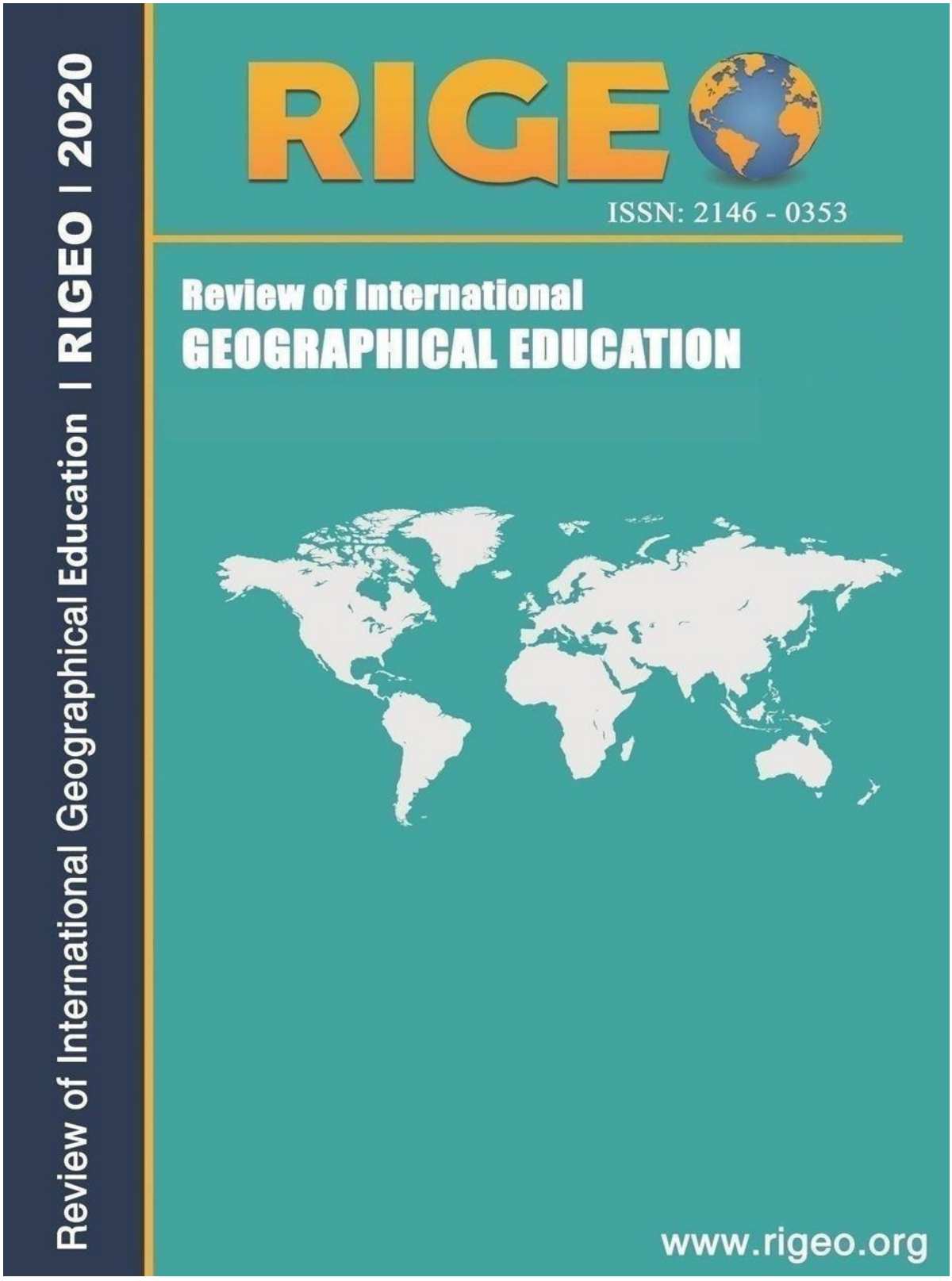
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A Comparison of the Physicochemical Properties and Usability of Acyclovir Ointments

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Abstract:

Both popular brand-name medications and generic alternatives to such medications may have different additive kinds and ratios when it comes to external medicine. This research aimed to examine the sensory test findings and physicochemical features of three different Acyclovir (ACV) creams: one brand-name, two generic. Because the three creams differed in the amount of water and oil they contained, near-infrared (NIR) spectroscopy showed that their absorption spectra changed. There was little difference in the NIR absorption spectra of ACV-B and ACV-C. Crystallization was seen in all of the ACV-C creams and droplets upon microscopic examination. Using powder X-ray diffraction, we were able to identify ACV-A and ACV-B diffraction peaks. According to the results of the viscoelasticity assessment, subjecting ACV-B and ACV-C to a stress of 35 ◦C had no effect on their viscoelasticity compared to subjecting them to a stress of 25 ◦C, however ACV-A's viscoelasticity did decrease. Comparing ACV-A to the other two creams, it was shown to have a better yield value, viscosity, and stress tolerance. A sensory test found that ACV-A was significantly different from ACV-B and ACV-C in terms of adhesiveness, spreadability, and feel. Because of these variations in additive kinds and ratios, we found that the creams' viscosity and elasticity varied. One possible explanation for these variations is because they have different physical characteristics. Furthermore, the sensory test's findings indicated that variations in viscoelasticity and spreadability were indicative of distinct physical characteristics.

1. Introduction

It is a significant obligation for medical workers to choose generic medications that are particularly safe, effective, and patient-acceptable. The quality of generic pharmaceuticals is often questioned by doctors and pharmacists due to the fact that they vary in additives like preservatives and coloring agents, even if they contain the same active components as brand-name drugs (Versantvoort et al., 2008). While dissolving tablet quality is the only way to reevaluate pharmaceutical quality in Japan, generic medications are as effective and less expensive than brand-name pharmaceuticals. Many people believe that the information on generics is insufficient due to the absence of clinical data and information regarding the clinical effectiveness and safety of these medications (Iijima et al., 2004; Jeong et al., 2010). These reasons might be to blame for the fact that generic pharmaceuticals, which make up half of the drug market in the US and UK (Del Tacca et al., 2009; Bramlage and Goldis, 2008), have failed to gain much headway in Japan.

There is a difference in the additives used by generic and brand-name medications. Some studies have shown that the various chemicals used to make Famotidine orally disintegrating tablets cause them to disintegrate and taste differently (Tokuyama et al., 2009). It has been observed that the various vehicles used to apply skin patches for percutaneous absorption of tulobuterol cause them to peel off in different ways. Complaints of patches coming off while switching from brand-name to generic patches were also common in clinical practice (Kobayashi and Asai, 2007). A drug's characteristics may vary from those of its brand-name equivalent if its production is different, even when the active components and additives are same. Reportedly, various sustained-release formulations may have varying release durations (Vetchy et al., 2007). The use of preparations necessitates the collection of information on their additives, manufacturing methods, and qualities, even when they share the same ingredients.
One common guanine analog antiviral is acyclovir (ACV). When phosphorylated in infected cells, it takes on its active form and inhibits viral multiplication (Renjini Joseph and Girish Kumar, 2011; Suzuki et al., 2006). Cold sores and genital herpes are two types of herpes simplex virus infections that ACV may help prevent and cure. The significance of additives in the development of brand-name medications was shown in guinea pig and rat studies.

topical administration of apple cider vinegar; variations in the amount of polyethylene glycol in apple cider vinegar creams were shown to influence the rate of skin absorption (Spruance et al., 1984; Samir et al., 1997). Because of their high additive content—which includes thickening agents and pH adjusters—creams are quite sensitive to changes in additive quality. It has been suggested that variations in percutaneous absorption may be caused by variations in the ingredients used in the several generic ACV creams that have been on the market since 1993 (Trottet et al., 2005). However, there has been a lack of research comparing the qualities of ACV creams, and the variations in their texture and appearance have not been investigated. In order to help in the process of comparing and choosing between generic and brand-name ACV creams, this research physicochemically evaluated the properties of various creams

based on the additives they contain. To further investigate if creams might be chosen based on physical evaluation alone, including feel, they were further tested in human sensory experiments.

2. Materials and methods

2.1. Materials

This research made use of three distinct 5% ACVs: ACV-A (GlaxoSmith Kline K.K.), ACV-B (Sandoz Co., Ltd., Japan), and ACV-C (Toko Pharmaceutical Industrial Co., Ltd., Japan), the original and two generic versions of the product. The three items were given the names ACV-A, ACV-B, and ACV-C at random. Special reagent grade reagents were used for all other reagents.

2.2. Near infrared method and data analysis

A Swiss-made NIRFlex N-500 analyzer (Büchi Labortechnik AG.) was used to examine all of the samples. The thirty-two scans obtained at 4 cm−1 intervals from 1000 to 4000 cm−1 were integrated using Vision software (Foss NIR Systems, Inc., Laurel, MD, U.S.A.) to record the transmittance spectra. In order to calculate the transmittance spectra of each dry-syrup powder, a reference (air) spectrum was created by combining 32 scans in advance. Utilizing the appropriate NIR-Ware software modules and NIRCal chemometric tools, the spectral data underwent processing and analysis.

2.3. Water content measurement

At room temperature, a CA-06 Karl-Fisher moisture content meter (Mithubishi chemical Co., Ltd., Japan) with a coulometric titration system (n = 3) was used to determine the water content via titrimetry. We bought the Kar1-Fisher reagents from Mithubishi Chemical Co., Ltd. The catholite was AQUAMICRON® AX RS and the anolite was AQUAMICRON® CNU.

2.4. Observation of microscopy

An Olympus BX51 microscope was used for polarization microscopy. Also used was a polarizing plate with a 488 nm wavelength.

2.5. Measurements of powder X-ray diffractometry

Japanese manufacturer Rigaku MiniFlexTMII diffractometer was used to measure powder X-ray diffraction patterns. Here are the measurement conditions: target: Cu; filter: Ni; voltage: 30 kV; current: 15 mA; time constant: 0.5 s; scanning speed: 4◦/min; and measuring range: 2θ = 5-35◦.

High-performance liquid chromatography assay

Half a gram of each cream was precisely measured and put into a centrifuge tube with a stopper for the test. Centrifuged at 10,000 rpm for 30 minutes at 25 ◦C, after adding 20 mL of chloroform/0.01 mol/L sodium hydroxide (1:1) and shaking the mixture. The lowest part of the layer was passed through a 0.45 μm filter, and the resulting filtrate was used as the sample solution. The ACV was dried for 24 hours at 105 ◦C before being used to create a calibration curve. An HPLC system developed by Shimadzu, the LC-20ADvp, was used to test ACV. ACV assay condi- tions were a column of Inertsil ODS-3 (4.6 mm × 250 mm, φ5 μm), column temperature of 35 ◦C, mobile phase of pH2.5 phosphate buffer/methanol = 950/50, and detection wavelength of 254 nm; conditions were tailored for ACV to produce a peak at 7 min. After that, we ran a statistical test (Turkey's test) using R 2.1.1.

2.6. Determination of viscosity

Viscosity was measured at a temperature of 20 ◦C using a type- E rotational viscometer, model TVE-20H (Toki Sangyo). Then 1 mL of each cream was poured into a sample cup and viscosity was measured at 1 rpm using a 1◦34′ × R24 cone rotor; measuring time was 900 s, and viscosity was read after 240 s of rotation. Creams were incubated in a water bath at 20 ◦C prior to measurement.

2.7. Viscosity and viscoelasticity measurements

Viscosity and viscoelasticity were measured at 25 ◦C and 35 ◦C using a Rheometer (HAAKE MARS; Thermo Scientific Co.) with a 1◦′ × R35 cone rotor. The conditions of viscous measurement were a sample amount of 0.2 mL and a gap of 0.051 mm. A flow test was used to determine the relative viscosity of all formulations with the following parameters: For the upcurve, a continuous ramp with shear rate as controlled variable (0–

1000 s^{-1}), log mode, and a 1 min ramp duration were applied. The same procedure was used for the downcurve with reversed shear rate (1000–0 s^{-1}) to mea- sure thixotropy and yield stress. The measurement conditions 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.

$\tan \delta = G''/G'$
$\tan \delta$: loss tangent
G'': loss elastic modulus (Pa)
G': storage elastic modulus (Pa)

2.8. *Spreadability measurements*

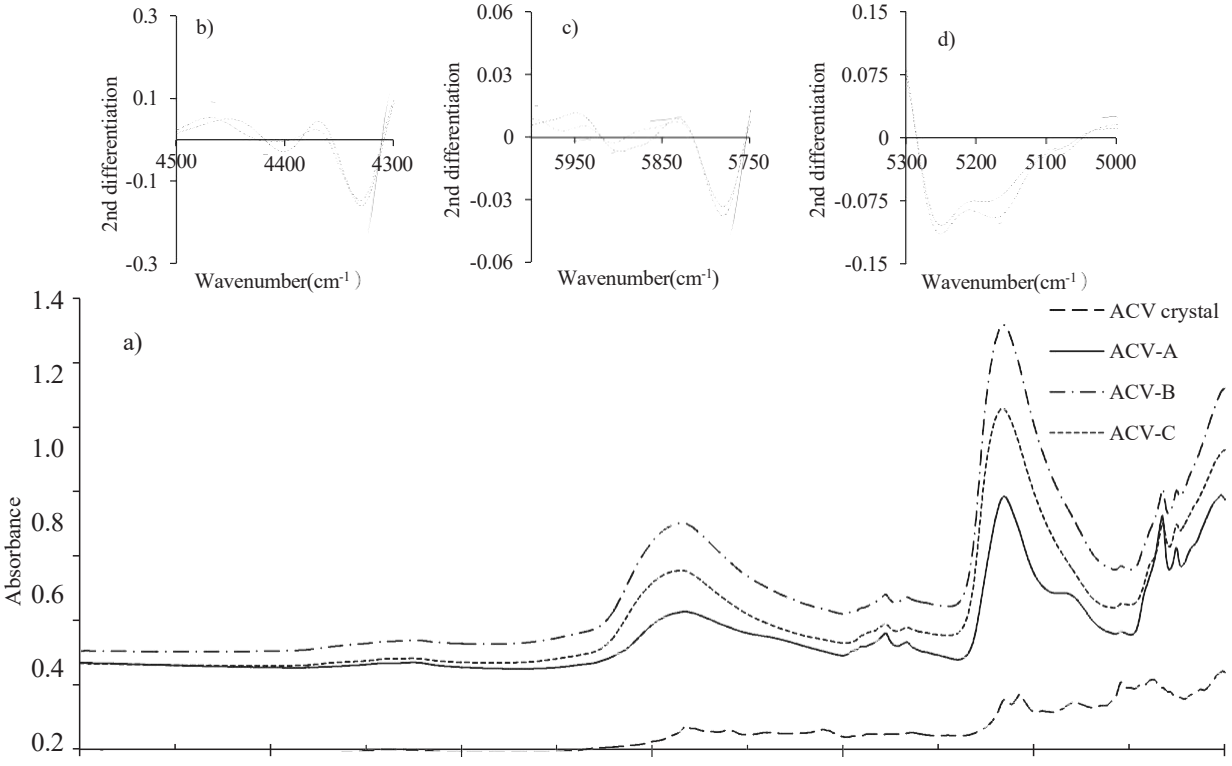
Spreadability was measured at 25 °C using a Spread Meter (Rigo Co.) and the spread diameter was measured after 10, 30, 60, 120,
180, 240, 300, 360, 600, and 900 s.

Yield values were computed from the following formula using the value after 240 s.

$F = 47{,}040 \times G \times V/\pi^2 \times D^5$
F: yield value (dyne/cm^2)
G: weight of the glass board (g)
V: amount of sample (cm^3)
D: the diameter when a spread of a sample stops (mm).

2.9. *Sensory test*

The sensory test was carried out by the single-blind method and each sample, A, B, and C, was distributed at random. As an assess- ment method, five properties—texture, extensibility, cohesiveness, smell, and availability—were evaluated in four steps. Moreover,



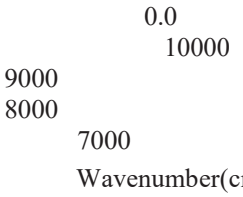


Fig. 1. Near-infrared spectra and 2econd differentiation Near-infrared spectra of ACV. (a) Near-infrared spectra of ACV crystal and creams observed to 4000–10000 cm^{-1},
(b) 2econd differentiation Near-infrared spectra of ACV-creams observed to 4300–4500 cm^{-1}, (c) 2econd differentiation Near-infrared spectra of ACV-creams observed to 5750–6000 cm^{-1}, (d) 2econd differentiation Near-infrared spectra of ACV-creams observed to 5000–5300 cm^{-1}.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 0.1 g sample of cream A, B, or C. The cream was rubbed onto the back of a hand using a finger and 10 circular motions. Each property indicated on the assessment sheet was evaluated within 5 min, and the next assessments were made at 5-minute intervals. Subsequent applications were applied similarly. Creams were not applied to the same part and a differ- ent finger was used each time. The subjects avoided applying hand cream etc. to a test part within the hour leading up to the test. The subjects were 30 healthy, adult volunteers with an average age of
24.2 ± 6.7 years old (20 years old–57 years old). The male-female
ratio of the subjects was 14:16. Those who had medical histories of allergies or side effects to these medicines were excluded as can- didates. The evaluation obtained was changed into an evaluation with a ranking score of 1–4. We then used R 2.1.1 and performed a statistical test (Tukey's test). In addition, the sensory analysis of this research was conducted under the approval of Josai Univer- sity's Life Science Research Ethics Screening Committee after fully explaining this research and obtaining written consent from the test subjects involved.

3. Results and discussion

To compare differences in the types and content of additives in each of the creams, near-infrared absorption spectroscopy of ACV powder, ACV-A, ACV-B, and ACV-C was performed (Fig. 1). Spectra for ACV-A, ACV-B, and ACV-C were found to lack the peak produced by ACV powder. This is presumably because the creams had a low ACV content of 5%, so ACV was not detected.

Table 1
Additives list of ACV creams.

Formulation	Additives
ACV-A	Liquid paraffin, dimetylpolisiloxane, propylene glycol, white petrolatum, glycerol, lcetearyl alcohol, sodium lauryl sulfate, glyceryl stearate, polyoxyethylene(196) polyoxypropylene(67) glycol
ACV-B	Liquid paraffin, dimetylpolisiloxane, propylene glycol, white petrolatum, cetanol, glyceryl monostearate, polyethlene glycol monostearate
ACV-C	Liquid paraffin, dimetylpolisiloxane cetanol, glycerol, stearic acid, glyceryl stearate, polyoxyl stearate, hydrogenated castor oil, 1.3-butanediol, squalane, behenic acid, isopropyl myristate, sodium hydrate

Spectra due to olefin groups (–CH_2) from the oil base (Takeno et al., 2008) were observed in the vicinity of 4200–4400 cm^{-1} and 5600–5800 cm^{-1} as were spectra in the vicinity of 5100–5400 cm^{-1} due to hydroxyl groups (–OH) from water (Diaz-Arnold et al., 1992). ACV-A had the lowest oil and water content, followed by ACV-C and then ACV-B. The water content measurement was per- formed in Karl-Fisher moisture content meter. As a results, The water content in a cream of formulation ACV-A, ACV-B, and ACV-C was 22.2 ± 0.7, 52.3 ± 0.3 and 47.0 ± 1.3%, respectively. ACV-A had the lowest water content, followed by ACV-C and then ACV-B. Dif- ferent

spectra were observed for the 3 creams in the vicinity of 4350–4500 cm^{-1} and in the vicinity of 5800–6000 cm^{-1} according to second-derivative absorption spectra. ACV-A lacked the peak in the vicinity of 5100–5300 cm^{-1} that ACV-B and ACV-C had. It showed an additive of each formulation in Table 1. It was con- firmed that each formulation was different in a kind of a contained additives. Differences in the second derivative of near-infrared

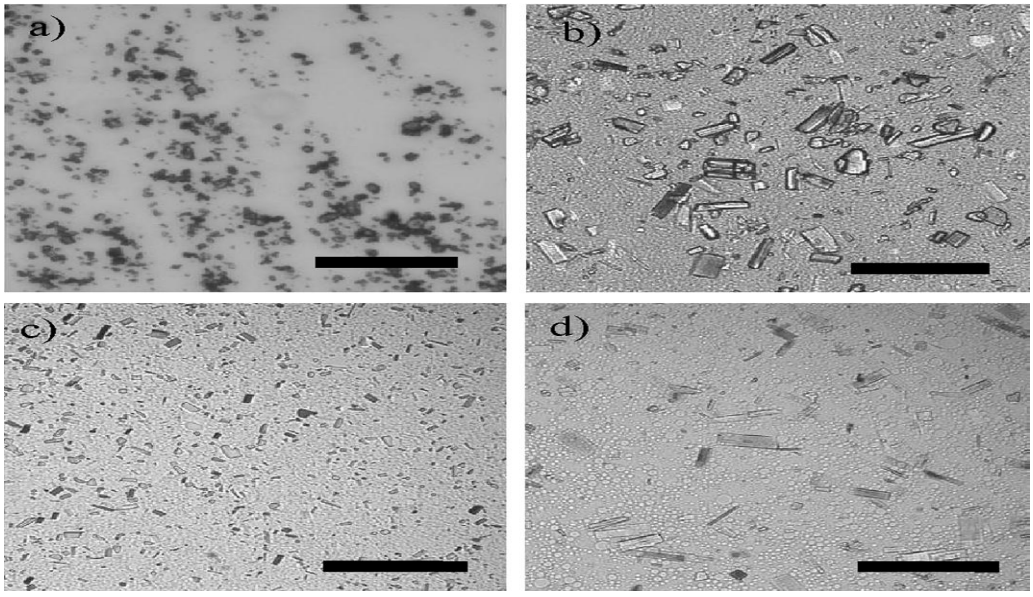
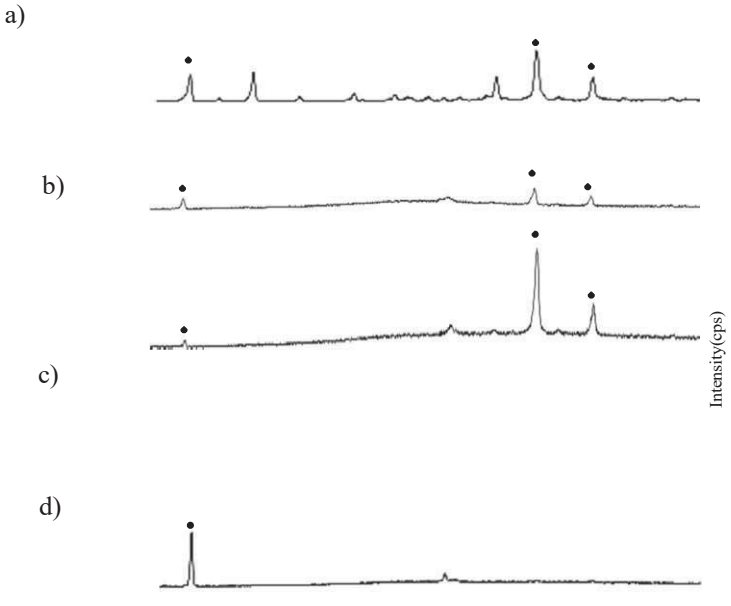


Fig. 2. Light microscopy of ACV crystal and creams respectively. Scale bars indicate 50 µm. (a) ACV crystal, (b) ACV-A, (c) ACV-B, (d) ACV-C.

To examine the emulsification of each of the creams, polariza- tion microscopy of ACV powder, ACV-A, ACV-B, and ACV-C was performed. Results revealed crystallization in each of the creams. ACV powder was found to have plate crystals while ACV-A, ACV- B, and ACV-C had plate and needle-shaped crystals. ACV-C was also found to have droplets, so its emulsification was not uniform, indicating a different dispersibility (Fig. 2).

X-ray powder diffraction patterns of ACV-A, ACV-B, ACV-C, and ACV crystals were obtained in order to study the crystals observed in polarization microscopy (Fig. 3). ACV powder had characteristic peaks at $2\theta = 6.8^{\circ}$, 26.0°, and 29.1°. ACV-A and ACV-B had a char- acteristic diffraction peak due to ACV, and ACV-C had a diffraction peak at $2\theta = 6.8^{\circ}$. Diffraction peaks for ACV-A, ACV-B, and ACV-C
were found to be due to ACV crystals, so the crystals detected in
ACV-A, ACV-B, and ACV-C may be ACV.

Crystals that are presumably ACV were noted in the 3 creams, so there may have been differences in ACV content. Thus, the ACV content in each of the creams was measured using HPLC. Results indicated that the ACV content was 99.1 ± 3.5 in ACV-A, 95.2 ± 0.1 in ACV-B, and 97.0 ± 1.9% in ACV-C. All 3 creams had an ACV con- tent of 95% or higher, there were no issues with the content in the\



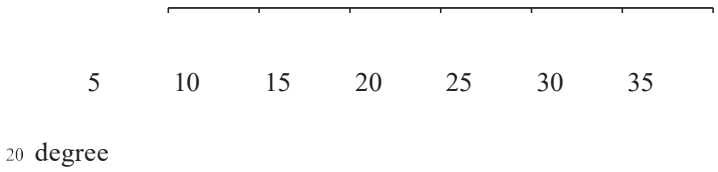


Fig. 3. A comparison of the powder X-ray diffraction patterns (PXDP) of ACV crystal and creams. (a) ACV crystal, (b) ACV-A, (c) ACV-B, (d) ACV-C. The diffraction peaks due to ACV crystal and creams were indicated by ●, respectively.

ratios of additives are reported to affect skin penetration (see, for example, Trottet et al., 2005), and differences in physicochemical properties may also affect differences in clinical efficacy. Study- ing the physicochemical properties of individual preparations is an important way for pharmacists to actively collect drug informa- tion and can provide useful information when selecting a cream containing a brand-name drug or generic drug.

4. Conclusion

Three ACV creams were compared in this study, and the researchers discovered that their ingredient kinds, ratios, oil content, and water content varied. The crystals were identified as potentially ACV using polarization microscopy and powder X-ray diffraction analysis.

Fig. 6. Sensory test of ACV creams. A: ACV-A, ■ :ACV-B, u:ACV-C. **: $p < 0.01$, ***: $p < 0.001$, tukey test. ($n = 30$, mean ± S.D.).

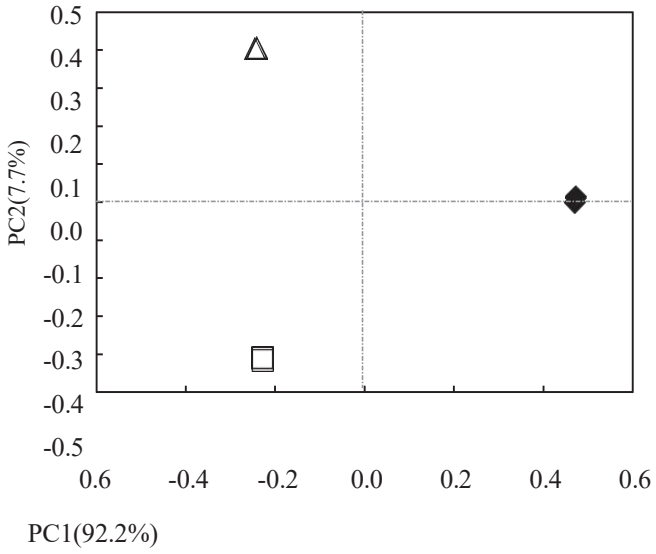


Fig. 7. Principal component analysis of ACV creams. Ç:ACV-A, A:ACV-B, △:ACV-C. in the 3 creams. In addition, droplets were found in ACV-C, so dif- ferences in emulsification were noted. Differences in the viscosity, viscoelasticity, and spreadability of the 3 creams were noted. Near- infrared spectroscopy suggested that these differences reflected differences in the oil and water content of the creams. The attributes of viscoelasticity and spreadability in sensory testing were affected by different results in physical testing. Results of assessment of physical properties were found to be correlated with sensory test results.

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when comparing ACV-A to ACV-B and ACV-C in PC1 (% contribution: 92.2%), but no differences were seen when comparing ACV-B and ACV-C (Fig. 7). According to the results of the human sensory test, PC1 was associated with either viscoelasticity or spreadability. When tested for spreadability, ACV-B and ACV-C were shown to be equally effective. This suggests that the spread meter's findings were consistent with the creams' actual hardness. Viscosity was found to be connected to tan δ in relation to viscoelasticity. Skin conditioners and ointments are reportedly evaluated for viscoelasticity, a method for evaluating the physical

characteristics of semisolids (Moji et al., 2002; Hong et al., 2010; Kobayashi et al., 1982). Furthermore, according to Takahashi et al. (1999), tan δ is linked to meals that are pasty and sticky, and it is linked to creams that have viscoelasticity. The sensory testing findings may have been influenced by tan δ since the creams' characteristics were investigated.
There seems to be a connection between sensory testing and physical testing, according to the present research. The consistency and final composition of a cream may vary depending on the emulsification method used. Differences in emulsification, viscosity, viscoelasticity, spreadability, and additives may all contribute to a distinct feel in a clinical context. One promising non-destructive technique for identifying changes in preparations in such cases is near-infrared absorption spectroscopy (Afonina et al., 2004). Since patients are expected to apply the creams directly, the perception of a distinct texture is believed to have a direct role in influencing compliance (Shibata et al., 2005). Adherence and compliance might be enhanced if a preparation that suits individual tastes could be selected based on assessment of its physical qualities. Furthermore, variations in the kinds and

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