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Difference in physical properties between brand-name and generic topical 0.3% heparinoid lotions

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Physical properties of a topical 0.3% heparinoid lotion brand-name drug and two generic drugs were evaluated by the spread-meter test for slope, intercept, and yield values and by the fluidity test for the time to flow 100 mm. The effect of application-surface temperature was compared for the specification value of 25 ± 0.5℃ with 31 ± 0.5℃ and 33 ± 0.5℃, which approximated skin temperatures. In the spread-meter test, the generic drugs flowed out within 14 s, which was too short to measure their characteristics properties. The expansion diameters at 5 s of the generic drugs were approximately 1.5 times that of the brand-name drug, confirming their high fluidity. The slopes of the brand-name drug measured at simulated skin temperatures were significantly higher than that at 25 ± 0.5℃ and the yield values were significantly lower, respectively indicating that the product spread more easily and became softer at skin temperatures. The fluidity results indicated that the generic drugs were significantly more fluid than the brand-name drug. These test results revealed that the physical properties differed between the brand-name and generic drugs, indicating that they are more suitable for different topical applications.

Key Words: topical heparinoid lotions, physical properties, generic drugs, skin temperature, spread meter

Introduction

The Japanese government is currently promoting the use of generic drugs as a policy to control increasing medical costs[1]. The Minister of Health, Labour and Welfare approves generic drugs based on evidence that they are confirmed to be equivalent to the respective brand-name drug in a bioequivalence study. It is, however, not necessary for generic drugs to be completely "identical" to the brand-name drug, and so generic drugs can contain different additives[2]. Although the physical properties of drugs have been reported to differ depending on additives of different pharmaceutical formulations[3,4], the bioequivalence study on generic drugs does not validate these properties. Some studies have reported that topical preparations with different physical properties may cause differences in functional usability or even in efficacy[3,4]. It was also reported that generic patches for topical application usually differ in physical properties from those of the brand-name drug[5,6], and that patients placed special emphasis not only on the efficacy but also on functional usability[7]. Furthermore, in application of an ointment or gel preparation, the functional usability of different physical properties affects the drug compliance and it was therefore recommended that the formulation of a topical preparation should be selected by the patients who use it[8]. Physical properties are key information for medical professionals to select a suitable pharmaceutical preparation or conduct pharmaceutical counselling.

In the Japanese Pharmacopoeia (JP XVII), lotions are as defined as "*Lotions are external liquids in which active substance(s) are dissolved, emulsified or finely dispersed in an aqueous*

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vehicle" and is classified into "emulsion lotion", "solution lotion" and "suspending lotion". Especially "emulsion lotion" is a formulation form prepared by emulsifying the base composed of the oily components and the aqueous components with the surfactants. Since previous study, the spread-meter test was used for the physical property comparison of the lotions[5], we used the spread-meter test to explore the difference in the physical properties of brand-name drug A, generic drugs B and C in this experiment.

Concerning topical heparinoid ointments or creams, some physical properties have been reported[9,10], but only a few studies have compared the brand-name and generic topical 0.3% heparinoid lotions. In addition, whereas studies on physical properties are usually conducted at room temperature, no study has been done under conditions that approximate skin temperature.

In this study, the physical properties affecting functional usability were compared between the brand-name and two generic topical 0.3% heparinoid lotions at temperatures close to actual skin temperature, to provide information to enable selection of the most appropriate drug for a specific patient application.

Methods

1. Materials

Brand-name topical 0.3% heparinoid lotion A and generic lotions B and C were used. Before the tests, the drugs were held for 1 h in a water bath (Thermominder SDminiN, No. 3062017, TAITEC, Japan) that was set to 25°C.

2. Test methods

2-1. Spread-meter test

The test followed the *Method using Spread Meter*, as specified by JIS K5701-1:2000, Lithographic inks-Part 1: Test methods[11]. The temperature of the laboratory was held at 25 ± 2℃. In addition to the value of 25 ± 0.5℃ specified by the standard, the application-surface temperatures of the spread meter were also set to 31 ± 0.5℃ or 33 ± 0.5℃ to simulate actual mean skin temperature[12]. Each drug was applied onto the meter to measure the spread diameter (mm) at selected times (5, 10, 50, 100, 150, or 200 s). When the drug flowed beyond at least one of the four sides of the fixing plate of the spread meter, the time to scale-over was measured (scale-over time). The test was conducted six times for each application-surface temperature. Mean values of slope (S) [11], intercept (IC) [11,13], yield value (YV) [11], and scale-over time were calculated as follows:

$$S = (D_2 - D_1)/\log 10\ (T_2/T_1), \quad (1)$$

where D_1 and D_2 are the spread diameters (mm) at measuring times (s) T_1 and T_2, respectively, where $T_2 > T_1$, $5 \leq T_1$, $T_2 \leq 100$, and $\Delta T = (T_2 - T_1) > 40$. In this test, T_1 was set to 10 s and T_2 to 100 s.

$$IC\ (\mathrm{mm}) = D_2 - 2(D_2 - D_1) = 2D_1 - D_2. \quad (2)$$

$$YV\ (\mathrm{Pa}) = (4.8\ WVG)/(\pi^2 D_\infty^5), \quad (3)$$

where W is the mass of the loading glass-plate (kg), V is sample volume (m^3), G is the standard free-fall velocity (m/s^2), and D_∞ is the maximum spread diameter (m) at 200 s.

2-2. Fluidity test

The test followed the measurement method of *Fluidity* by Horisawa et al[14]. Using a syringe, 0.5 mL of the test drug preparation was dropped onto an acrylic resin plate, the elevation angle of which was set to 45° , and the time (s) taken to move a distance of 100 mm was measured in a room held at 25 ± 2℃. Each test was conducted six times and the mean values calculated. When the distance moved by the cut-off time (300 s) was less than 100 mm, the distance moved at that time point was measured and the mean values calculated.

3. Statistical analysis

The spread diameter at 5 s was compared between the brand-name and generic drugs, and the slope, intercept, and yield values measured at the application-surface temperature at 25 ± 0.5℃ were compared with those at 31 ± 0.5℃ and 33 ± 0.5℃ using the multiple comparison Dunnett's T3 test. The statistical significance

level was set at a *p*-value below 0.05. All analyses were conducted using *SPSS* software (version 20.0, IBM, Japan).

Results

2-1. Spread-meter tests

Figure 1 shows the spread-meter test results. Brand-name drug A slowly spread until 200 s at all application-surface temperatures. The mean values of spread diameters on the application-surface temperature at 25 ± 0.5℃ were 48.92 ± 0.49 mm (mean ± standard deviation, S.D.) and 61.00 ± 2.43 mm at 5 and 200 s, respectively. Similarly, these values were 49.67 ± 0.75 mm and 65.92 ± 1.07 mm at 31 ± 0.5℃ and 49.67 ± 0.61 and 64.83 ± 1.51 mm at 33 ± 0.5℃ after 5 and 200 s, respectively. In contrast, the spread diameters of generic drugs B and C were measurable only at 5 s. The mean scale-over times of generic drugs B and C were 10.5 ± 2.26 s and 8.2 ± 1.17 at 25 ± 0.5℃, respectively, 8.8 ± 0.41 s (B) and 8.2 ± 0.98 s (C) at 31 ± 0.5℃, and 9.8 ± 0.75 s (B) and 7.8 ± 0.75 s (C) at 33 ± 0.5℃. All drugs spread out from within 14 s at all application-surface temperatures. In consequence, it was not possible to calculate the characteristic values of *S*, *IC*, and *YV* of the

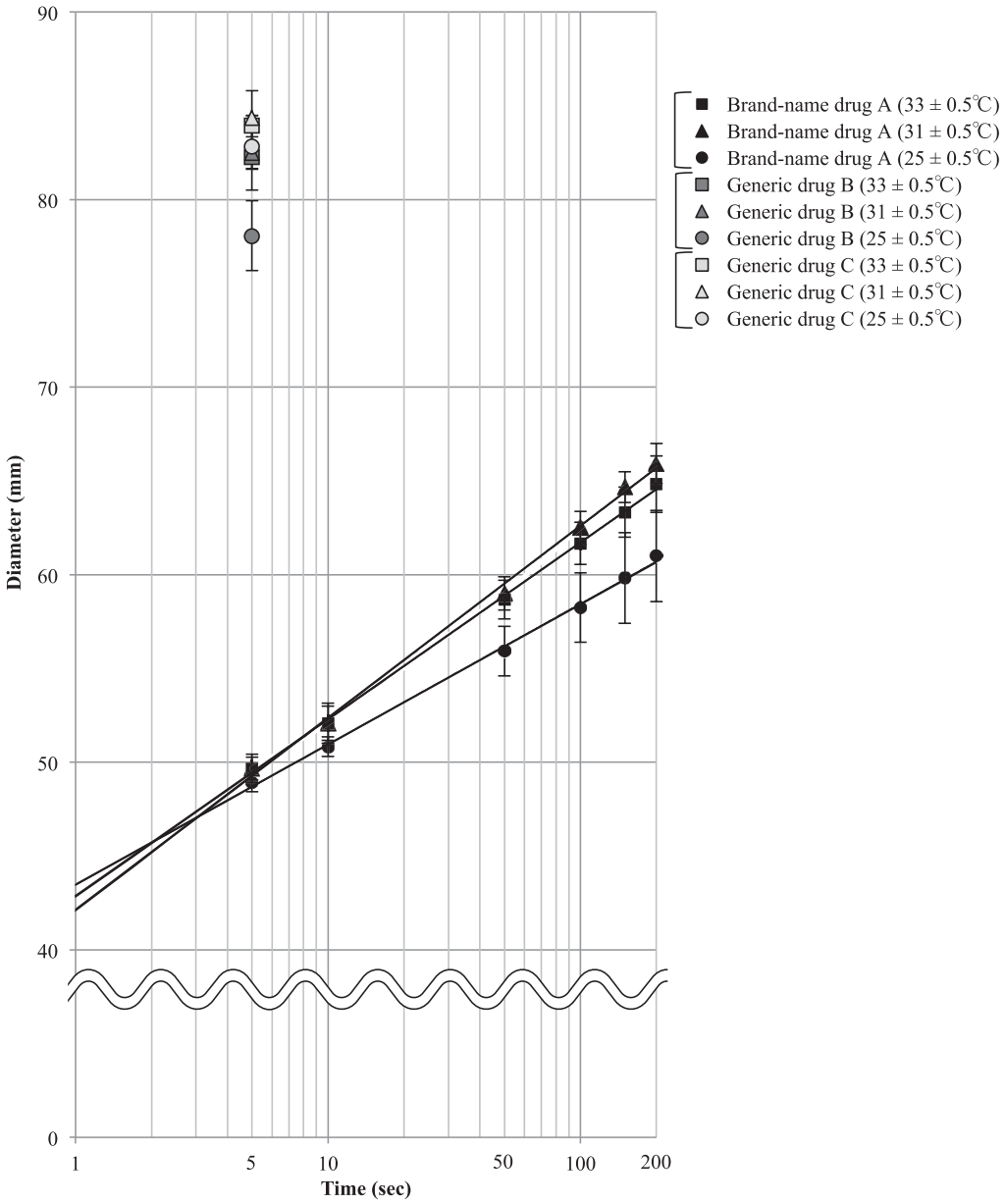

Fig. 1. Mean values of spread diameter of 0.3% topical heparinoid lotions measured by spread meter at different application-surface temperatures. (*n* = 6, mean ± standard deviation)

generic drugs.

Figure 2 shows the mean values of the 5 s spread diameters of the three drugs at each application-surface temperature. In comparison with brand-name drug A (48.92 ± 0.49 mm at 25 ± 0.5℃), the spread diameters of generic drugs B and C were significantly larger at 78.08 ± 1.86 mm ($p < 0.001$) and 82.83 ± 1.21 mm ($p < 0.001$), respectively. Even at 31 ± 0.5℃ and 33 ± 0.5℃, the mean spread diameters of the generic drugs at 5 s were significantly larger than that of brand-name drug A ($p < 0.001$ for all

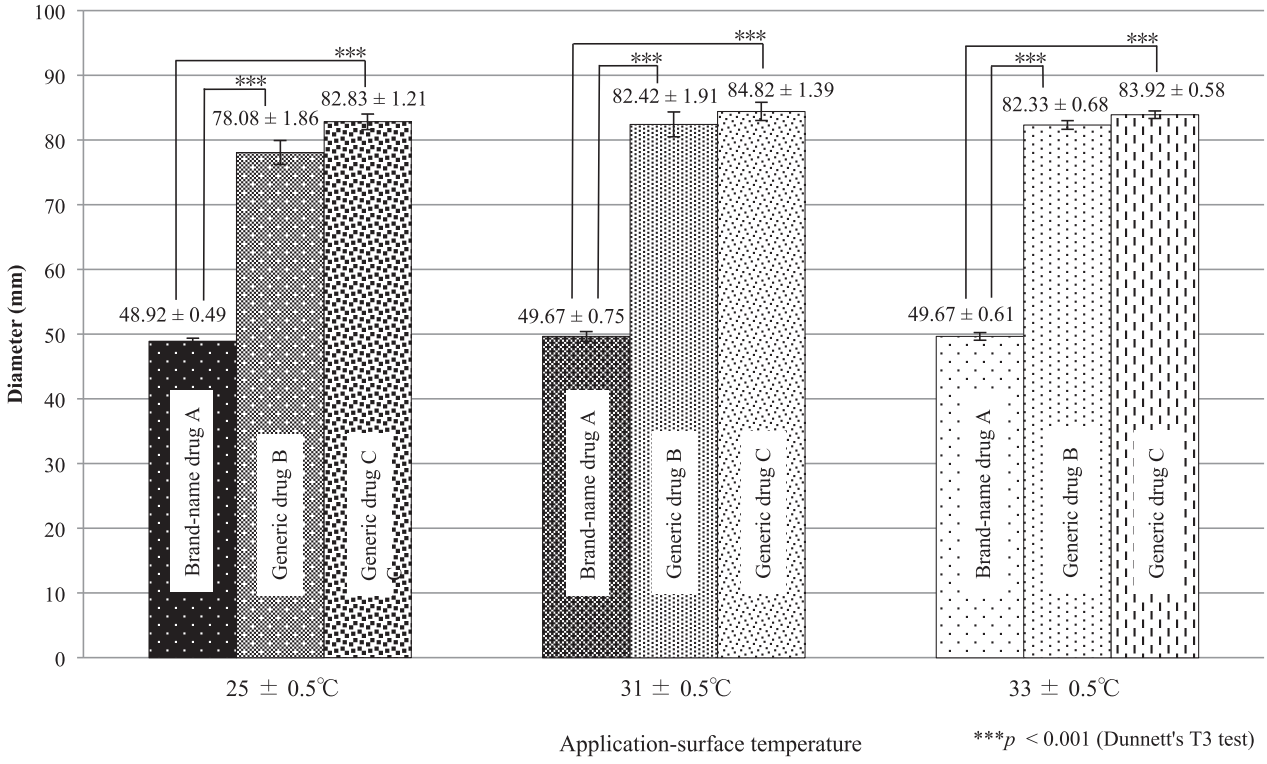

Fig. 2. Spread diameter at 5 s of brand-name and generic 0.3% heparinoid lotions measured by spread meter at different application-surface temperatures. (n = 6, mean ± standard deviation)

cases).

Table 1 shows the *S*, *IC*, and *YV* indices for brand-name drug A at each application-surface temperature. When looking at changes with application-surface temperature, the *S* value of 10.42 ± 0.20 at 31 ± 0.5℃ was significantly higher than that of 7.42 ± 1.59 at 25 ± 0.5℃ ($p < 0.05$). There was no significant difference between the value of 9.58 ± 0.38 at 33 ± 0.5℃ and that at 25 ± 0.5℃. *IC* showed no significant difference in comparison of values of 43.42 ± 1.46 mm at 25 ± 0.5℃ with 41.67 ± 0.98 mm at 31 ± 0.5℃ and 42.50 ± 1.14 mm at 33 ± 0.5℃. *YV* was 0.22 ± 0.02 Pa at 31 ± 0.5℃ and 0.24 ± 0.03 Pa at 33 ± 0.5℃, both values being significantly lower than that of 0.33 ± 0.07 Pa at 25 ± 0.5℃ ($p < 0.05$ in all cases).

2-2. Fluidity tests

Table 2 shows the fluidity test results. Brand-name drug A did not reach 100 mm within the cut-off time of 300 s: the mean distance moved was 75.17 ± 1.72 mm. In contrast, the mean times for movement of 100 mm of generic drugs B and C were 0.69 ± 0.07 s and 0.51 ± 0.04 s, respectively.

Discussion

The purpose of this study is to compare the differences in physical properties of brand-name and generic drugs. Generally, variations in quality include variations among lots of the same product and variations in brand-name drug and other generic drug of the same pharmaceutical compound. However, with regard to the former, only pharmaceuticals conforming to approved

Table 1. Slope (*S*), intercept (*IC*), and yield value (*YV*) of 0.3% heparinoid lotions measured by spread meter. (*n* = 6, mean ± standard deviation)

	Application-surface temperature	*S*	*p*-value	*IC* (mm)	*p*-value	*YV* (Pa)	*p*-value
Brand-name drug A	25 ± 0.5°C	7.42 ± 1.59	—	43.42 ± 1.46	—	0.33 ± 0.07	—
	31 ± 0.5°C	10.42 ± 0.20	0.015*	41.67 ± 0.98	0.104	0.22 ± 0.02	0.021*
	33 ± 0.5°C	9.58 ± 0.38	0.052	42.50 ± 1.14	0.562	0.24 ± 0.03	0.049*
Generic drug B	25 ± 0.5°C	N.D.**	—	N.D.	—	N.D.	—
	31 ± 0.5°C	N.D.	—	N.D.	—	N.D.	—
	33 ± 0.5°C	N.D.	—	N.D.	—	N.D.	—
Generic drug C	25 ± 0.5°C	N.D.	—	N.D.	—	N.D.	—
	31 ± 0.5°C	N.D.	—	N.D.	—	N.D.	—
	33 ± 0.5°C	N.D.	—	N.D.	—	N.D.	—

* $p < 0.05$ (Dunnett's T3 test)

** not determined

Table 2. Time taken by 0.3% heparinoid lotions to move 100 mm on acrylic resin plate. (*n* = 6, mean ± standard deviation)

	Time (s)	Distance at cut-off time (mm)
Brand-name drug A	> 300 (cut-off time)	75.17 ± 1.72
Generic drug B	0.69 ± 0.07	—
Generic drug C	0.51 ± 0.04	—

standards are in the market and it is considered that there is no variation in quality among lots of the same product in the market. Therefore, in this study, we do not consider the physical properties due to differences between lots and focused on physical differences between products of brand-name and generic drugs.

The spread meter is used to calculate the slope, intercept, and yield values of ointment preparations[9,15]. In these tests, brand-name drug A slowly spread until 200 s after the start of the test, making it possible to measure the spread diameter; however, generic drugs B and C flowed out of the fixing plate within 14 s, making it impossible to calculate their values. The physical properties of generic drugs B and C suggested a definite greater spread in comparison with brand-name drug A. Furthermore, the mean spread diameters of generic drugs B and C at 5 s were more than 1.5 times larger than that of brand-name drug A at the three application-surface temperatures tested.

Brand-name drug A is categorized for lotion preparation, having excellent spreadability when compared with ointments and creams containing the same active ingredient (Hirudoid® Cream 0.3%, Hirudoid® Soft Ointment 0.3%, and Hiludoid® Lotion 0.3%. Pharmaceutical Interview Forms, revised in Feb. 2016 (Ver.9)); however, generic drugs B and C were more spreadable than brand-name drug A. Generic drugs B and C are accordingly presumed to spread too far at narrow application sites, such as fingers and arms, when compared with drug A: the generic drugs will remain for a shorter period at the affected site, but may be more easily applied onto broad sites,

such as the back and chest, within a short time.

Of the property characteristics calculated for brand-name drug A, *S* was 10.42 ± 0.20 at 31 ± 0.5℃, which was larger than the value of 7.42 ± 1.59 measured at 25 ± 0.5℃. This allowed better spreading at higher temperature. *YV* was 0.22 ± 0.02 Pa at 31 ± 0.5℃ and 0.24 ± 0.03 Pa at 33 ± 0.5℃, compared with 0.33 ± 0.07 Pa at 25 ± 0.5℃, indicating that it became softer with higher application temperature. In these tests, the *IC* value showed no significant difference at the different temperatures. It is therefore considered necessary to evaluate these physical properties of topical preparations, which are likely to significantly affect the method of application and functional usability, at an application-surface temperature approximating that of skin.

In the fluidity test, fluidity was considered to be higher when the time required to move a specified distance was shorter. When compared with brand-name drug A, generic drugs B and C both reached 100 mm distance within 0.78 s, suggesting that the fluidity of these preparations is quite high. All three drugs can be efficiently applied without waste to sites such as the palm and back of a hand, which are relatively easy to keep horizontal; however, the highly fluid generic drugs may drop off or spill over to other than the target at affected sites such as the face or neck, which are difficult to keep horizontal. This results not only in excessive drug use, but also influences its efficacy because insufficient drug is retained at the affected site[15]. In contrast, in cases of application onto a broad area, such as the back and extremities, the highly flowable generic drugs B and C are more convenient to apply and can shorten the application time, when compared with brand-name drug A. For example, it was considered that generic drugs B and C were suitable for pain owing to circulatory disturbance with a wide affected part and brand-name A was suitable for thrombophlebitis with a narrow affected part.

The additives are different between brand-name drug A and generic drugs B and C. The additives include the oily components, the surfactants, etc. The oily components are mixed in the additives of brand-name drug A. However, the additives of generic drugs B and C do not contain the oily components. It was inferred that difference of additives influences physical properties in this study.

In this pilot study based on the use of an appropriate application-surface temperature to compare the physical properties of brand-name and generic drugs, the results revealed that their physical properties did differ: it was not possible to calculate the indices *S*, *IC*, or *YV* of the generic drugs. Pharmacists should therefore select drugs appropriate for the patient application based on their physical properties.

Conflicts of Interest

The authors declare no conflicts of interest.

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