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Original Article

Characterization of prescription and OTC formulations of vidarabine cream

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ABSTRACT

The aim of this study, to assess the uniformity of content, viscosity, spreadability, near-infrared absorption spectroscopy and water content of vidarabine cream (Ara-A: bland name, Ara-B: generic and Ara-C: Over the Counter). Moreover, this study assessed the physicochemical properties of the creams. The Uniformity test indicated that the VDN content was uniform and equivalence was observed. As results of viscosity, Ara-B differed from those in Ara-A and Ara-C. The yield value was calculated based on measured flattening and was 1109.8 dynes/cm^2 for Ara-A, 527.7 dynes/cm^2 for Ara-B, 1200.1 dynes/cm^2 for Ara-C. Measurement of water content revealed that Ara-A, and -C had water content of around 56.3%, Ara-B had water content of 59.9%. NIR absorption spectroscopy revealed that Ara-B had the highest absorption peak due to hydroxyl groups, followed by Ara-A, then -C. In order to evaluate the feel on the skin, friction generated by Ara-A and-C was around 90 N, Ara-B was 54.4 N. The drug spread is good about the skin friction, spreadability might be affecting the human sensory.

Keywords: vidarabine cream, spreadability, friction, physicochemical properties

INTRODUCTION

National medical expenses are increasing as human lifespans increase in length. The responsibilities of a pharmacist in a pharmacy range from preparing medications to advising patients on taking those medications and safely providing medications. In community medicine, however, pharmacists play other roles as well. One such role is in "self-medication," which is a concept that has recently garnered attention [1]. A pharmacy is a key site and a pharmacist is a key figure in self-medication in the community. The pharmacy and pharmacist must help to maintain and improve the health of local residents. The World Health Organization (WHO) defines self-medication as "the selection and use of medicines by individuals to treat self-recognized illnesses or symptoms." Self-medication has various beneficial consequences [2].

Self-medication is the cornerstone of independent health management. Individuals can, for example, learn to manage their own health, they can gain an accurate understanding of medications and medical care, and they can forego the effort and expense of being seen by a medical facility if they have a minor illness [3]. In addition, self-medication can curb medical expenses covered by national health insurance. If an individual feels unwell or he or she notices precursors of an illness, then that individual needs to endeavor to prevent or treat that illness using over the counter (OTC) medications or supplements. Reducing visits to medical facilities will substantially curb medical expenses covered by national health insurance and help to prevent lifestyle-related diseases. "OTC medicines" are drugs that can be bought at a dispensing pharmacy or drug store without a prescription. Some OTC drugs were formerly prescription drugs that have been approved for sale over the counter (an "Rx-to-OTC switch") [4]. These drugs have expanded the scope of self-medication.

Vidarabine was formerly a prescription drug that has now been approved for OTC sale as vidarabine cream. Vidarabine is a drug for the treatment of a herpesvirus infection. Herpesvirus infections are caused by *Herpesviridae*, a family of DNA viruses including the herpes simplex and Varicella zoster viruses, and herpesvirus infections cause blisters on the skin [5]. Vidarabine is effective at inhibiting

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DNA viruses in the *Herpesviridae* family [6]. In Japan, 3 vidarabine creams are currently available commercially: a brand-name preparation named ARASENA-A Cream, a generic preparation named Casal Cream, and an OTC preparation named ARASENA S Cream. However, few studies have examined the equivalence of these prescription (brand name and generic forms) and OTC preparations. A pharmacist who is aware of the properties of OTC preparations would be able to provide valuable advice for self-medication by patients.

To test this hypothesis, the physicochemical properties of a brand-name VDN cream were compared to those of two leading generic or OTC VDN creams. This study sought to observe the characteristics of preparations, determine their viscosity, spreadability, near-infrared absorption spectroscopy and assay those preparations as a quality test. Furthermore, this study performed a skin friction test and it assessed the dermatological indications for the creams.

MATERIALS AND METHODS

Materials: VDN creams were purchased from commercial suppliers. The brand-name cream that was used was ARASENA-A Cream 3% (Mochida Pharmaceutical Co., Ltd.), a generic cream that was used was Casal® Cream 3% (Maruho Co., Ltd.), and an OTC cream that was used was ARASENA S Cream (Sato Pharmaceutical Co., Ltd.). The properties of and additives in each formulation are shown in Table 1.Vidarabine crystals were purchased from Tokyo Kasei Co., Ltd. Other reagents were special commercial grade (Wako Pure Chemical Industries Co., Ltd.).

Table 1 Additive of VDN cream each formulation

Formulation name	Lot No.	Serial No	Additive
ARASENA-A Cream 3%	022	Ara-A	stearic acid, palmitic acid, cetanol, glyceryl monostearate self mulsifying, concentrated glycerin, D-sorbitol solution (70%), sodium hydroxide, potassium hydroxide, methyl parahydroxybenzoate, propyl parahydroxybenzoate
Casal® Cream 3%	6A07V	Ara-B	liquid paraffin, white petrolatum, polydimethylsioxane, cetearyl alcohol, behenyl alcohol, concentrated glycerin, 1,3-butylene glycol, macrogol 1500, glyceryl triisooctanoate, citric acid hydrate, sodium citrate hydrate, glyceryl triisooctanoate, citric acid hydrate, sodium citrate hydrate, polyoxyethylene hydrogenated castor oil 60, lauromacrogols, glyceryl monostearate, ethyl-4-hydroxybenzoate, xanthan gum
ARASENA S Cream	XXWL	Ara-C	stearic acid, palmitic acid, cetanol, glyceryl monostearate self mulsifying, glycerin, D-sorbitol solution, sodium hydroxide, potassium hydroxide, paraben

Methods

Uniformity of content test: For the assay, 1.0 g of each cream was accurately weighed and placed in a stoppered centrifuge tube. Then 40 mL of diisopropyl ether /0.1 N HCl (1:1) was added and the solution was shaken (200 rpm for 5 min, at 25 °C). The lower layer was removed and 20mL of 0.1 N HCl was added to the upper layer and the solution was shaken. This step was repeated three times. 0.1M HCl was added to the lower layer to reach 100 mL. This served as the sample solution. A calibration curve was prepared using VDN. VDN was assayed using high-performance liquid chromatography (HPLC: e2695, Waters). VDN assay conditions were a column of Inertsil® ODS-3 (4.6mm × 150mm, φ5μm), a column temperature of 40 °C, a mobile phase of 0.1 M KH_2PO_4, and a detection wavelength of 258 nm; conditions were tailored for VDN to produce a peak at 30min.

Measurement of flattening: Spreadability was measured using a spread meter (Rigo) with a measuring temperature of 25 °C. Spread diameter was measured after 5, 10, 30, 60, 120, 180, 240, 300, 360, 600 and 900 s. The yield value was calculated from the following formula using the spread diameter after 120 s.

$F = 47040*G*V/\pi^2*D^5$

F: yield value (dyne/cm^2)

G: glass plate weight (115.5 g)

V: sample size (cm^3)

D: diameter (mm) when sample spreading stopped

Viscosity and viscoelasticity: 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'x R24 cone rotor. Dynamic viscosity was measured at 1 rpm and was read after rotation for 200 s. The viscoelasticity was measured at a shear rate of 0 s-1-10 s-1→ 10 s-1-0 s recovery of viscosity per second (Epa (Pa·s)), stress (Tau (Pa)). The viscoelasticity of each

sample was measured 3 times under the same conditions.

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

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 10000-4000 cm^{-1} spectra were recorded for 8 sec at a temperature of 25ºC. Each sample was placed in a sample cup, and near-infrared absorption spectra were measured at 1 nm intervals.

pH measurement: The pH of each cream was measured using a pH meter (Sartorius Co., Ltd.). In addition, 0.05 g of each cream was weighed and measured and then dispersed in 5 mL of distilled water to prepare a dispersion. Measurement was performed 3 times at room temperature.

Retention on filter paper test: Point-one g of each cream was precisely weighed. Each cream was spread on filter paper (φ70 mm, 38.47 cm^2) 3 times (3 times along the entire length of the paper and 3 times along the side of the paper) and left to stand for 10 min. Fifty mL of physiological saline was added and the mixture was shaken (25°C, 100 rpm, 5 min). Afterwards, the filter paper was added to a solvent mixture (diisopropyl ether/0.1M HCl = 25 mL/25 mL) and the resulting mixture was shaken for 5 min. The lower layer was removed, separated by centrifugation (25 °C, 10000 rpm, 30 min), and filtered using 0.45 μm filter. The filtered solution served as the sample. The sample was assayed using HPLC. Saline was used to simulate sweat.

Measurement of skin friction: The skin friction produced by each sample was measured using the Frictiometer FR700 (Curage+Khazaaka). Point-one g of each sample was applied to artificial skin, and skin friction at 25 °C was measured by agitation for 21 seconds at 25 rpm.

Statistical analysis: Statistical analysis was performed using Tukey's test, with $p < 0.05$ considered to indicate a significant difference.

RESULTS AND DISCUSSION

Uniformity of content test: A uniformity of content test was conducted to assess the equivalence of VDN content in each formulation. Results indicated that the VDN content in Ara-A was 101.4%, that in Ara-B was 100.8%, and that in Ara-C was 101.6% (Table 2). Tukey's test revealed no differences in the uniformity of content in the three creams.

Table 2 Content uniformity of creams (n=4)

Formulation	Uniformity (mean±S.D.)
Ara-A	101.4±0.2
Ara-B	100.8±0.1
Ara-C	101.6±2.0

Measurement of flattening: The creams were evaluated for their spreadability and their yield value was determined using a spread meter [7]. The diameter of the spread of a cream in 120 s was 30.2 cm for Ara-A, 35.0 cm for Ara-B, and 29.2 cm for Ara-C (Table 3, Fig. 1). The slope of the spread of Ara-B over time differed from that of Ara-A and Ara-C. Ara-A had a yield value of 1109.8 dyne/cm^2, Ara-B had a yield value of 527.7 dyne/cm^2, and Ara-C had a yield value of 1200.1 dyne/cm^2 (Fig. 2). The spreadability of the formulations presumably indicates differences in moisture content and additives. Ara-C contains white petrolatum and Ara-B contains a liquid paraffin. These additives are presumably responsible for the viscous properties of the creams. The yield value for Ara-B indicates a shift in stress from elastic deformation to flow deformation. The yield value for Ara-B was lower than that for Ara-A and Ara-C, indicating a cream with greater spreadability.

Table 3 Spreadability of VDN creams at 25ºC

Formulation	Spreadability (meam± S.D.)
Ara-A	30.3±0.8
Ara-B	35.0±0.9
Ara-C	29.7±0.3

Value of the spreadability after 120 seconds. n=3

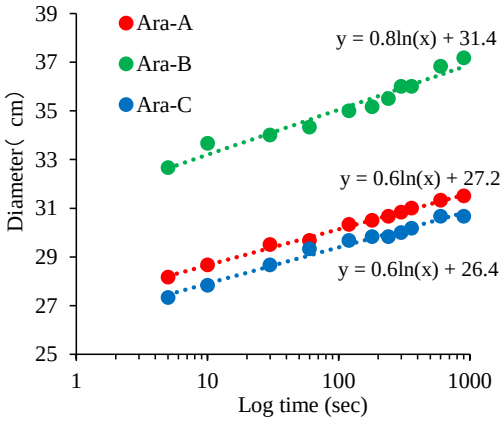

Fig. 1 Average diameter of VDN creams in Logarithm time

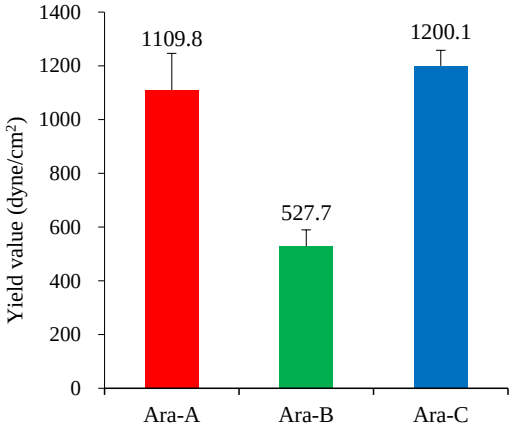

Fig. 2 Yield value of VDN creams at 25°C
Value of the spreadability after 120 seconds. (mean±S.D., n=3)

Measurements of Viscosity and viscoelasticity: The viscosity of each cream was measured in order to examine the spread of each cream in response to stress. Those measurements are shown in Fig. 5. After 200 s, Ara-A had a viscosity of 1.01 Pa·s, Ara-B had a viscosity of 0.42 Pa·s, and Ara-C had a viscosity of 1.02 Pa·s (Fig. 3). Ara-A and Ara-C contain similar additives, so they behaved similarly. However, the additives in Ara-B differed from those in Ara-A and Ara-C, so this difference in additives presumably resulted in different viscosity measurements.

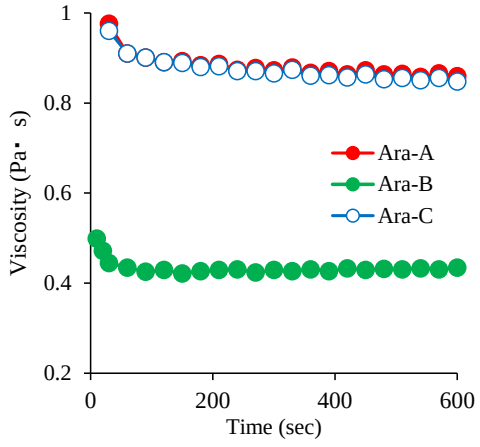

Fig. 3 Viscosity curves of VDN creams

Since differences in the viscosity of each cream were noted, the viscoelastic properties of Ara-A, Ara-B, and Ara-C were evaluated (Fig. 4). Ara-B had little shear stress and its viscosity and viscoelasticity differed from those of Ara-A and Ara-C. Thus, the latter two are firm creams with a high shear stress, so Ara-B is more pliable than Ara-A and Ara-C. This correlates with the viscosity results. The rheogram when shear stress increased did not match the rheogram when it decreased. Instead, a hysteresis loop was exhibited. This is because the internal structure needs time to recover [8], so Ara-B had a structure that was less susceptible to damage than did Ara-A or Ara-C.

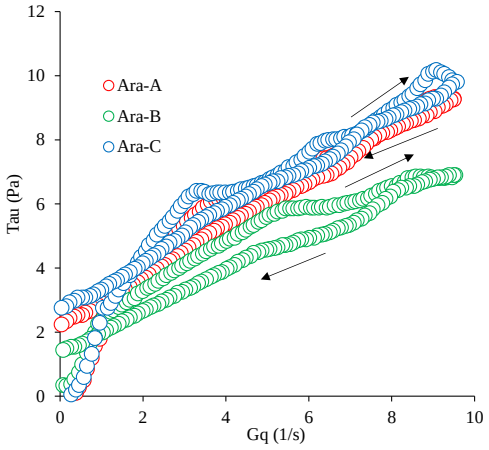

Fig. 4 Shear stress versus shear speed curves of VDN creams

Repeated measurements were made to identify changes in the robustness of the internal structure and changes in the viscosity and viscoelasticity of each cream (Fig. 5). When subjected to repeated stress, Tau (viscosity) for Ara-A and Ara-C decreased in the 2nd and 3rd runs in comparison to the 1st run. Thus, the internal structure of Ara-A and Ara-C is disrupted by shear stress, and Ara-A and Ara-C display similar viscosity and viscoelasticity. However, the Tau for Ara-B changed little even when the cream was repeatedly subjected to shear stress. This indicates that Ara-B has a viscoelasticity that allows it to retain its internal structure somewhat even when subjected to shear stress. The yield value and spreadability similarly indicated that the initial spreadability of Ara-A and Ara-C differ from that of Ara-B.

The flow curve area for Ara-B decreased as the cream was subjected to shear stress. Thus, Ara-B is more pliable and its structure is less susceptible to disruption even when the cream is subjected to stress. Ara-A and Ara-C are firm creams that become more pliable when subjected to repeated stress.

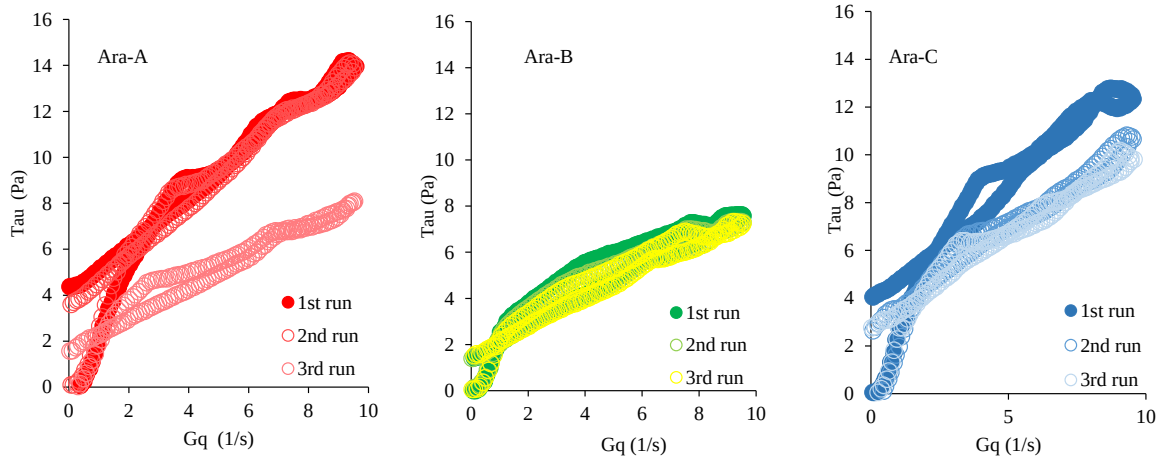

Fig. 5 Viscoelasticity curves of each VDN creams at repeated measurements

Measurement of water content: The water content in each formulation was determined. Results indicated that Ara-A had a moisture content of 56.4 ± 0.9%, Ara-B, had a moisture content of 59.8 ± 0.4%, and Ara-C had a moisture content of 56.3 ± 2.0%. This indicated that the moisture content in each formulation differed.

Evaluation of Near-infrared absorption spectroscopy: Near-infrared absorption spectra were recorded to verify the differences in water or oil content in each formulation (Fig. 6). An absorption spectrum due to the olefin group ($-CH_2$) of the oleaginous base is observed in the vicinity of 4300cm^{-1} and 5800cm^{-1} [9]. The spectrum due to the hydroxyl group (-OH) caused by moisture is known to be observed around 5200cm^{-1} [10]. The current study evaluated the oil and water content of each formulation with a focus on these spectra. The second derivative of the near-infrared absorption spectrum (Fig.6-b) revealed that Ara-B had spectral intensity around 4300cm^{-1} due to the olefin group which was lower than that of Ara-A and Ara–C. Moreover, Ara-B had a lower spectral intensity in the vicinity of 5200cm^{-1} due to the hydroxyl group compared to Ara-A and Ara-C (Fig. 6-a). Infrared absorption spectra revealed that Ara-B has a higher water content than Ara-A and Ara-C, and this finding correlated with the measured water content. Viscosity measurements indicated that the spreadability of Ara-B differed from that of the other two formulations. That is, the difference in moisture or oil content and emulsification of each formulation are factors that are presumably responsible for the spreadability of the formulation.

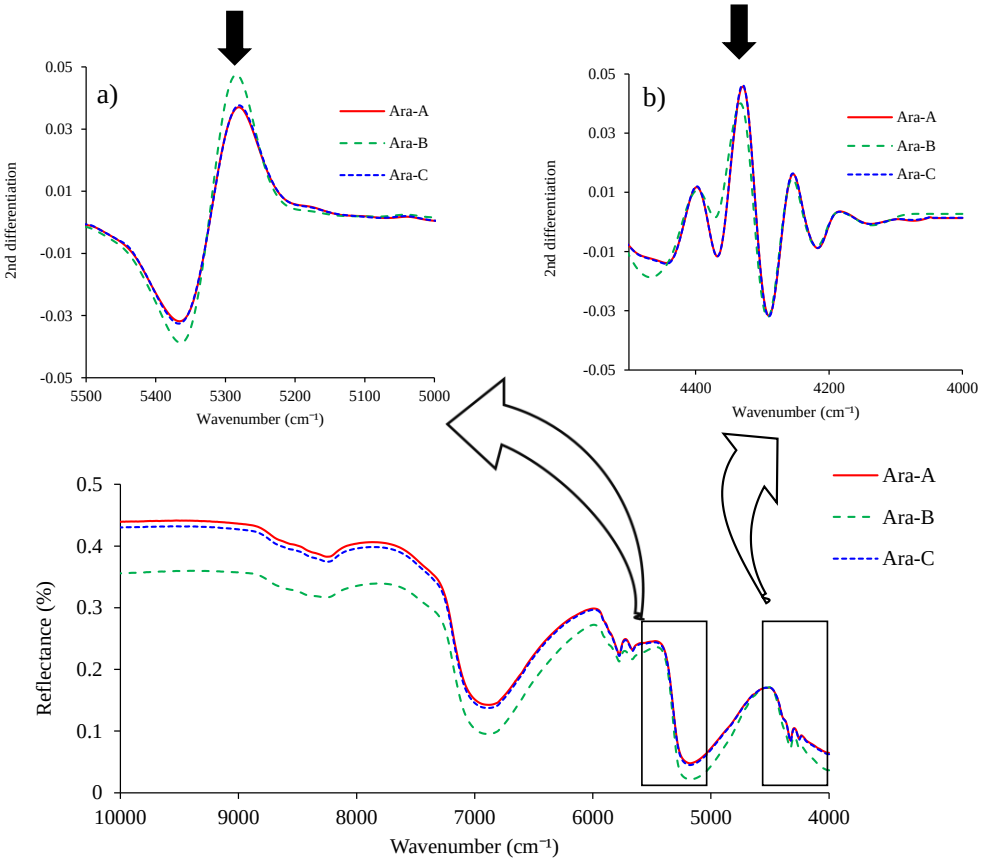

Fig. 6 Near-infrared absorption spectra of VDN creams. Observed to 4000-10000 cm^{-1}.
a) 2nd differential Near-infrared absorption spectra of VDN creams. Observed to 5000-5500 cm^{-1},
b) 2nd differential Near-infrared absorption spectra of VDN creams. Observed to 4000-4500 cm^{-1}.

Since there were differences in the additive content and different additives in the formulations, these differences presumably affected the water content and oil content of the formulations. Principal component analysis [11] was used to analyze the principal component of the difference among the three formulations (Fig. 7). The principal component (PC1) for Ara-A and Ara-C differed from that for Ara-B. Given the evaluation of the physical properties of the creams and signs of differences in the spreadability of the creams, PC1 presumably reflects differences in the water content of each formulation.

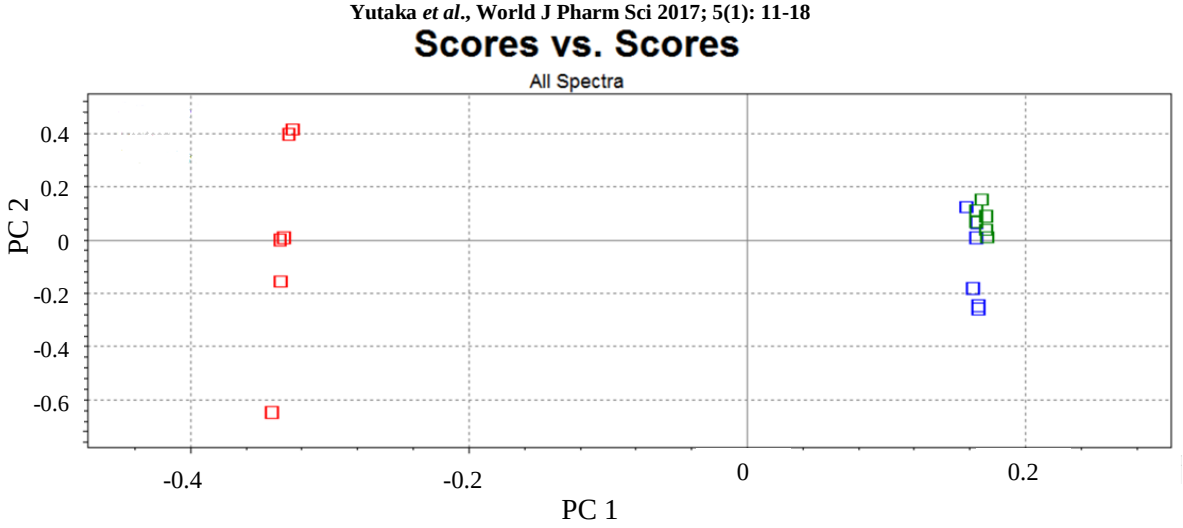

Fig. 7 Principal component analysis
Green square: Ara-A, Red square: Ara-B, Blue square: Ara-C

Study on pH measurement: pH was measured to evaluate the adaptability of each formulation to the skin. Each sample was dispersed in distilled water to form a suspension. Ara-A had a pH of 6.68 ± 0.04, Ara-B had a pH of 4.84 ± 0.06, and Ara-C had a pH of 6.66 ± 0.05. In suspension, Ara-A had a pH of 6.94 ± 0.03, Ara-B had a pH of 5.05 ± 0.02, and Ara-C had a pH of 7.04 ± 0.02. These results, verified that Ara-A and Ara-C had a neutral pH that was roughly comparable. Ara-C had a weakly acidic pH. Ara-A and Ara-C are formulated with sodium hydroxide and potassium hydroxide as pH-adjusting agents. Ara-B is formulated with sodium citrate hydrate as a pH-adjusting agent. The pH of Ara-B differed from that of Ara-A and Ara-C, so the difference in pH-adjusting agents presumably led to differences in the pH of the three formulations. Generally, a formulation that is weakly acidic to neutral is desirable for application to the skin. Results indicated that Ara-A, Ara-B, and Ara-C caused little skin irritation, so all three are appropriate formulations for use on the skin.

Retention on filter paper test: Creams are typically affected by sweat [12]. Thus, the current study used normal saline to simulate sweat in order to evaluate how readily VDN creams would be removed [13]. Ara-A had a retention rate of 72%, Ara-B had a retention rate of 50%, and Ara-C had a retention rate of 69% (Fig. 8). Ara-B had a lower rate of retention compared to the other two creams. Measurements of flattening suggested that Ara-B spread more readily than Ara-A or Ara-C. Thus, Ara-B covers a greater area in a thinner layer than Ara-A or Ara-C do. When Ara-B comes into contact with normal saline, it spreads further, so it tends to easily come off the skin. In addition, Ara-B has a higher water content than Ara-A or Ara-C, which presumably explains its greater ease of use. These findings presumably indicate that Ara-A and Ara-C will be retained on the skin more so than Ara-B during profuse sweating.

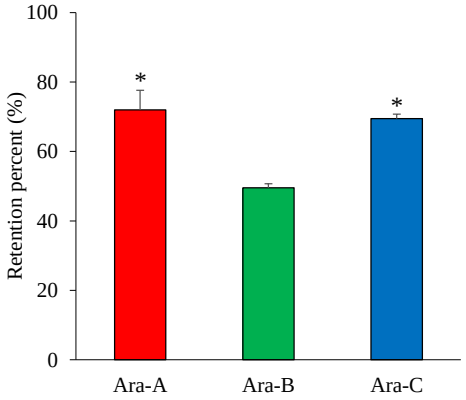

Fig. 8 Retention of filter paper test
Results were expressed as mean±S.D.(n=4)
* : p<0.01 vs Ara-B (Tukey test).

Measurement of skin friction: The Frictiometer was used to measure the force of friction in order to evaluate the feel of the creams when applied to the skin (Fig. 9). A study by Neto et al. reported the use of the Frictiometer to evaluate the feel of cosmetics on the skin [14]. After 20 s, friction generated by Ara-A was 83.8 N, friction generated by Ara-B was 54.4 N, and friction generated by Ara-C was 91.6 N. The magnitude of the force of friction followed the same pattern as the yield value calculated with a spread meter. The force of friction is known to be inversely correlated with a cream's spreadability and slipperiness and it is known to be correlated with a cream's stickiness. Thus, Ara-B would presumably not be as sticky as

Ara-A or Ara-C and it would spread easily when applied to human skin.

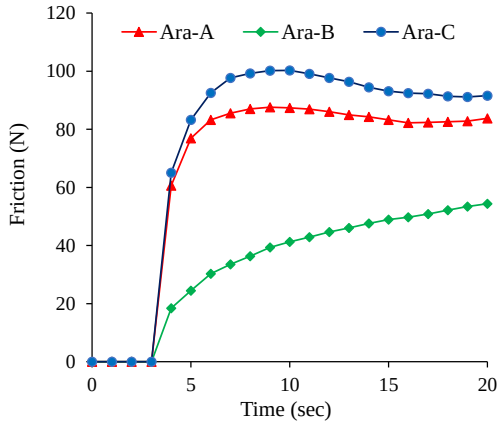

Fig. 9 Skin friction of VDN creams respectively

CONCLUSION

A uniformity of content test revealed that Ara-A, Ara-B, and Ara-C had equivalent VDN content. Microscopy revealed that the creams had good dispersibility. Evaluation of the properties of each cream indicated the physicochemical properties of Ara-A, Ara-B, and Ara-C. A retention on filter paper test and a skin friction test revealed that the properties of Ara-A and Ara-C differed from those of Ara-B. This study is an example of an investigation of the properties of formulations in a model scenario involving a brand-name cream, a generic cream, and an OTC cream. In the future, an important role of pharmacists will be to investigate the properties of OTC formulations. This will help maintain the health of the community and encourage appropriate self-medication.

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Conflicts of Interest:

The authors declare no conflict interest.

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