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Differences in the rheological properties and mixing compatibility with heparinoid cream of brand name and generic steroidal ointments: The effects of their surfactants



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ABSTRACT

Most steroidal ointments contain propylene glycol (PG) and surfactants, which improve the solubility of corticosteroids in white petrolatum. Surfactants aid the uniform dispersal of PG within white petrolatum. Since the surfactants used in generic ointments are usually different from those used in brand name ointments, we investigated the effects of surfactants on the rheological properties of three brand name ointments and six equivalent generic ointments. We detected marked differences in hardness, adhesiveness, and spreadability among the ointments. Further examinations of model ointments consisting of white petrolatum, PG, and surfactants revealed that the abovementioned properties, especially hardness and adhesiveness, were markedly affected by the surfactants. Since steroidal ointments are often admixed with moisturizing creams prior to use, we investigated the mixing compatibility of the ointments with heparinoid cream and how this was affected by their surfactants. We found that the ointments containing glyceryl monostearate demonstrated good mixing compatibility, whereas those containing non-ionic surfactants with polyoxyethylene chains exhibited phase separation. These results were also consistent with the findings for the model ointments, which indicates that the mixing compatibility of steroidal ointments with heparinoid cream is determined by the emulsifying capacity of the surfactants in their oily bases.

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1. Introduction

In Japan, the government has suggested that the use of the generic drugs could help to reduce the cost of the country's healthcare system, and this also applies to topical medicines such as ointments. As is the case for orally administered drugs, generic ointments usually have different ingredients from brand name ointments [1–4]. For orally administered drugs, differences in ingredients between brand name and generic drugs usually do not result in variations in their bioavailability; i.e., clinical tests indicate that they are bioequivalent [5]. On the other hand, for topical medicines it is likely that differences in the ingredients of brand name and generic medicines will result in differences in their rheological properties such as their hardness, adhesiveness, spreadability, and viscosity, which could in turn affect the way they feel and/or the skin absorption of the drugs contained within

them. In fact, in a study by Yamamoto et al. of five brand name steroidal ointments and seven corresponding generic products, differences in spreadability were detected between the brand name ointments and the equivalent generic ointments [2]. They suggested that the differences in the spreadability of the brand name and generic products might have been caused by species and quality differences in the ointment bases and additives used. Another study found differences in the viscosity and elasticity of brand name acyclovir creams and two generic products, which caused them to feel different [6]. Furthermore, differences in the concentration of solubilized steroids in white petrolatum were detected by Ohtani et al. [1], which seemed to induce changes in their physiological activities.

Steroidal ointments often contain propylene glycol (PG) as a solvent because corticosteroids are poorly soluble in white petrolatum, which is used as a base, and the solubilized concentration of steroids is often lower than the displayed concentration [1,3]. In addition to PG, non-ionic surfactants are added to such ointments to uniformly disperse PG within the white petrolatum base and increase the solubility of the steroids, although the amounts of PG and surfactants added seem to be small compared with those used

Abbreviations: PG, propylene glycol; POE, polyoxyethylene; HLB, hydrophilic-lipophilic balance

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in oily creams. Therefore, their appearance and properties are intermediate between those of ointments and oily creams.

Usually, the surfactants contained in generic ointments differ from those found in brand name ointments. Some ointments contain surfactants with low hydrophilic–lipophilic balance (HLB) values, such as glycerol fatty acid esters (usually glyceryl monostearate; HLB 3.8), which are suitable for preparing water-in-oil emulsions. Other ointments contain surfactants with high HLB values, such as polyoxyethylene (POE) hydrogenated castor oil 40 (HLB 12.5) and 60 (HLB 14.0), and POE(10) oleyl ether (HLB 12.4). These surfactants are suitable for preparing oil-in-water emulsions [7]. However, few studies have examined the differences between the rheological properties of brand name ointments and the equivalent generic ointments as mentioned above [2,4,6]. Furthermore, no previous studies clarified the effects of particular surfactants on the rheological properties of steroidal ointments.

Steroidal ointments are often prescribed together with moisturizing creams during the treatment of atopic dermatology and psoriasis, and admixtures of steroidal ointments and moisturizing creams are often prepared to improve patient compliance [8–11]. However, it is possible that the production of such admixtures changes the release profiles of the steroids within them [12,13]. In vitro studies have also suggested that the production of such admixtures also influences the permeability and skin penetration of the steroids within them [8,14]. Furthermore, admixing steroidal ointments with other semisolid formulations often causes the steroids to degrade [15].

In addition, problems associated with mixing incompatibility, such as phase separation and bleeding, have also been detected in admixtures of two different ointments, an ointment and a cream, or two different creams [9,12,15,16]. Although it is possible that the mixing compatibility of brand name steroidal ointments and the equivalent generic ointments differs due to differences in their surfactants, no previous studies have clarified the effects of particular ointment surfactants on the mixing compatibility of steroidal ointments with other ointments and creams.

Therefore, in this study we first compared the rheological properties (the hardness, adhesiveness, and spreadability) of three brand name ointments and six equivalent generic ointments containing difluprednate, dexamethasone propionate, or clobetasol propionate. In addition, we examined the effects of particular surfactants on the abovementioned properties by preparing model ointments consisting of white petrolatum, PG, and a surfactant, which are present in each of the examined brand name/generic ointments, and assessed their rheological properties. We also investigated the mixing compatibility of the steroidal ointments with a brand name oil-in-water type heparinoid cream and the influence of their surfactants on this because steroidal ointments are often admixed with oil-in-water type or water-in-oil type heparinoid cream in the clinical setting. Throughout this study, we tried to clarify the relationships between the hydrophilic/hydrophobic nature of the surfactants contained within the ointments and the ointments' rheological properties or mixing compatibility.

2. Materials and methods

2.1. Materials

The following steroidal ointments were used: Myser[®] ointment (Mitsubishi Tanabe Pharma Co., Osaka, Japan), which contains 0.05% difluprednate, and two equivalent generic products, Saibath[®] ointment (Maeda Pharmaceutical Industry Co., Toyama, Japan) and Stibron[®] ointment (Iwaki Seiyaku Co., Tokyo, Japan); Methaderm[®] ointment (Okayama Taiho Pharmaceutical Co., Bizen, Japan), which contains 0.1% dexamethasone propionate, and two

equivalent generic products, Mainvate[®] ointment (Maeda Pharmaceutical Industry Co.) and Delmusatt[®] ointment (Toko Pharmaceutical Industry Co., Tokyo, Japan); and Dermovate[®] ointment (GlaxoSmithKline K.K., Tokyo, Japan), which contains 0.05% clobetasol propionate, and two equivalent generic products, Dertopica[®] ointment (Iwaki Seiyaku Co.) and Myalone[®] ointment (Maeda Pharmaceutical Industry Co.). Hirudoid[®] cream (Maruho Co., Osaka, Japan) was used as a heparinoid cream, and Sunwhite[®] P-1 (Nikko Rika Co., Tokyo, Japan) was used as a high-grade white petrolatum product. High-grade POE hydrogenated castor oil 40 and 60 were kindly provided by Nikko Chemicals (Tokyo, Japan), and POE(40) sorbitan tetraoleate was also kindly donated by NOF Co. (Tokyo, Japan). Glycerol monostearate, sorbitan sesquioleate, POE(7) oleyl ether, POE(50) oleyl ether and all other reagents were obtained from Wako Pure Chemical Industries (Osaka, Japan).

2.2. Evaluation of the ointments' hardness and adhesiveness

The hardness and adhesiveness of the ointments containing difluprednate, dexamethasone propionate, or clobetasol propionate, as well as those of the model ointments were measured with a COMPAC-100II rheometer (Sun Scientific Co., Tokyo, Japan) at room temperature (about 25 °C) by recording the loads at which the loading bar (diameter: 10 mm) was inserted to a depth of 5 mm and detached at a table travel speed of 60 mm/min, respectively. The hardness of each ointment was obtained from the level at which the insertion load plateaued. The adhesiveness of each ointment was assessed based on the area under the curve of the load following the detachment of the loading bar.

2.3. Evaluation of the ointments' spreadability

The spreadability of the ointments was evaluated with a spread meter (Imoto Machinery Co., Kyoto, Japan). The ointments were spread on the plate of the spread meter at room temperature (about 25 °C), and then the changes in their diameters were measured at 20, 30, 50, 100, 200, and 500 s after the addition of a load [17]. The spreadability of the ointments was assessed from the slope of the regression line between the logarithm of the time since the addition of the load and the diameter of the ointment after it was spread on the plate.

2.4. Microscopic analysis

The internal structures of the ointments were examined by microscopic analysis using a BX53 microscope (Olympus, Tokyo, Japan) equipped with a phase contrast observation system at magnification of 1000 times.

2.5. Preparation of model ointments

Model ointments were prepared by melting white petrolatum at 75 °C in the presence of PG and surfactants under gentle mixing. The model ointments were obtained by allowing the mixtures to cool down to room temperature. The concentration of PG was kept at 10% w/w.

2.6. Examination of mixing compatibility

The mixing compatibility of the steroidal ointments with a brand name heparinoid cream was examined using a quick centrifugation-based test of phase separation: an optical examination assessing the extent of phase separation after the mixture had been subjected to centrifugation. Five grams of each steroidal ointment were added to an equal amount of the brand name heparinoid cream, Hirudoid[®] cream, and mixed twice with an NR-

50 rotation/revolution mixer (Thinky Co., Tokyo, Japan) at 1000 rpm for 30 s. The admixture was then inserted into a glass centrifuge tube and centrifuged at 3000 rpm for 10 min with a KN-70 centrifuge (Kubota Co., Tokyo, Japan). Then, the change in the appearance of the mixture, e.g., whether any phase separation or bleeding occurred, was examined. Mixing compatibility was also examined by microscopically examining the structure of each ointment and cream admixture using samples that had not yet been subjected to centrifugation.

The mixing compatibility with Hirudoid[®] cream of model ointments containing various amounts of surfactants was examined using the centrifugation method. The ratio of the separated phase to the whole length of the admixture was used as an index of mixing compatibility.

3. Results

3.1. Hardness and adhesiveness of brand name and generic ointments containing difluprednate, dexamethasone propionate, or clobetasol propionate

We examined the rheological properties of brand name and generic ointments containing difluprednate, dexamethasone propionate, or clobetasol propionate, whose constituents are shown in Table 1. As rheological properties, we first measured hardness and adhesiveness, which have an important impact on how an ointment feels [18,19]. Since the ointments' rheological properties might have changed over time due to the oxidation of the white petrolatum within them, we carried out the experiments within two months of the ointment bottles being opened.

Table 1

Additives other than white petrolatum and propylene glycol that were contained in brand name and generic ointments containing 0.05% difluprednate (a), 0.1% dexamethasone propionate (b), or 0.05% clobetasol propionate (c).

(a)		
A (brand-name)	B (generic)	C (generic)
Myser [®] ointment	Saibath [®] ointment	Stibron [®] ointment
POE oleyl ether White beeswax Liquid paraffin	POE hydrogenated castor oil 60	Glyceryl monostearate Liquid paraffin White beeswax pH adjuster
(b)		
D (brand-name)	E (generic)	F (generic)
Methaderm [®] ointment	Mainvate [®] ointment	Delmusatt [®] ointment
Glyceryl monostearate Liquid paraffin Lanolin alcohol Propylene carbonate	POE hydrogenated castor oil 40	POE sorbitan tetraoleate Liquid paraffin
(c)		
G (brand-name)	H (generic)	I (generic)
Dermovate [®] ointment	Dertopica [®] ointment	Myalone [®] ointment
Sorbitan sesquioleate	Glyceryl monostearate White beeswax Liquid paraffin Adipic acid isopropionate pH adjuster	POE hydrogenated castor oil 40 Citric acid hydrate

The hardness and adhesiveness of the ointments differed, as shown in Fig. 1a for ointments A, B, and C, which all contained difluprednate. The hardness and adhesiveness of generic ointment C were about 2.5-fold greater than those of brand name ointment A and generic ointment B. Likewise, as shown for the brand name and generic ointments containing dexamethasone propionate (ointments D, E, and F; Fig. 1b) or clobetasol propionate (ointments G, H, and I; Fig. 1c), the hardness and adhesiveness of the ointments differed. The hardness and adhesiveness of the total nine ointments exhibited the following order: G, C > H > D > E, F, I > B > A. Among the first four ointments, ointments C, H, and D contained glyceryl monostearate, and ointment G contained sorbitan sesquioleate, as a surfactant, respectively. These surfactants have low HLB values and are used for preparing water-in-oil emulsions. On the other hand, ointments E, F, I, B, and A, which exhibited low hardness and adhesiveness values, contained surfactants with POE chains; i.e., POE oleyl ether (ointment A), POE hydrogenated castor oil 60 (ointment B), POE hydrogenated castor oil 40 (ointments E and I) or POE sorbitan tetraoleate (ointment F). These surfactants have high HLB values, which are considered to be useful for preparing oil-in-water emulsions. These findings suggest that the physicochemical properties of the ointments' surfactants modified the hardness and adhesiveness of the ointments.

3.2. Spreadability of brand name and generic ointments containing difluprednate, dexamethasone propionate, or clobetasol propionate

We next examined the spreadability of the ointments. Spreadability is also an important physicochemical property of ointments because it is an indicator of the utility of the ointment [6,19]. As shown in Fig. 2a–c, spreadability also differed among the ointments. The spreadability of the ointments exhibited the following order: F > E > B > I > D > G > A > H > C. Ointments A, C, and H were markedly less spreadable than the other ointments. Interestingly, ointments A, C, and H contained white beeswax as an additive, whereas the other ointments did not. Therefore, the presence of white beeswax might result in a reduction in spreadability. The surfactant glyceryl monostearate also seems to be associated with reduced spreadability because the spreadability of ointments C, D, and H, which contained glyceryl monostearate, was low (C and H) or moderate (D). On the other hand, the ointments that contained surfactants with POE chains in the absence of white beeswax exhibited excellent spreadability (B, E, F, and I). Therefore, surfactants also seem to affect ointment spreadability.

3.3. Hardness and adhesiveness of model ointments containing propylene glycol and surfactants

The present findings indicated that surfactants have marked effects on the rheological properties of ointments, especially their hardness and adhesiveness. To elucidate the contributions of each ingredient to the ointments' hardness and adhesiveness, we prepared model ointments consisting of white petrolatum and 10% w/w PG and 5% w/w surfactants. As shown in Fig. 3a, the addition of PG decreased the hardness and adhesiveness of the model ointments by about 50%. The subsequent addition of 5% w/w glyceryl monostearate restored the hardness and adhesiveness of the model ointments to almost baseline levels. On the other hand, the addition of the same concentration of a POE chain-containing surfactant (POE hydrogenated castor oil 40 or POE(40) sorbitan tetraoleate) resulted in slightly decreased hardness and adhesiveness values.

We also examined the concentration-dependent effects of glyceryl monostearate and a POE chain-containing surfactant (POE(50) oleyl ether) (concentration of glyceryl monostearate: 1–5% w/w; concentration of POE(50) oleyl ether: 5–20% w/w). As shown in Fig. 3b, the

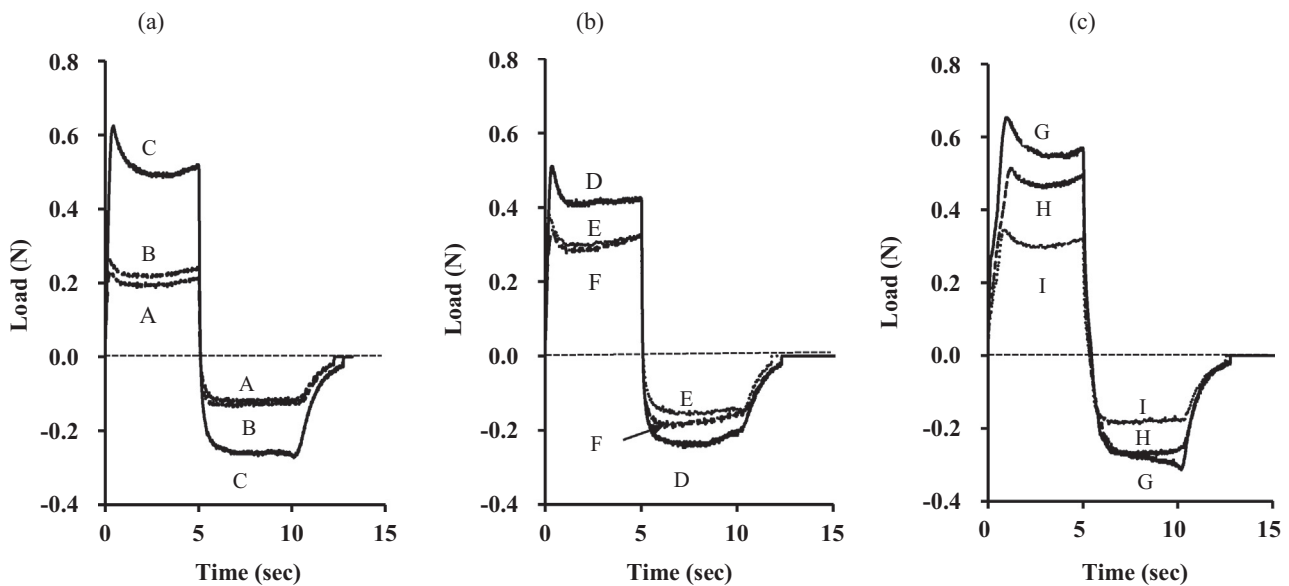


Fig. 1. The hardness and adhesiveness of brand name and generic ointments containing difluprednate (a), dexamethasone propionate (b), or clobetasol propionate (c) A, D, and G: brand name ointments; B, C, E, F, H, and I: generic ointments The hardness of the ointment was assessed from the level at which the insertion load plateaued, whereas adhesiveness was assessed based on the area under the curve of the detachment load. Data are shown as the means of four experiments.

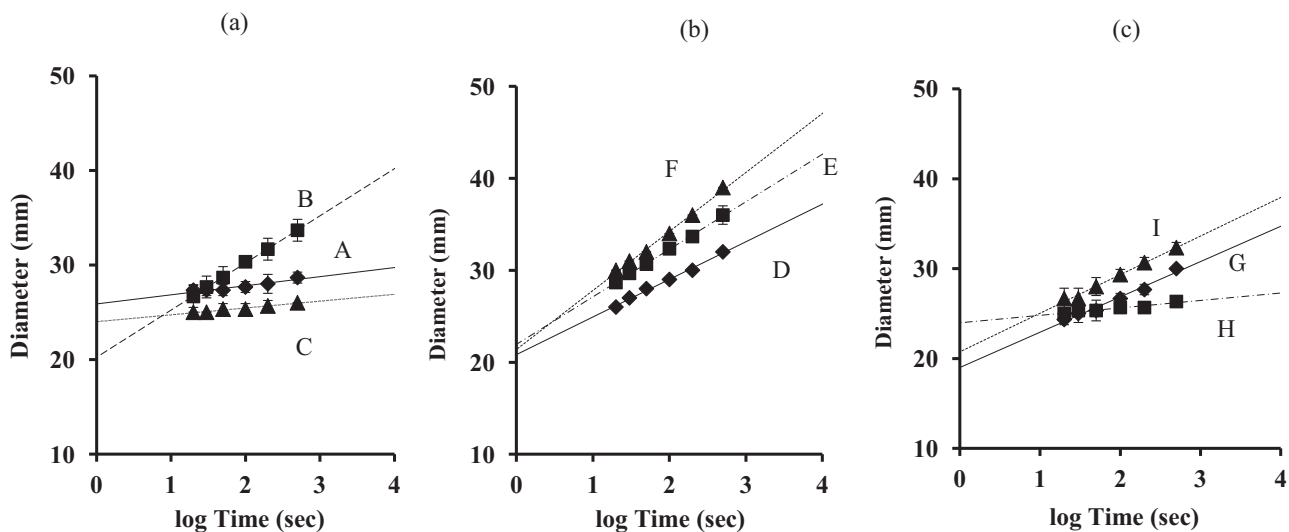


Fig. 2. Spreadability of brand name and generic ointments containing difluprednate (a), dexamethasone propionate (b) or clobetasol propionate (c). A, D, and G: brand name ointments; B, C, E, F, H, and I: generic ointments. Data are shown as the means \pm S.D. of four experiments. The slopes of the plotted lines (A, 0.96; B, 4.98; C, 0.72; D, 4.09; E, 5.17; F, 6.42; G, 3.93; H, 0.83; I, 4.30) represent the spreadability of the ointments.

addition of glyceryl monostearate resulted in dose-dependent increases in hardness and adhesiveness (up to approximately twice their original values at a concentration of 5% w/w). On the other hand, POE (50) oleyl ether caused slight reductions in hardness and adhesiveness at 5% w/w. Interestingly, it induced dose-dependent increases in these parameters at higher concentrations, but even at 20% w/w, the increases were less marked than those induced by 5% w/w glyceryl monostearate, as shown in Fig. 3c. These results were consistent with the findings obtained for the commercially available ointments (Fig. 1a–c).

3.4. Structures of brand name and generic ointments

To clarify how the surfactants affected the rheological properties of the ointments, we examined the ointments' structures microscopically. As shown in Fig. 4a–c for the ointments containing difluprednate, particle dispersion (presumably PG particles) was observed

in all of the ointments. In particular, a homogeneous particle structure was observed in the ointments containing glyceryl monostearate, which is considered to be a useful surfactant for preparing water-in-oil emulsions, as shown in Fig. 4c for ointment C.

3.5. Mixing compatibility of brand name and generic ointments with heparinoid cream

Steroidal ointments are used to treat patients suffering from atopic dermatitis. In this setting, they are often mixed with a moisturizing cream such as heparinoid cream to improve patient compliance. However, mixing ointments with creams often induces phase separation or bleeding [12,16,20]. Therefore, the mixing compatibility of the steroidal ointments with a brand name oil-in-water emulsion-type heparinoid cream (such admixtures are often used clinically) was examined using a quick centrifugation-based test of phase separation and confirmed by a microscopic observation. Heparinoid cream

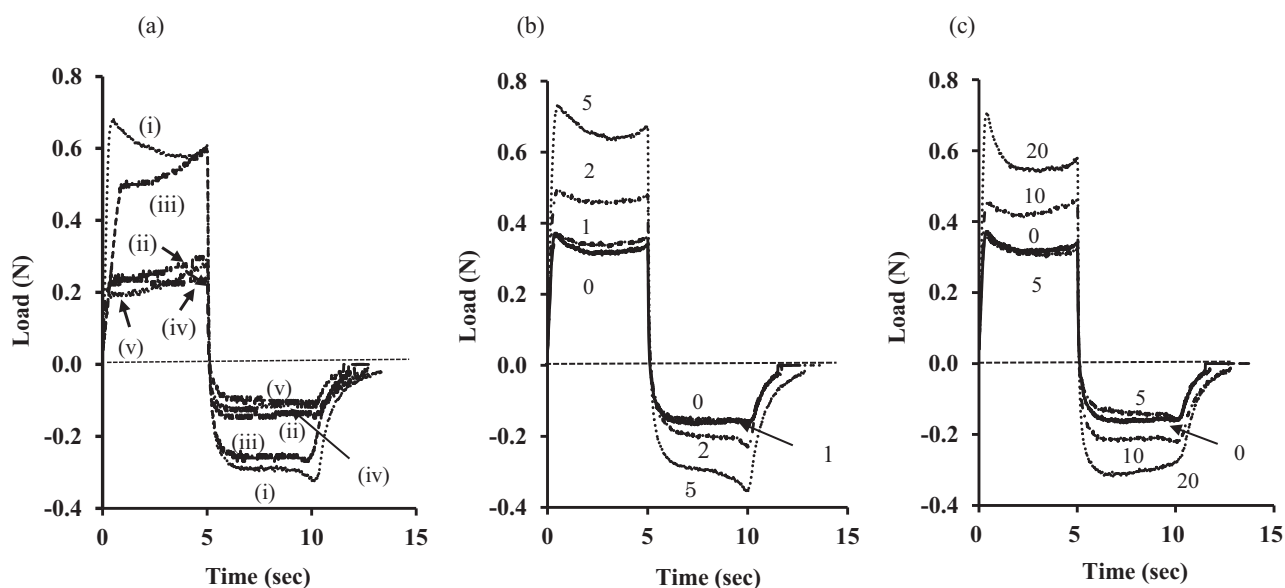


Fig. 3. Effects of surfactants on the hardness and adhesiveness of model ointments consisting of white petrolatum, propylene glycol, and surfactants. Data are shown as means of four experiments. In the presence of PG, its concentration was kept at 10% w/w. In the experiment shown in Fig. 3a, the concentration of the surfactants was kept at 5% w/w; (i) without additives, (ii) with PG, (iii) with PG and glyceryl monostearate, (iv) with PG and POE hydrogenated castor oil 40, (v) with PG and POE(40) sorbitan tetraoleate. In the experiments shown in Fig. 3b for the effects of glyceryl monostearate and in Fig. 3c for POE(50) oleyl ether, respectively, the numbers represent the concentrations of the surfactants expressed as percentage weight values.

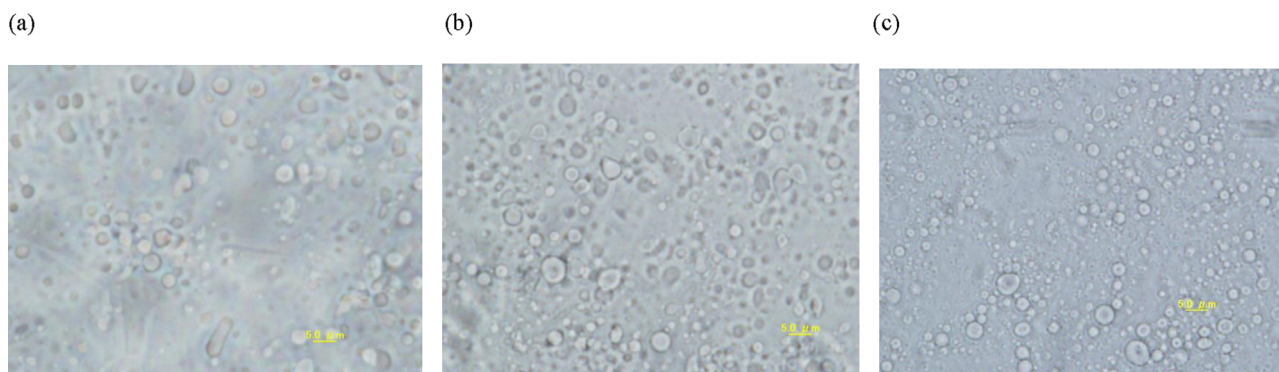


Fig. 4. Phase contrast micrograph of brand name and generic ointments containing difluprednate. (a) Brand name ointment A, (b) generic ointment B, and (c) generic ointment C.

contains glycerol and isopropyl alcohol as hydrophilic solvents and white petrolatum as a hydrophobic base. As for its main surfactant, it contains stearic acid and potassium hydroxide, which react to produce potassium stearate.

Photographs obtained during the centrifugation-based examinations of the ointments containing difluprednate (ointments A, B, and C) are shown in Fig. 5 as examples. Homogeneous mixing was observed in the admixtures composed of ointment C, D, G, or H and heparinoid cream (weight ratio:1:1). These ointments contained glyceryl monostearate (ointments C, D, and H) or sorbitan sesquileate (ointment G). These surfactants have low HLB values and are suitable for preparing water-in-oil emulsions. On the other hand, phase separation was seen in the admixtures containing ointment A, B, E, F, or I and heparinoid cream at a weight ratio of 1:1. All of these ointments contain surfactants with POE chains; i.e., POE oleyl ether (ointment A), POE hydrogenated castor oil 60 (ointment B) or 40 (ointments E and I), or POE sorbitan tetraoleate (ointment F). These surfactants become hydrophilic via the formation of hydrogen bonds between the ether oxygen atoms of their oxyethylene chains and

water molecules; therefore, they have high HLB values and are suitable for preparing oil-in-water emulsions. These findings suggest that the physicochemical properties of the surfactants in the steroidal ointments determined their mixing compatibility with heparinoid cream.

3.6. Effects of surfactants on the mixing compatibility of white petrolatum with heparinoid cream in the presence of propylene glycol

To examine the abovementioned suggestion, we investigated the effects of the surfactants on the mixing compatibility of white petrolatum with heparinoid cream in the presence of 10% w/w PG. As shown in Fig. 6, which shows the dose-dependent effects of the surfactants, glyceryl monostearate induced homogeneous mixing at the lowest concentration, and sorbitan sesquileate induced it at the next lowest concentration. Griffin reported HLB values of 3.8 for glyceryl monostearate and 3.7 for sorbitan sesquileate [21], but in calculations based on their theoretical chemical formulas Pasquali et al. suggested that these surfactants have HLB values of 4.1 and 4.9, respectively [22].

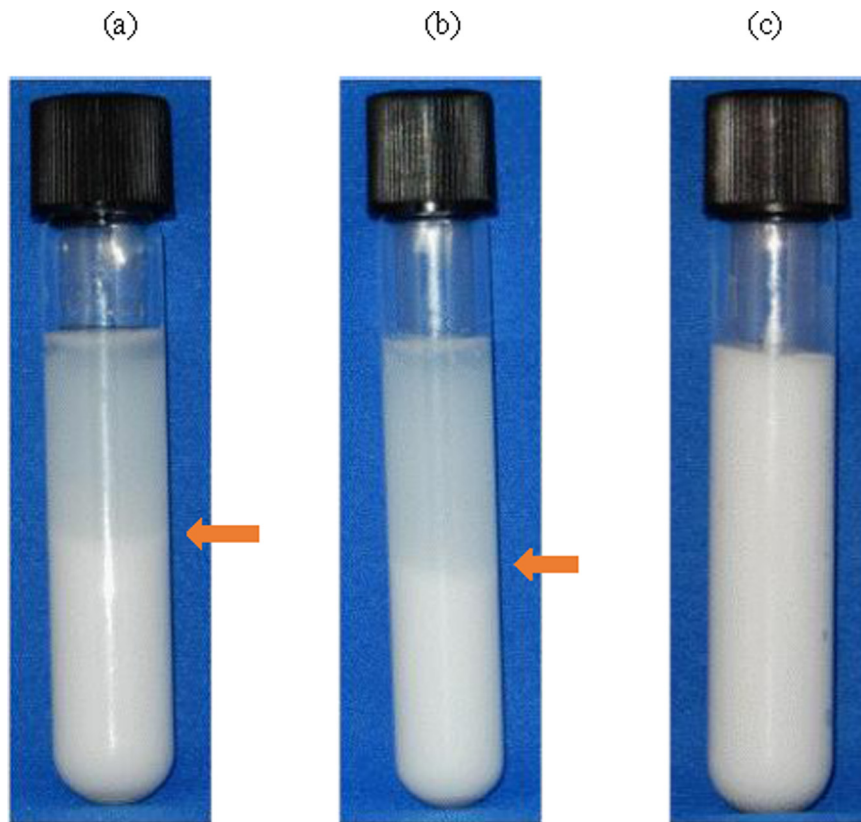


Fig. 5. Mixing compatibility of admixtures with heparinoid cream of brand name or generic ointments containing difluprednate at one to one weight ratio. (a) Brand name ointment A, (b) generic ointment B, and (c) generic ointment C. The reproducibility of our findings was confirmed by performing the experiments in triplicate.

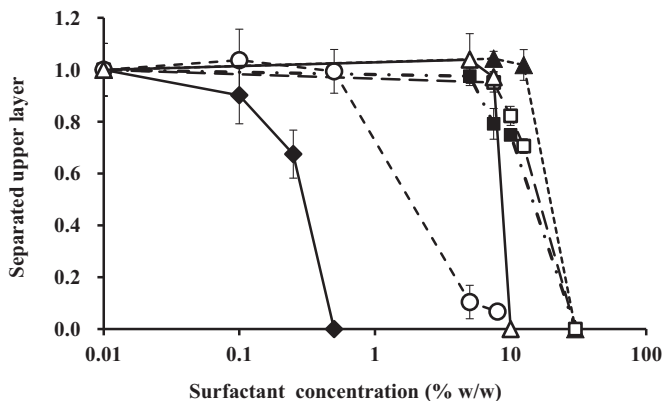


Fig. 6. Effects of surfactants on the phase separation of admixtures with heparinoid cream of model ointments at one to one weight ratio. The length of the separated upper layer in the absence of surfactants was defined as 1.0. The closed diamonds, open circles, open squares, open triangles, closed squares, and closed triangles, indicate the results for the ointments containing glyceryl monostearate, sorbitan sesquioleate, POE(40) hydrogenated castor oil, POE(7) oleyl ether, POE(50) oleyl ether, POE(40) sorbitan tetraoleate, respectively. Data are shown as the means \pm S. D. of four experiments.

The calculations performed by Pasquali et al. produced more accurate results for surfactants without POE chains.

Higher concentrations of the POE hydrogenated castor oil 40 (HLB:12.5), POE(7) oleyl ether (HLB:10.7), POE(50) oleyl ether (HLB:18.0), and POE(40) sorbitan tetraoleate (HLB:11.8) were required to induce homogeneous mixing. POE(7) oleyl ether, which is more hydrophobic than POE(50) oleyl ether, was fully effective at lower concentrations than POE(50) oleyl ether. These findings agree with our speculation based on the results shown in Fig. 5, and suggest that the mixing compatibility of steroidal ointments with heparinoid cream is

determined by the HLB values of their surfactants; i.e. the emulsifying capacity of their surfactants in oily conditions.

4. Discussion

To allay patients' concerns regarding the use of generic medicines, it should be confirmed that particular brand name and generic drugs are bioequivalent, and such drug pairs should also produce similar sensations during their use. However, as was revealed in the present study of steroidal ointments, the rheological properties of ointments can vary markedly due to differences in their ingredients, as suggested by previous studies [2,6]. The findings obtained for the ointments containing difluprednate, dexamethasone propionate, or clobetasol propionate, and those acquired for the model ointments indicated that certain rheological properties, especially low hardness and adhesiveness values, are associated with the use of surfactants containing POE chains to promote the dispersal of PG, which is often added to steroidal ointments to improve the solubility of the steroids in the ointment base. As for hardness and adhesiveness, the dispersion state of the hydrophilic solvent seems to be important. The relatively large liquid particles found in the ointments containing surfactants with POE chains seemed to reduce the ointments' hardness and adhesiveness.

The spreadability values of the steroidal ointments exhibited a different order (from highest to lowest) from their hardness and adhesiveness values. Therefore, it is reasonable to assume that different factors affect each rheological property. The network structure of the solid components of petrolatum within its liquid components is expected to play an essential role in spreadability, since this is a typical feature of semi-solid materials. The present findings suggested that white beeswax might change the balance

of the solid materials and liquid materials, and result in a reduction in spreadability. Further studies are necessary to reveal the mechanisms responsible for the effects of each component on ointment spreadability.

Variations in the properties of white petrolatum, which is used as an ointment base, can also affect ointments' rheological properties because the rheological properties, especially the viscosity, of white petrolatum might vary among different manufacturers (under investigation). Moreover, the apparatus and manufacturing processes used by each steroidal ointment manufacturer are known to differ, which might also affect the rheological properties of steroidal ointments. It has been reported that the rheological properties of ointments are affected by the network structure of the solid components of petrolatum within its liquid components [23]. However, it remains unclear how the network structure of white petrolatum affects each rheological property.

Topical formulations are often admixed with white petrolatum, other ointments, or creams. Such mixing induces changes in their rheological properties, stability, and the skin permeation of their active ingredients [8,11–14,20,24–26]. It is possible that differences in the rheological properties of steroidal ointments affect the skin permeation of their active ingredients since it has been reported that the rheological properties of creams influence the skin permeation of their active ingredients [24,25]. Further studies are required to examine this issue.

Moreover, such mixing can cause phase separation or bleeding [12,16,20]. The present studies on the mixing compatibility of steroidal ointments with oil-in-water emulsion-type heparinoid cream have revealed that ointments that contain glyceryl monostearate as a surfactant display good mixing compatibility, and ointments containing non-ionic surfactants with POE chains demonstrate mixing incompatibility, although stability tests are required to confirm these findings. As for the mixing compatibility of ointments containing sorbitan sesquioleate with heparinoid cream, it seems to vary according to the results revealed in this study and those of another study on other steroidal ointments containing this surfactant (under investigation).

In the present study, experiments involving model ointments indicated that the mixing compatibility of steroidal ointments with heparinoid cream can be predicted based on HLB values calculated from their theoretical chemical formula (it has been reported that such values are able to predict the hydrophilicity/hydrophobicity of surfactants without POE chains more accurately) [22]. Heparinoid cream contains potassium stearate as its main surfactant, which is produced via a reaction between the cream's constituents; i.e., stearic acid and potassium hydroxide. It also contains alkyl alcohols as co-surfactant components. However, heparinoid cream does not seem to form stable emulsions when it is mixed with steroidal ointments in which oily white petrolatum is employed as a base.

The obtained findings suggest that the mixing compatibility of ointments containing oily bases with heparinoid cream is determined by the emulsifying capacity of the ointments' surfactants in oil-rich conditions. Therefore, we can estimate the compatibility of steroidal ointments with heparinoid cream by checking what surfactants they contain. We are currently attempting to establish rules for determining the mixing compatibility of ointments with other ointments and creams including water-in-oil emulsion type creams based on the surfactants contained within the ointments.

5. Conclusion

We detected marked differences in the hardness, adhesiveness and spreadability of three brand name and six generic ointments containing difluprednate, dexamethasone propionate, or

clobetasol propionate. The present findings regarding commercially available ointments and model ointments indicate that the rheological properties of steroidal ointments, especially their hardness and adhesiveness, are determined by the presence of PG and the surfactants they contain, which seems to be related to the dispersion state of PG in the oily base.

Experiments examining the mixing compatibility of various steroidal ointments with heparinoid cream revealed that ointments containing glyceryl monostearate as a surfactant exhibited good mixing compatibility. On the other hand, ointments containing non-ionic surfactants with POE chains displayed mixing incompatibility. These findings were consistent with those obtained in the experiments involving model ointments. The results of this study indicate that the mixing compatibility of ointments that contain white petrolatum as a base with heparinoid cream is determined by the emulsifying capacity of the ointments' surfactants. Therefore, during the selection of steroidal ointments, attention should be paid to the surfactants they contain.

Conflicts of interest

The authors report that they have no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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