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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.



## 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 Industrial 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). Glyceryl 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-