, were purchased from Mitsubishi Chemical Co.

2.2.5. High-performance liquid chromatography assay

For the assay, 1.0 g of each ointment was weighed accurately and placed in a stoppered centrifuge tube. Then 40 mL of chloroform/water (1:1) was added and the solution was shaken and then centrifuged (4000 rpm for 30 min, at 25 °C). The portion of the lower layer was filtered with a 0.45 μm filter, and the filtrate served as the sample solution. A calibration curve was prepared using TA that had separately been dried for 24 h at 105 °C. TA was assayed using high-performance liquid chromatography (HPLC: e2695, Waters). TA assay conditions were a column of Inertsil ODS-3 (4.6 mm \times 250 mm, \emptyset 5 μm), column temperature of 35 °C, mobile phase of water/acetonitrile = 2/1, and detection wavelength of 240 nm; conditions were tailored for TA to produce a peak at 9 min.

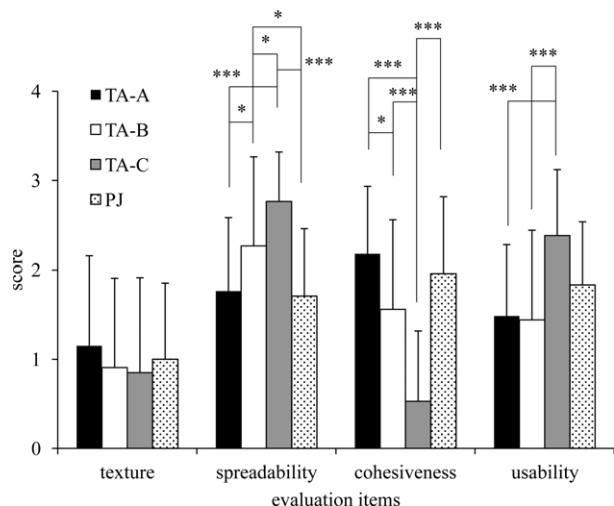


Fig. 1. Sensory test of TA ointments and PJ. *** $p < 0.001$, * $p < 0.01$, Tukey test ($n = 34$ Mean \pm SD).

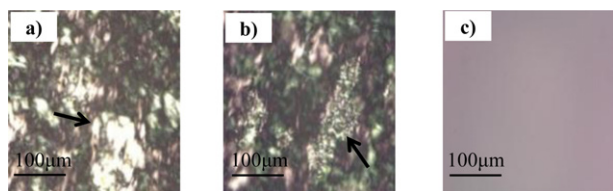


Fig. 2. Light microscopy of TA ointments. (a) TA-A, (b) TA-B, and (c) TA-C.

2.2.6. Viscosity and viscoelasticity measurements

Viscosity at 1-s intervals (Epa (Pa s)), stress (Tau (Pa)), and the loss tangent ($\tan \delta$) were measured using a Rheometer (HAAKE MARS Thermo SCIENTIFIC Co., Ltd.) with a $1^\circ \times R35$ cone rotor at 35°C and 25°C . The conditions for measurement of viscosity were a sample amount of 0.2 mL and a gap of 0.051 mm. The shear rate was gradually raised from a low shear rate (0 s^{-1}) for 1 min and then lowered again to a low shear rate (0 s^{-1}) for 1 min to analyze the return of viscosity. In addition, viscosity was measured in the range of 1–100 Pa for TA-A and TA-B and in the range of 1–1000 Pa for TA-C. The conditions for measurement of viscoelasticity were a sample amount of 2 mL and a gap of 1 mm. Stress was raised gradually from 1 Pa to 10 Pa.

$$\tan \delta = G''/G'$$

$\tan \delta$ is the loss tangent, G'' is the loss elastic modulus (Pa) and G' is the storage elastic modulus (Pa).

A human sensory test was conducted with TA ointments designated TA-A, TA-B, and TA-C and Vaseline (petroleum jelly, denoted here as PJ) (Fig. 1). Significant differences between TA-A, TA-B, and TA-C in terms of texture were not noted. Significant differences between TA-A vs. TA-B ($p < 0.01$), TA-A vs. TA-C ($p < 0.001$), and TA-B vs. TA-C ($p < 0.01$) in terms of spreadability were noted. Significant differences between TA-B vs. PJ ($p < 0.01$) and TA-C vs. PJ ($p < 0.001$) were also noted. Significant differences between TA-A vs. TA-B ($p < 0.01$), TA-A vs. TA-C ($p < 0.001$), and TA-B vs. TA-C ($p < 0.001$) in terms of cohesiveness were noted. Significant differences between TA-C vs. PJ ($p < 0.001$) were noted. Significant differences between TA-A vs. TA-C ($p < 0.001$) and TA-B vs. TA-C ($p < 0.001$) in terms of usability were noted.

Polarization microscopy was next performed to determine the emulsification of TA-A, TA-B, and TA-C (Fig. 2). Results revealed that TA-C had good dispersibility. In contrast, TA-A and TA-B produced crystallization, and both were found to have poor dispersibility.

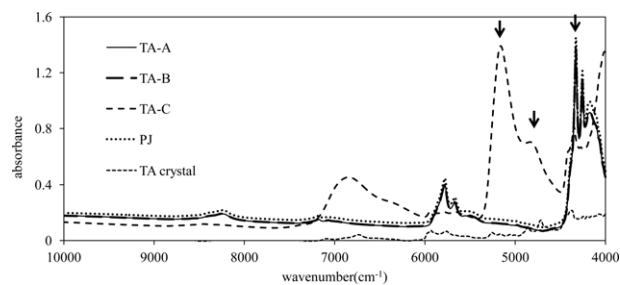


Fig. 3. Near infrared absorption spectrometry of TA. TA crystal, TA ointments, and Vaseline (PJ).

Table 2

Measurement of water content .

Water content (%)		
TA-A	TA-B	TA-C
0.06 \pm 0.02	0.08 \pm 0.08	36.7 \pm 1.19

Values are Mean \pm SD ($n = 3$).

NIR absorption spectrometry was performed on TA-A, TA-B, TA-C, TA crystal, and Vaseline (petroleum jelly) (Fig. 3). TA-A, TA-B, and TA-C lacked the absorption spectra characteristic of TA powder. TA-A and TA-B produced absorption spectra similar to those of PJ, an additive. In contrast, TA-C produced a spectrum unlike those of TA-A, TA-B, or PJ. The second derivative of the NIR absorption spectra (Fig. 4) revealed spectra due to olefin groups ($-\text{CH}_2$) from oil bases [13] at around $4200\text{--}4400\text{ cm}^{-1}$ (Fig. 4a). However, TA-C produced a spectrum located at around $4200\text{--}4400\text{ cm}^{-1}$, unlike TA-A and TA-B. Different spectra were produced by TA-A, TA-B, and TA-C at around $4500\text{--}4800\text{ cm}^{-1}$ (Fig. 4b). Spectra presumably due to hydroxyl group ($-\text{OH}$) content [14] were produced at around $5100\text{--}5300\text{ cm}^{-1}$ (Fig. 4c).

NIR spectroscopy revealed spectra due to hydroxyl groups ($-\text{OH}$) produced at around $5100\text{--}5300\text{ cm}^{-1}$ by TA-A, TA-B, and TA-C, so water content was measured using a Karl-Fischer moisture content meter with a coulometric titration system. Measured water content was $0.06 \pm 0.02\%$ for TA-A, $0.08 \pm 0.08\%$ for TA-B, and $36.7 \pm 1.19\%$ for TA-C. TA-C was found to have a higher water content than TA-A and TA-B (Table 2).

TA-C produced crystals, so its TA content may differ. Thus, TA content in the ointments was measured using HPLC. The TA content in TA-A was 96.6%, that in TA-B was 95.2%, and that in TA-C was 99.9%. All of the ointments were found to have TA content of 95% or higher.

Viscoelasticity was measured to examine the effects of differences in the additives in preparations on viscosity. Measured flow curves for individual ointments at 25°C and at 35°C are shown in Fig. 5. Subjection to stress was found to produce a hysteresis loop for TA-A and TA-B but produced no such loop for TA-C (Fig. 5a). Temperature was measured as the temperature was changed from 25°C to 35°C , revealing a decrease in the area of the hysteresis loop. Stress was found to decrease with a temperature of 35°C compared to one of 25°C (Fig. 5b). In addition, TA-A and TA-B were found to have a greater percent decrease in stress than was TA-C.

Measurements of viscoelasticity are shown in Fig. 6. These measurements revealed that TA-A and TA-B had a greater $\tan \delta$ than did TA-C.

4. Discussion

NIR absorption spectrometry, measurement of water content, microscopy, and analysis of aspects such as rheology revealed differences in the physicochemical properties of the ointments. Results of the human sensory test suggested that the feel of the ointments

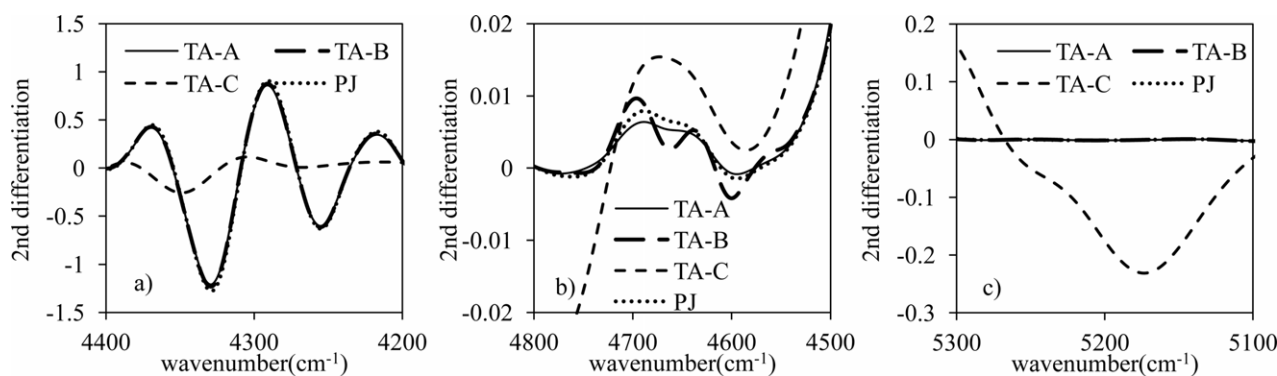


Fig. 4. 2nd-Derivative near-infrared absorption spectra of triamcinolone acetone (TA) ointments and Vaseline (PJ). (a) 2nd-derivative near-infrared absorption spectra of TA ointments and PJ observed at 4200–4400 cm^{-1} , (b) 2nd-derivative near-infrared absorption spectra of TA ointments and PJ observed at 4500–4800 cm^{-1} , and (c) 2nd-derivative near-infrared absorption spectra of TA ointments and PJ observed at 5100–5300 cm^{-1} .

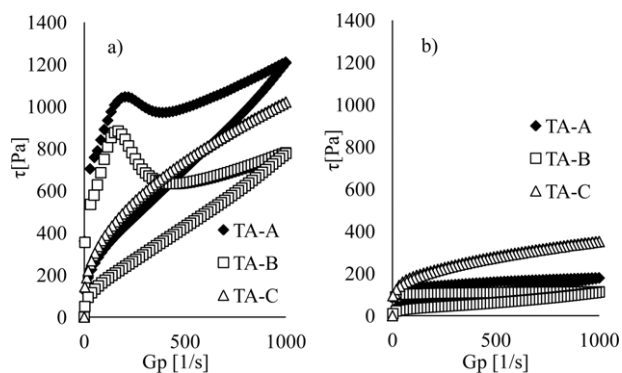


Fig. 5. Shear stress vs. shear speed curves for TA. (a) 25 °C, and (b) 35 °C.

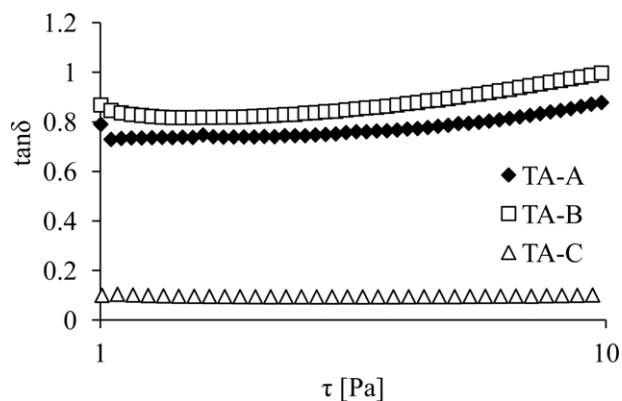


Fig. 6. $\tan \delta$ vs. τ for TA ointments.

differed. Results suggested a correlation between physicochemical properties and results on the human sensory test. Based on these findings, measuring physicochemical properties using various pieces of equipment may provide information correlated with feel in humans.

The sensory test did not indicate that TA-A and TA-B had “a good feel.” In contrast, the test indicated that TA-C had “a good feel.” This finding may indicate the effects of the presence or absence of crystallization, water content, and spreading. The particles in food produce gritty and unpleasant sensation with feel in humans by Lina et al have been reported [15]. Crystal is affected the usability as well ointments.

Microscopy indicated potential differences in the dispersibility of the ointments.

NIR absorption spectroscopy did not reveal an absorption spectrum specific to TA powder. Presumably, it was not detected since the TA content in preparations was 0.1%. Spectra due to olefin groups ($-\text{CH}_2$) produced at around 4200–4400 cm^{-1} by TA-A and TA-B were not produced by TA-C [13]. Different spectra at around 4500–4800 cm^{-1} were produced by TA-A, TA-B, and TA-C. Differences between ointments in terms of the spectra at 5100–5300 cm^{-1} , presumably due to hydroxyl groups ($-\text{OH}$), were noted [14]. These findings indicate that differences in spectra are presumably due to the differences in the types and content of additives in ointments. Differences in the absorption of $-\text{OH}$ groups that NIR absorption spectroscopy revealed and measurements of water content indicated a higher water content for TA-C, followed almost equally by TA-A and TA-B. Based on the above results, there were differences in oil and water content and differences in ingredients in each of the creams. Accordingly, differences in the physical properties of viscosity, viscoelasticity, and spreadability may reflect differences in emulsification. The different physical properties of these creams are likely to result in a different feel when the creams are actually applied. Differences in the types and content of additives in preparations affect water and oil content. The presence of crystals and differences in dispersibility may have affected feel in the sensory test.

Assessments of both the viscosity and elasticity of semisolid preparations such as ointments and creams are reflected in assessments of their internal structures [16]. Determining rheology is a relatively simple and effective technique to compare the structural characteristics of creams and an efficient way to obtain information regarding their resistance to force. Assessments of structural characteristics are known to be an indicator of structural stability [17]. TA-A and TA-B had a greater area under the flow curve and underwent greater stress, suggesting that they had a stronger internal structure that was less susceptible to disruption compared to TA-C. Differences in susceptibility to temperature changes may be due to a different oil content and water content, i.e. the properties of bases. Oil has a lower specific heat than water, so it is readily affected by temperature. Typically, human skin temperature is considered to be about 32 °C [18]. When topical preparations are actually used, they are rubbed into the skin, resulting in a temperature higher than 32 °C due to the heat of friction. In the current study, measurement was done at 35 °C, reflecting use of a topical preparation. Physical behavior of preparations inside their containers and on the skin may differ.

TA-A and TA-B had a greater $\tan \delta$ than TA-C, so they had a proportionately larger viscosity component. This may have led to greater cohesion.

Typically, adding a solubilizing agent is known to ensure stability even at high temperatures and result in a highly viscous preparation. TA-B contained crotamiton, a solubilizing agent, and TA-B had slightly

greater viscosity than TA-A. Tajiri et al. studied the correspondence between flow curves and assessments of spreadability, and they reported that addition of a stabilizer hampered spreadability [19]. A preservative that TA-A contained but that TA-B did not presumably resulted in TA-B having better spreadability in the sensory test than TA-A. The feel of TA-C was due to differences in water content, presumably resulting in the better spreadability of TA-C. In general, the formulation of good spreadability and without being sticky is good usability. Watery formulation is easy to extent and without the sticky. Accordingly, TA-C, watery formulation, was used feeling good.

Tan δ is known to be associated with the pastiness and stickiness of foods. Thus, tan δ is, when talking about ointments, closely correlated with cohesiveness on a sensory test [20]. TA-A and TA-B had a greater tan δ and a greater cohesiveness, suggesting a correlation with the sensory test in the current study as well.

Based on the above results, differences in types and ratios of additives in TA ointments and differences in oil and water content due to those types and ratios of additives were reflected in differences in physical properties, i.e. dispersibility and viscoelasticity. Differences in physical properties are surmised to cause differences in feel when ointments are actually applied. In such instances, NIR absorption spectroscopy, a non-destructive method of analysis, is a useful way to identify differences in preparations [21]. Physical assessment based on NIR absorption spectra leads to information on how preparations feel to patients and should provide indications of individual preferences. Thus, physical assessment of preparations can be used as a way to gather information on drugs, and such assessment can provide useful information when selecting brand-name or generic drugs. A study reported that differences in the types and ratios of additives affect skin penetration [18]. Differences in physical properties are surmised to potentially lead to differences in clinical efficacy. Differences in physical properties may also affect skin penetration. In fact, skin penetration is attributed to physicochemical properties (lipophilicity and hydrophilicity) [22]. Brand-name drugs and generic drugs are considered to have equivalent quality, but their physical properties may differ. Thus, examining the correlation between physical properties and skin penetration is a topic for the future.

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