Brief Report

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Differences in fluidity and viscosity of brand-name and generic injectable ointment

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SUMMARY Generic medications contain the identical active ingredient in the same concentration as their branded counterparts and are administered in the same manner, aiming to deliver comparable efficacy, dosage, and clinical outcomes. Nevertheless, variations in additives and formulation processes, particularly noticeable in topical medications, can influence factors like ease of use and patient adherence. Therefore, in this study, we aimed to compare the rheological attributes of branded and generic injectable ointments, assessing disparities in formulation performance and their impact on patient care. Posterisan® Forte and Hemoporison® ointments were used as the branded and generic versions, respectively, and their viscosity, ductility, and viscoelastic properties were evaluated. Posterisan® Forte showcased enhanced spread ability, maintaining uniform flow characteristics across varying temperatures, whereas Hemoporison® displayed pronounced thixotropic properties and stiffness, suggesting potential benefits for applications necessitating reversible viscosity adjustments and heightened rigidity. Despite sharing identical additives, observable differences in physical characteristics highlight the necessity of understanding formulation traits, which could influence ointment behavior. Alterations in fluidity and viscosity may affect how patients perceive and apply the medication, potentially influencing treatment outcomes and the occurrence of adverse effects.

Keywords Generic drugs, brand-name drugs, injectable ointments, rheological properties, patient treatment

1. Introduction

Generic drugs, which contain the same active ingredient in the same amount as their brand-name counterparts, are administered *via* the same route, and are designed to provide equivalent efficacy, dosage, and clinical effect. Because they bypass the need for extensive drug discovery research and clinical trials (except for bioequivalence studies), generic drugs are typically more affordable. As such, their utilization is advocated for the dual purpose of reducing national healthcare expenditures and alleviating patient financial burdens (*1*).

In Japan, revisions in reimbursement policies have led to a significant expansion in the utilization of generic drugs, with approximately 80% of drugs by sales volume being generics as of September 2023. However, in terms of value, generics account for only 56.7% of drug usage. This discrepancy is partly attributed to the slow adoption of generic alternatives for expensive medications. Moreover, differences in additives and formulation processes between generic and brand-name drugs, particularly in topical formulations, can impact factors such as usability and patient adherence to treatment. For instance, variations in properties like viscoelasticity, even in common additives like white Vaseline, can influence the quality and user experience of topical medications (*2*). Although pharmaceutical formulation guidelines emphasize the importance of ensuring efficacy, safety, quality, and stability, post-marketing considerations such as supply stability and promoting proper medication adherence are equally crucial (*3,4*). Regardless of a drug's efficacy, therapeutic outcomes are contingent upon patients adhering to correct dosage and administration instructions. In the case of topical medications, which are directly applied to the site of action, factors such as texture and usability play a pivotal role. Furthermore, in injectable ointments, the amount of medication dispensed depends on the force applied during administration. Elderly patients, whose physical abilities may decline, may encounter difficulties in administering ointments

effectively, impacting treatment outcomes (*5*).

Therefore, in this study, we aimed to compare the rheological characteristics of brand-name and generic injectable ointments to evaluate potential differences in formulation performance and their implications for patient treatment. Although both brand-name and generic injectable ointments used in this study shared the same additives, discrepancies in physical properties were observed. This emphasizes the importance of understanding formulation characteristics, which may affect ointment behavior.

2. Materials and Methods

2.1. Materials

Posterisan® forte ointment (lot: 7A187, Maruho Co., Ltd., Osaka, Japan) was utilized as the brand-name drug, while Hemoporison® ointment (lot: G142, J-Dorph Pharmaceutical Co., Ltd., Shiga, Japan) served as the generic drug. In terms of composition, both ointments contained identical ingredients: dead Escherichia coli flotation fluid and hydrocortisone, with purified lanolin, white petroleum jelly, and phenol as additives (Table 1).

2.2. Ductility test of ointments

The viscosity and ductility of the injectable ointments was evaluated using a parallel spread meter (Rigo, Tokyo, Japan). The diameter spread of the ointment sandwiched between two glass plates was recorded for up to 300 s. The relationship of the sample diameter to the logarithmic value of the elapsed time was plotted. Viscosity was compared based on the intercept value of this straight line, while the ease of ductility of each formulation was compared based on the slope of the straight line. Ointment ductility tests were conducted three times at 25°C and 37°C for each formulation.

2.3. Evaluation of viscoelasticity of ointments using a rheometer

Rheological measurements of the ointments were performed using a HAAKE MARS rheometer (Thermo Fisher Scientific K.K., Tokyo, Japan) equipped with a parallel plate PP35 (diameter 35 mm, gap 0.3 mm) to measure stress value (Pa), storage modulus (G') and loss modulus (G"). For rate-dependent measurements, stress values were recorded while varying the shear rate from 0 to 500 s^{-1} and then from 500 to 0 s^{-1}, and the area values surrounding the outward and return curves were presented as thixotropy. Stress-dependent measurements were conducted at 25°C and 37°C at a constant frequency (1 Hz) to determine the storage modulus (G'), indicating solid-like properties, and the loss modulus (G"), indicating liquid-like properties.

3. Results and Discussion

Ductility refers to the ability of a material to deform under stress, which in the context of ointments relates to their spread ability and ease of application. We conducted experiments using a spread meter under varied temperature conditions to assess both the reference and generic products. The ductility of Posterisan® forte and Hemoporison® ointments were compared at two different temperatures: room temperature (25°C) and body temperature (37°C) (Figure 1). At 25°C, both ointments differed in their ductility levels. At 37°C, ductility generally increased for both ointments, suggesting easier application on the skin. Posterisan® Forte ointment demonstrated a more facile spread compared to the Hemoporison® ointment, with a significant difference observed under both temperature conditions. To quantitatively com-pare the flow and spread, we utilized the following equation:

$$S = (D2 - D1) / \log10 (T2 / T1) + IC \quad [eq. 1]$$

where S and IC indicate slope and intercept of the equation 1, respectively; D1 and D2 indicate diameter of spread (mm) after time duration T1 and T2 (s).

T1, T2: Measurement time (s) $T2 > T1$, $5 \leq T1$ and $T2 \leq 100$,

$$\Delta T = (T2 - T1) > 40 \quad [eq. 2]$$

The slope of the graph in Figure 1 indicates greater

Table 1. Composition of the ointments used in the study

	Name	Company	Active pharmaceutical ingredients	Additive 1	Additive 2	Additive 3
Brand-name	Posterisan® forte ointment	Maruho Co., Ltd., Osaka, Japan	0.163 ml of a suspension solution of dead *E. coli* bacteria (containing approximately 259 million bacteria) and 2.5 mg of hydrocortisone per Japan Pharmacopoeia	Refined lanolin	White Vaseline	Phenol
Generic-drug	Hemoporison® ointment	J-Dorph Pharmaceutical Co., Ltd., Shiga, Japan	0.163 ml of a suspension solution of dead *E. coli* bacteria (containing approximately 259 million bacteria) and 2.5 mg of hydrocortisone per Japan Pharmacopoeia	Refined lanolin	White Vaseline	Phenol

sample flow with a larger value. The sample flow (S) of Posterisan® Forte ointment differed between the two temperatures, with S = 0.1184 at 25°C and S = 0.0908 at 37°C. Conversely, for the Hemoporison® ointment, the sample flow values were almost identical, with S = 0.0863 at 25°C and S = 0.0841 at 37°C. The spread was determined from the intersetion of the vertical axes as depicted in Figure 1 (T = 1). A higher IC value indicates lower viscosity and greater flow of the sample. For the Posterisan® Forte ointment, the IC values were almost equal, with IC = 2.6784 at 25°C and IC = 2.7434 at 37°C. Conversely, differences were observed for the Hemoporison® ointment, with IC = 2.5005 at 25°C and IC = 2.6567 at 37°C (Table 2). These results indicate that for the Posterisan® Forte ointment, sample flow decreases as the temperature increases, indicated by the decrease in S from 25°C to 37°C. However, for Hemoporison® ointment, the difference in sample flow between the two temperatures was very small, indicating minimal change in sample flow with temperature increase. Overall, this suggests that the sample flow of Posterisan® Forte ointment is more temperature-sensitive compared to Hemoporison® ointment.

The characterization of thixotropic behavior entails examining the area enclosed by the shear rate versus shear stress curves for both the forward and reverse directions, which delineates the yield history following the application of shear. The shear rate-dependent properties of Posterisan® Forte and Hemoporison® ointments at 25°C are illustrated in Figure 2. Upon increasing the shear rate (dg/dt) from 0 to 500 s^{-1}, the corresponding shear stress values (τ) approximately doubled, measuring 1,200 Pa and 2,100 Pa for the Posterisan® Forte and Hemoporison® ointments, respectively. Notably, the area beneath the return curve, indicative of thixotropy, exhibited notable discrepancies between the two formulations. Specifically, the area for Hemoporison® ointment surpassed that of Posterisan® Forte ointment.

Figure 3 shows the relationship between shear stress on the horizontal axis and the storage modulus (G') and loss modulus (G") on the vertical axis, both expressed on a logarithmic scale. For both ointments, the storage modulus (G') at 25°C exhibited a linear region unaffected by increasing shear stress and thus maintaining a solid-like structure. The G' value within this linear region reflects the

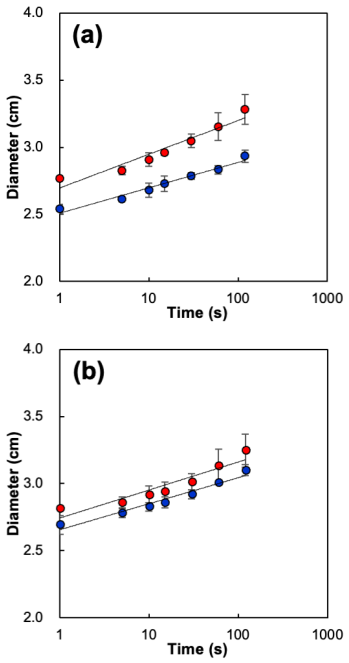

Figure 1. Ductility of Posterisan® forte (red circles) and Hemoporison® (blue circles) ointments at 25°C (a) and 37°C (b).

Table 2. The slope and intercept values of Posterisan® forte and Hemoporison® ointments at 25°C and 37°C

Ointment	Temperature (°C)	slope value	Intercept value
Posterisan® Forte	25	0.1184	2.6784
	37	0.0908	2.7434
Hemoporison®	25	0.0863	2.5005
	37	0.0841	2.6567

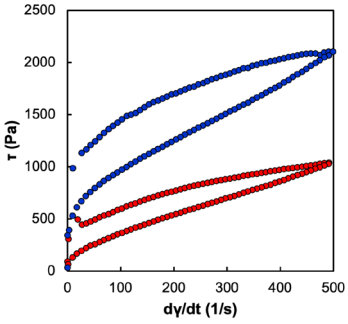

Figure 2. The rate-dependent thixotropic properties of Posterisan® forte (red circles) and Hemoporison® (blue circles) ointments at 25°C.

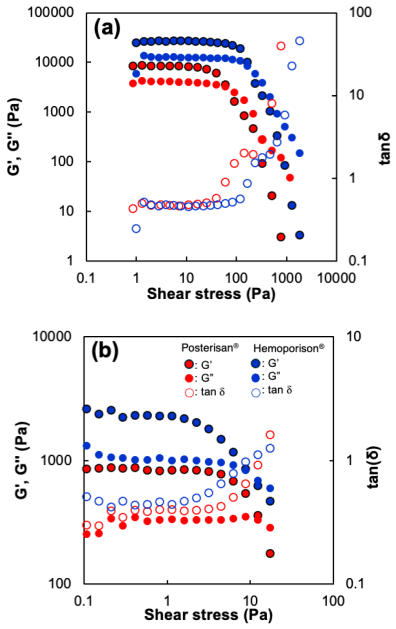

Figure 3. The rate-dependent properties of Posterisan® forte and Hemoporison® ointments at 25°C (a) and 37°C (b).

hardness of the ointment, with Hemoporison® ointment (27,000 Pa) demonstrating higher hardness compared to Posterisan® Forte ointment (8,500 Pa). With increasing shear stress, G' gradually decreased, followed by a rapid decline with additional stress application. The comparison by temperature revealed a notable disparity between the formulations at 25°C; however, at 37°C, both ointments exhibited lower values than those at 25°C, suggesting a temperature-dependent alteration in their rheological properties. At 37°C, the viscosity of Posterisan® Forte ointment measured 800 Pa, whereas that of Hemoporison® ointment was 2,200 Pa. Despite a decrease in viscosity relative to 25°C, Hemoporison® maintained a higher viscosity, hinting at inherent differences in composition or formulation. Regarding the loss modulus (G'), Posterisan® Forte ointment exhibited a higher value at 25°C, indicative of greater energy dissipation during deformation, potentially influencing its flow and deformation characteristics. The behavior at 37°C indicated a convergence between the two formulations, with the loss modulus (G'') closely mirroring the storage modulus (G'). This convergence suggests a mitigated distinction between the formulations at elevated temperatures compared to those at 25°C. These findings underscore the significance of temperature in modulating the rheological properties of the formulations, revealing differential responses under varying conditions.

The study provides valuable insights into the rheological behavior of Posterisan® Forte and Hemoporison® ointments, highlighting differences in spread ability, thixotropic properties, and stiffness between the two formulations. Injectable ointments are preferred to be easily extrudable from the tube at the intended usage temperature of 25°C, indicating good spread ability. Additionally, it is desirable for the ointment to maintain its shape after injection at body temperature (37°C). Using a spread meter, we compared the elongation of the ointments at 25°C and 37°C, assuming the temperature during use and after injection, respectively (Figure 1). At 25°C, the elongation of Posterisan® Forte ointment was significantly higher than that of the Hemoporison® ointment. In contrast, at 37°C, Posterisan® Forte ointment tended to elongate more, but not significantly more than the Hemoporison® ointment. Posterisan® Forte demonstrated superior spread ability, maintaining consistent flow values across different temperatures, whereas Hemoporison® exhibited greater thixotropic behavior and stiffness, indicating potential advantages in applications requiring reversible viscosity changes and increased rigidity. These variations in rheological properties between brand-name and generic ointments could impact patient experience and treatment efficacy. Changes in fluidity and viscosity may influence patient perception and application behavior, potentially affecting treatment outcomes and the risk of side effects. Therefore, precise guidance on application amounts is essential to ensure appropriate use and minimize potential adverse effects. Although generic drugs are increasingly popular, concerns about their quality persist among patients, particularly regarding differences in additives and formulation properties (*6*). Although both Posterisan® Forte and Hemoporison® ointments used in this study share the same additives, discrepancies in physical properties were observed. This emphasizes the importance of understanding formulation characteristics, including container hardness and injection diameter, which may affect ointment behavior. Further research is needed to explore the implications of these findings in clinical practice, considering individual differences in usability and therapeutic efficacy. Additionally, ongoing investigation into other drugs and their rheological properties is warranted to optimize their use and enhance patient outcomes in pharmaceutical and cosmetic applications.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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