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Relationship between the usability and physicochemical properties of triamcinolone acetonide ointments

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ABSTRACT

The purpose of this study was to examine the physicochemical properties of TA ointments and conduct a human sensory test to assess the properties of those ointments. Physicochemical assessment was done via near-infrared (NIR) absorption spectroscopy, measurement of water content, microscopy, and measurement of viscoelasticity. The human sensory test examined 5 aspects (texture, cohesiveness, spreadability, smell, and feel). Three TA ointments were used: TA-A, a brand-name preparation, and TA-B and TA-C, two generics. The sensory test revealed significant differences between TA-A and TA-B and TA-C in terms of cohesiveness and spreadability. Significant differences between TA-A and TA-C and between TA-B and TA-C in terms of feel were noted. Microscopic examination revealed that TA-C had good dispersibility while TA-A and TA-B produced crystallization. NIR spectroscopy revealed differences in absorption spectra attributed to oil and water content in TAA, TA-B, and TA-C. Measurement of water content indicated water content of 0.06 ± 0.02% for TA-A, 0.08 ± 0.08% for TA-B, and 36.7 ± 1.19% for TA-C. Assessment of viscoelasticity indicated that stress decreased for all 3 ointments at 35 °C compared to that at 25 °C. TA-A and TA-B were found to have a higher percent decrease in stress than was TA-C. These findings indicate that differences in the types and content of additives caused differences in the physicochemical properties of individual ointments. In addition, differences in physicochemical properties presumably resulted in the close correlation between cohesiveness and spreadability in the sensory test.

1. Introduction

Generic drugs contain the same active ingredients as brand-name drugs and are less expensive than their brand-name counterparts, but they are considered to have equivalent quality. Since generics and their brand-name counterparts have different additives such as preservatives and coloring agents, the quality of generics is often questioned by physicians and pharmacists [1]. Studies have questioned the equivalence of some generics to their brand-name counterparts in terms of clinical efficacy and safety, and there is a lack of clinical information and data on the clinical efficacy and safety of generics [2,3].

Drugs applied to the skin consist of transdermal preparations, in which drugs act by traveling throughout the body, and topical preparations, in which drugs are applied externally to a certain place on the skin. The latter are most often semisolid preparations in the form of ointments, creams, and gels, liquids such as lotions, and adhesive preparations such as cataplasms/gel patches and tapes. Bases differ vastly among brand-name topical preparations and their generic counterparts, and the characteristics of these bases may differ. Ointments are drugs largely consisting of additives such as thickening agents and pH adjusters. Clinical efficacy, adverse reactions, and feel may differ due to factors such as bases and additives and the site of use despite drugs having the same principal agent [4]. If the method and conditions of manufacture differ, then brand-name drugs may have different properties despite having the same content of active ingredients and the same additives. Sustained-release preparations that have the same components but different manufacturers must be viewed as clinically different drugs [5]. One example would be differences in the additives in brand-name and generic tulobuterol patches; these differences are reportedly a factor that affects drug release [6]. Thus, information such as differences in the types and ratios of additives, method of manufacture, and properties is needed regardless of whether drugs are brand name or generic.

Topical steroids are used clinically to treat various dermatoses such as eczema and dermatitis. Topical steroids are used as the principal treatment for inflammatory dermatoses and pruritus, such as atopic dermatitis [7]. These drugs are often prescribed by dermatology departments because of their anticipated anti-inflammatory action. However, local adverse reactions to topical steroids include skin atrophy, thinning skin, vasoconstriction, and skin infections due

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Table 1
Additives list for TA ointments.

Formulation	Additives
TA-A	Vaseline (PJ), methyl p-hydroxybennzoate, propyl p-hydroxybennzoate, purified lanolin
TA-B	Vaseline (PJ), crotamiton
TA-C	Crotamiton, propylene glycol, disodium edetate hydrate, carboxyvinyl polymer, acidity regulator

to compromised immunity. Caution regarding these adverse reactions is required, and prolonged use of these steroids is discouraged. Moreover, abrupt cessation of topical steroids produces a rebound phenomenon accompanying withdrawal, possibly causing a skin condition to temporarily worsen. Ceasing use of topical steroids is difficult, and there are instances when patients will resume using topical steroids because of their worsening skin condition due to the rebound phenomenon and anxiety. The potency of topical steroids is ranked in 7 groups based on the intensity of vasoconstriction [8]. Depending on the site of application, topical steroids must be appropriately selected and used based on their ranked potency.

Clinical study of topical steroids began with use of cortisone acetate to treat dermatoses by Goldman et al. in [9]. Numerous studies of their pharmacology and therapeutic efficacy [9–11] have been conducted. 16α-Hydroxycorticoids were developed when 16α-hydroxycortisol was synthesized by introducing a hydroxyl group at the C-16 position of the steroid nucleus. This compound had potent glucocorticoid activity and anti-inflammatory activity but did not cause Na retention. Later, triamcinolone, an analog of 9α-fluoroprednisolone with a 16α –OH, was successfully synthesized. Triamcinolone acetonide (TA) was developed by suspending triamcinolone in acetone to yield a drug with greater bioactivity than 9α-fluoroprednisolone. TA preparations are commercially available as ointments, creams, and injectables, and their usage differs depending on the patient's condition.

Researchers at the Laboratory of Drug Safety Management previously reported a correlation between the physicochemical properties and feel of antimicrobial and antiviral creams [12]. TA ointments are drugs with a "medium" ranking as a steroid. Brand-name and generic preparations are commercially available, but the additives in preparations differ, so differences in the physicochemical properties of individual TA ointments are expected. These differences in physicochemical properties are presumed to affect the feel of these ointments to humans, but these physicochemical properties and feel have not been studied.

Results of the current study should provide information on future drug selection and use in clinical practice. Thus, the current study physically assessed brand-name and generic TA ointments and it compared the properties of those ointments in conjunction with a sensory test with humans.

2. Materials and methods

2.1. Materials

Three different 0.1% TA ointments were used in the present study: the original product, TA-A (AlfresaPharma Co., Ltd., Japan), and two generic products, TA-B (Yoshindou Co., Ltd., Japan) and TA-C (Kaken Pharmaceutical Co., Ltd., Japan). The three products were randomly named TA-A, TA-B, or TA-C. Additives list of each formulation in Table 1. All other reagents were of special reagent grade.

2.2. Methods

2.2.1. Sensory test

The sensory test was carried out by the single-blind method and each sample (A, B, and C) was distributed at random. For assessment, four aspects—texture, spreadability, cohesiveness (3: yes, 2: slightly, 1: very few, and 0: no) were evaluated in four steps. And usability (3: good, 2: slightly good, 1: slightly worse, and 0: worse)—was evaluated in four steps. Moreover, we prepared a general opinion column on the assessment sheet. The test was conducted as follows: first, the subjects washed their hands, then wiped them with a paper towel and let them air-dry for 5 min. Thereafter each subject chose one 50 mg sample of ointment A, B, or C. The ointment was rubbed onto the back of a hand using a finger and a circular motion (10 times). Each aspect indicated on the assessment sheet was evaluated within 5 min, and the next assessment was done 5 min later. Subsequent ointments were similarly applied. Ointments were not applied to the same part and a different finger was used each time. The subjects avoided applying hand ointment to the tested area an hour prior to the test. The subjects were 34 healthy adult volunteers with an average age of 23.5 ± 3.51 years (22–58 years). The male-female ratio of the subjects was 16:18. The average age of the male was 26.5 ± 9.4 years (22–58 years) with an average age of women at the age of 23.7 ± 0.7 years (22–24 years). Those who had medical histories of allergies or side effects to these medicines were excluded as candidates. The evaluation obtained was changed into an evaluation with a score of 0–3. A statistical test was then performed using Turkey's test. In addition, the sensory test in this study was conducted with the approval of Josai University's Life Science Research Ethics Screening Committee after the study was fully explained to the test subjects and their written consent was obtained.

2.2.2. Microscopy

Polarization microscopy was performed using a KEYENCE model VHX-1000 microscope.

2.2.3. Near infrared (NIR) absorption spectrometry

Each sample was analyzed using a Fourier transform near-infrared absorption spectrometer, an NIRFlex N-500 analyzer (Buchi Labortechnik AG, Switzerland), 10,000–4000 cm^{-1} measurement frequency, at 4 cm^{-1} intervals. Measurement conditions were an optical path of 1 nm at 25 °C.

2.2.4. Water content measurement

The titrimetric determination of water content was performed at room temperature using a CA-06 Karl–Fischer moisture content meter (Mitsubishi Chemical Co., Ltd., Japan) equipped with a coulometric titration system ($n = 3$). The Karl–Fischer reagents, AQUAMICRON® AX RS as the catholyte and AQUAMICRON® CXU as the anolyte, were purchased from Mitsubishi Chemical Co.

2.2.5. High-performance liquid chromatography assay

For the assay, 1.0 g of each ointment was weighed accurately and placed in a stoppered centrifuge tube. Then 40 mL of chloroform/water (1:1) was added and the solution was shaken and then centrifuged (4000 rpm for 30 min, at 25 °C). The portion of the lower layer was filtered with a 0.45 μm filter, and the filtrate served as the sample solution. A calibration curve was prepared using TA that had separately been dried for 24 h at 105 °C. TA was assayed using high-performance liquid chromatography (HPLC: e2695, Waters). TA assay conditions were a column of Inertsil ODS-3 (4.6 mm × 250 mm, Ø5 μm), column temperature of 35 °C, mobile phase of water/acetonitrile = 2/1, and detection wavelength of 240 nm; conditions were tailored for TA to produce a peak at 9 min.