

Comparison of the Properties of Brand-Name and Generic Nadifloxacin Creams

Yutaka Inoue¹, Miruto Matsumoto¹, Masayuki Kimura¹, Toru Tanaka², Ikuo Kanamoto¹

¹Laboratory of Drug Safety Management, Faculty of Pharmaceutical Sciences, Josai University, Saitama, Japan,

²Laboratory of Biostatistics, Faculty of Pharmaceutical Sciences, Josai University, Saitama, Japan

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Summary. *Background and Objective.* In external preparations, types and ratios of additives are not necessarily the same for brand-name drugs and generic drugs. Thus, the physicochemical properties of preparations may differ despite the fact that they contain the same ingredients or additives. This study examined differences in brand-name and generic versions of nadifloxacin (NFX) creams.

Material and Methods. Three types of NFX creams (NFX-A, NFX-B, and NFX-C) were used. The viscosity of each preparation was determined, its yield value was calculated, and each preparation was subjected to light microscopy, x-ray powder diffraction, and near-infrared absorption spectroscopy.

Results. Comparison of viscosity of different preparations revealed that NFX-B had a lower viscosity than NFX-A and NFX-C (14.5 vs. 24.6 and 17.9 Pa·s). NFX-B also had a lower yield value than NFX-A and NFX-C. Microscopy revealed that NFX-A and NFX-B had satisfactory emulsification although crystallization was observed with NFX-C. Near-infrared absorption spectroscopy revealed changes in the absorption spectra of NFX-B in comparison with those of NFX-A and NFX-C that were due to differences in water content and differences in fat and oil content.

Conclusions. These findings confirmed that there were differences in the viscosity and flattening of NFX-A, NFX-B, and NFX-C. In addition, microscopy revealed differences in emulsification and it revealed the precipitation of NFX crystals in NFX-C. Near-infrared absorption spectroscopy revealed that differences in the type and amount of additives and water content in the creams had contributed to differences in the preparations.

Introduction

The rationalization of health care expenditures is a high priority for the governments of many countries in the industrialized world. Generic drugs contain the same active ingredients as their brand-name counterparts, but they have different additives such as preservatives and coloring agents (1). Generic formulations are made by the same manufacturer as the brand-name drug, but their quality is often questioned by physicians and pharmacists since the excipients used may differ. Generics registered with the European Medicines Agency (EMA) should include the same amount of the active ingredients but can have different excipients. Excipients that are given exceptions include preservatives, pH adjusters, antioxidants, thickening agents, buffers, and substances to adjust tonicity. Although generic formulations are always less expensive than the corresponding brand-name drugs, they are not always as safe or effective. In addition, generic drugs are considered to be of the same quality as the original drugs, but many feel that information about those

generics is inadequate (2). Among physicians, there are perceptions that generic drugs will immediately be discontinued and concerns about consistent supply. Such factors might explain why generic drugs have gained little attraction in Japan despite accounting for half of the drug market in the United States and the United Kingdom (3, 4). As stated earlier, although generic formulations are always less expensive than the corresponding brand-name drugs, they are not always as safe or effective. When a generic drug is registered with the EMA, the clinical efficacy and safety of that generic is considered essentially similar to the innovator or brand-name drug, and the same holds true for local-acting drugs. That said, topical agents in the form of ointments and creams are used to treat a local inflammation or rash, so reports have indicated that differences in additives and differences in additive content can lead to differences in penetration of and absorption by the skin, in turn affecting the therapeutic effectiveness of the ointment or cream (5–7). Penetration of the skin by the antiviral acyclovir (ACV) is reported to differ with preparations that contain different amounts of polyethylene glycol. All marketed ACV creams are not bioequivalent to the clinically proven innovator (8). Substantial differences in bio-

Correspondence to Y. Inoue, Laboratory of Drug Safety Management, Faculty of Pharmaceutical Sciences, Josai University; 1-1 Keyakidai, Sakado-shi, Saitama, 3500295, Japan
E-mail: yinoue@josai.ac.jp

availability are believed to bring into question the therapeutic equivalence of these formulations.

Nadifloxacin (NFX) is a tricyclic fluoroquinolone antibiotic with a benzoquinolizine skeleton and is the active ingredient in the world's first quinolone topical preparation, Acuatim® (9). Since it contains fluorine (F), NFX is a synthetic bactericidal fluoroquinolone with a broad-spectrum antibacterial activity against aerobic gram-positive and gram-negative bacteria and anaerobic bacteria including *Propionibacterium acnes* and *Staphylococcus epidermidis*; NFX is also clinically useful in treating acne vulgaris (10, 11). NFX has been found to have a broad antibacterial spectrum. Formulations are available in 3 forms – creams, lotions, and ointments – for use in accordance with the patient's condition. NFX creams that have recently come into use include both brand-name and generic versions. However, differences in the types or amounts of additives in a cream that is used locally would presumably affect the physicochemical properties of preparation, such as its emulsification and viscosity. To test this hypothesis, the physicochemical properties of a brand-name NFX cream were compared with those of two leading generic NFX creams. This study sought to observe the characteristics of preparations, determine their viscosity, and assay those preparations as a quality test. In addition, this study examined the molecular state of those preparations resulting from differences in additives they contained.

Materials and Methods

Reagents. The NFX creams used were those available commercially and were designated NFX-A (Acuatim®), NFX-B (NADIFLO®), and NFX-C (NADIROXISAN®). NFX crystals were purchased from Sigma-Aldrich. Acetonitrile, chloroform, sodium hydroxide, and acetic acid were of special commercial grade and were purchased from Wako Pure Chemical Industries.

Preparation of Humidity-Controlled Samples. NFX-A, NFX-B, and NFX-C were stored in a thermostated bath at 40°C for 7 days in a desiccator (relative humidity, 82%) in the presence of KCl-saturated aqueous solution.

Microscopy. Polarization microscopy was done using an OLYMPUS model BX51 microscope. In addition, a polarizing plate with a wavelength of 488 nm was used.

Determination of Viscosity. Viscosity was measured at 20°C using a type-E rotational viscometer (model TVE-20H) from Toki Sangyo. One milliliter of each cream was poured into a sample cup, and viscosity was measured at 1 rpm using a 1°34'×R24 cone rotor; measuring time was 900 s, and viscosity was read after 180 s of rotation. Creams were incubated in a water bath at 20°C before measurements.

Measurement of Flattening. Flattening was measured using a spread meter (Rigo) with a measuring temperature of 25°C. Spread diameter was measured after 10, 30, 60, 120, 180, 240, 300, and 360 s. The yield value was calculated from the following formula using the spread diameter after 360 s:

$$F = 47\,040 \times G \times V / \pi^2 \times d^5$$

Where F indicates yield value (dynes/cm³); G, glass plate weight (g); V, sample volume (cm³); d, diameter (mm) when sample spreading stopped.

Near-Infrared Absorption Spectroscopy. Near-infrared absorption spectra were recorded from 1000 to 2500 nm at 1-nm intervals using a Fourier-transform near-infrared analyzer (BUCHI NIRFlex N-500).

X-Ray Powder Diffraction. X-ray powder diffraction was measured at room temperature with a Rigaku Miniflex Diffractometer using CuK α radiation. Diffraction was done at 30 kV, 15 mA with a scanning speed of 4°/min and measurement range of 2 θ =5°–35°.

Assay. One gram of each cream was weighed accurately and placed in a stoppered centrifuge tube. Twenty milliliters of chloroform/0.01 mol/L sodium hydroxide (1:1) was added, and the solution was shaken and then centrifuged (4000 rpm for 30 min). The clear portion of the top layer was filtered with a 0.45- μ m filter, and the filtrate served as the sample solution. A calibration curve was prepared using NFX that had separately been dried for 24 h at 105°C. NFX was assayed with a high-performance liquid chromatograph (HPLC, LC-20ADvp, Shimadzu). NFX assay conditions were a column of Inertsil ODS-3 (4.6×250 mm, ϕ 5 μ m), column temperature of 35°C, mobile phase of water/acetonitrile/acetic acid=130/70/1, and detection wavelength of 280 nm; conditions were tailored for NFX to produce a peak at 15 min.

Results

In the current study, viscosity was determined using a rotational viscometer so that individual creams could be compared (Fig. 1). NFX-A, NFX-B, and NFX-C had a viscosity of 24.6 Pa·s, 14.5 Pa·s, and 17.9 Pa·s, respectively, so results in order of viscosity were NFX-A>C>B. A spread meter was used to compare the fluidity of the creams, and the results of this comparison are shown in Fig. 1 and Table 1. After 360 s, NFX-B had a spread diameter of 41.5 mm, NFX-C had a spread diameter of 39.9 mm, and NFX-A had a spread diameter of 35.3 mm. Flattening was greatest for NFX-B, followed by NFX-C and then NFX-A. As an indicator of hardness, the yield value was 498.4 dynes/cm² for NFX-A, 222.9 dynes/cm² for NFX-B, and 270.6 dynes/cm² for NFX-C. Thus, light microscopy was used to examine the emulsifi-

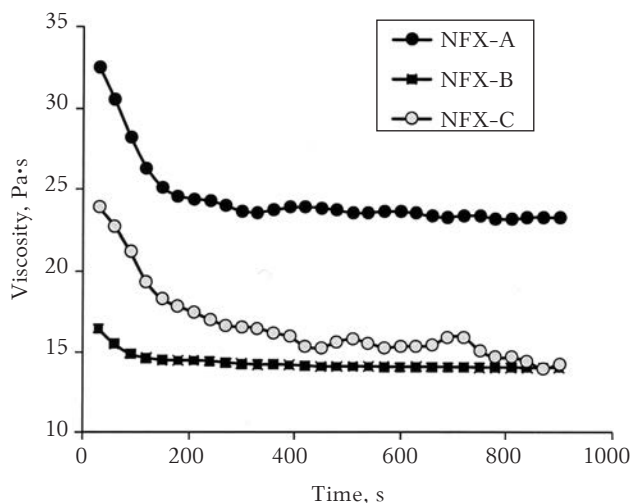


Fig. 1. Viscosity curves for nadifloxacin (NFX) creams at 20°C

Table 1. Spreadability of Nadifloxacin (NFX) Cream at 25°C (n=3)

Cream Type	Spreadability, mm			
	No. 1	No. 2	No. 3	Total, Mean (SD)
NFX-A	35.5	35.8	34.8	35.3 (0.5)
NFX-B	40.8	40.8	43.0	41.5 (1.3)
NFX-C	39.8	39.8	40.3	39.9 (0.3)

cation of the preparations. The results of polarization microscopy of NFX-A, NFX-B, NFX-C, and NFX crystals are shown in Fig. 2. Results revealed that NFX-A and NFX-B were evenly and uniformly dispersed in general. In contrast, NFX-C was found to have clefts and precipitation of needle-shaped crystals. These findings confirmed that NFX-A and NFX-B were uniformly emulsified, but crystals and voids were found in NFX-C, indicating that NFX-C was not uniformly emulsified. Since crystals were found in NFX-C, NFX-C was irradiated with light at a wavelength of 488 nm and observed. Its needle-shaped crystals were found to fluoresce. When NFX crystals were irradiated with light at a wavelength of 488 nm, they had similar fluorescence (Fig. 3).

X-ray powder diffraction patterns of NFX-A, NFX-B, NFX-C, and NFX crystals were obtained in order to study the crystals observed in polarization microscopy (Fig. 4). NFX crystals were found to have a characteristic peak at $2\theta=20.3^\circ$. NFX-A, NFX-B, and NFX-C were found to have peaks at approximately $2\theta=21.0^\circ$. However, an interesting finding is that NFX-C was found to have an x-ray diffraction peak at $2\theta=20.4^\circ$, unlike the peaks of NFX-A and NFX-B.

Near-infrared absorption spectroscopy was per-

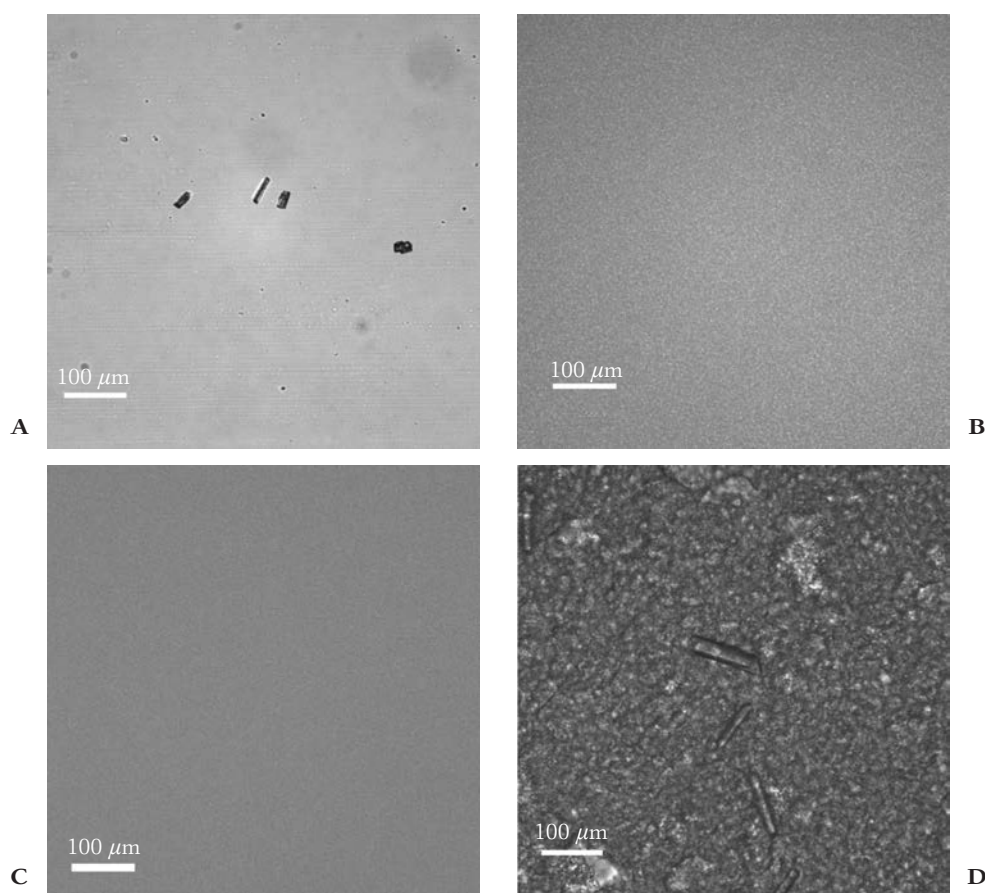


Fig. 2. Light microscopy of nadifloxacin (NFX) crystals and creams
A, NFX crystals; B, NFX-A; C, NFX-B; and D, NFX-C.

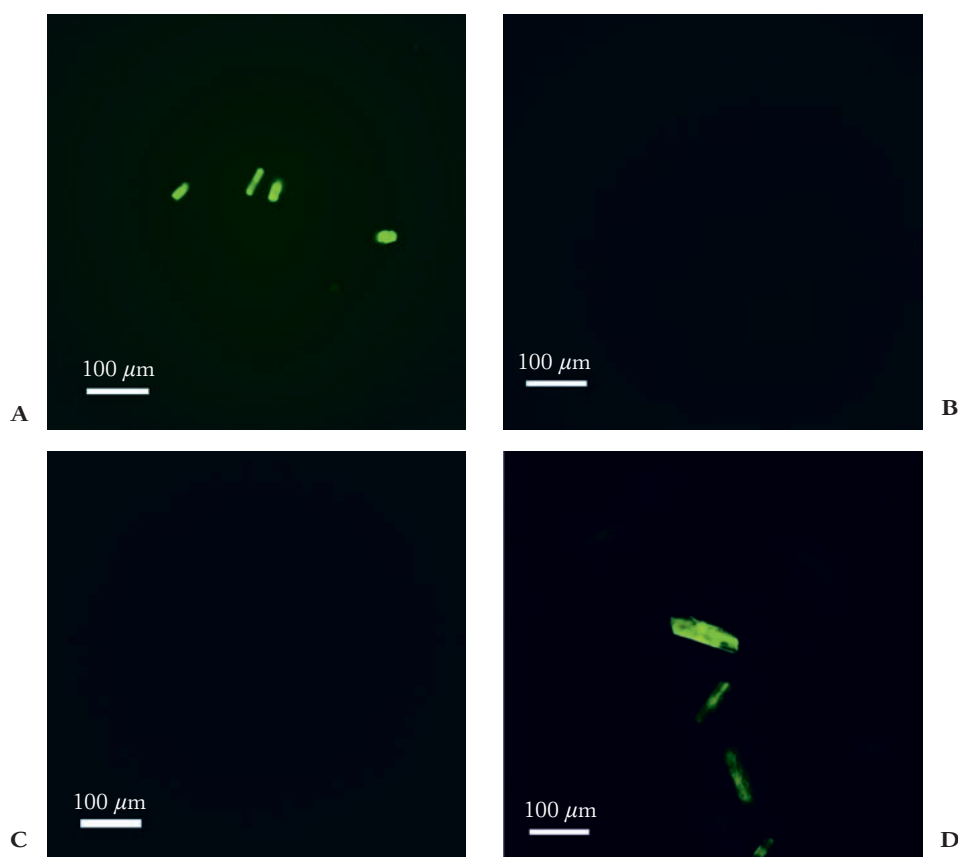


Fig. 3. Morphology of nadifloxacin (NFX) crystals and creams according to polarized light microscopy at a light wavelength of 488 nm

A, NFX crystals; B, NFX-A; C, NFX-B; and D, NFX-C.

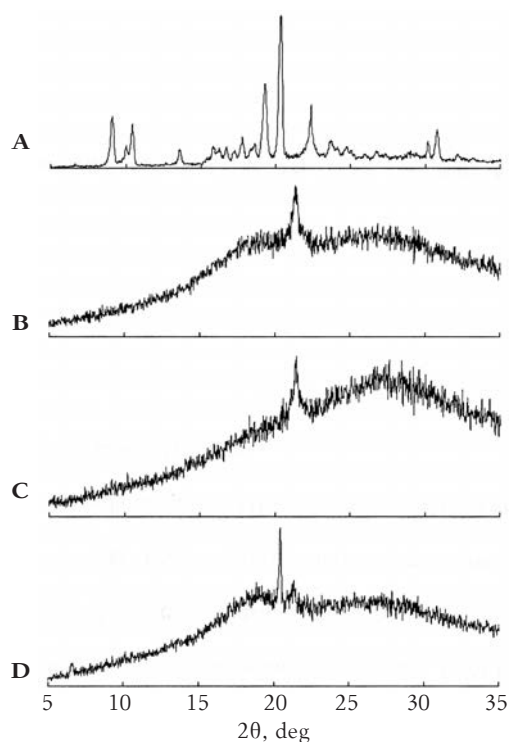


Fig. 4. Comparison of the x-ray powder diffraction patterns of nadifloxacin (NFX) crystals and NFX creams

A, NFX crystals; B, NFX-A; C, NFX-B; and D, NFX-C.

formed to examine the molecular state of the creams (Fig. 5). Results revealed that the spectra of NFX-A, NFX-B, and NFX-C lacked the characteristic peak of NFX crystals. Since the preparations had a low NFX content (1%), NFX peaks may have overlapped because of excipients in the preparations. With fatty bases, spectra resulting from olefin groups have been observed in the regions between 4200 and 4400 cm^{-1} as well as 5600 and 5800 cm^{-1} (12). As shown in Fig. 6, NFX-A and NFX-C had roughly the same content based on the second derivative of the near-infrared absorption spectra, but NFX-B was found to have slightly fewer fats and oils than did the other 2 creams. Spectra presumably due to differences in water content resulting from hydroxyl groups have been observed in the region between 5100 and 5400 cm^{-1} (13). Based on differences in absorption spectra, water content was highest in NFX-B, followed by NFX-C and then NFX-A; NFX-B in particular had a higher water content than the other 2 creams. Thus, the second derivative of near-infrared absorption spectra of excipients is shown in Fig. 7. Results indicated that spectra of individual excipients were similar regardless of the region; NFX-C was found to have a spectrum simi-

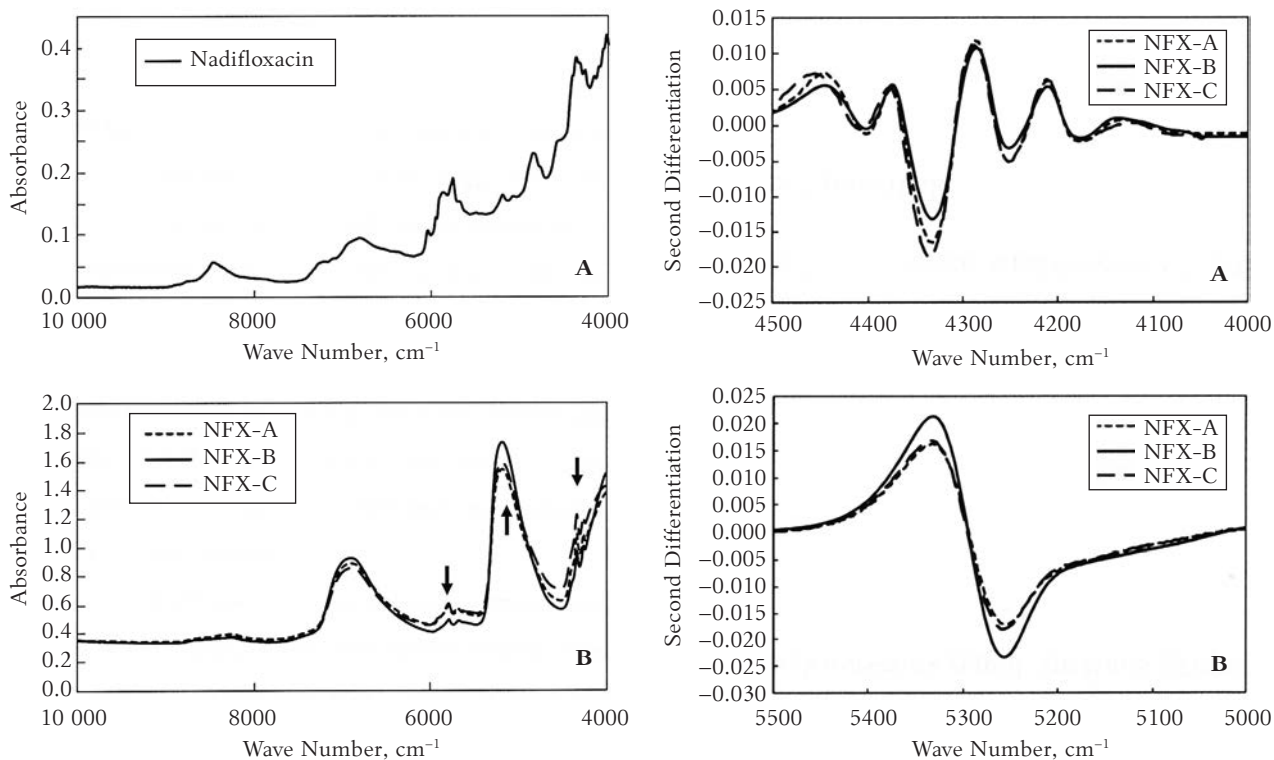


Fig. 5. Near-infrared spectra of nadifloxacin (NFX) crystals and NFX creams

A, NFX crystals; B, NFX-A, NFX-B, and NFX-C.

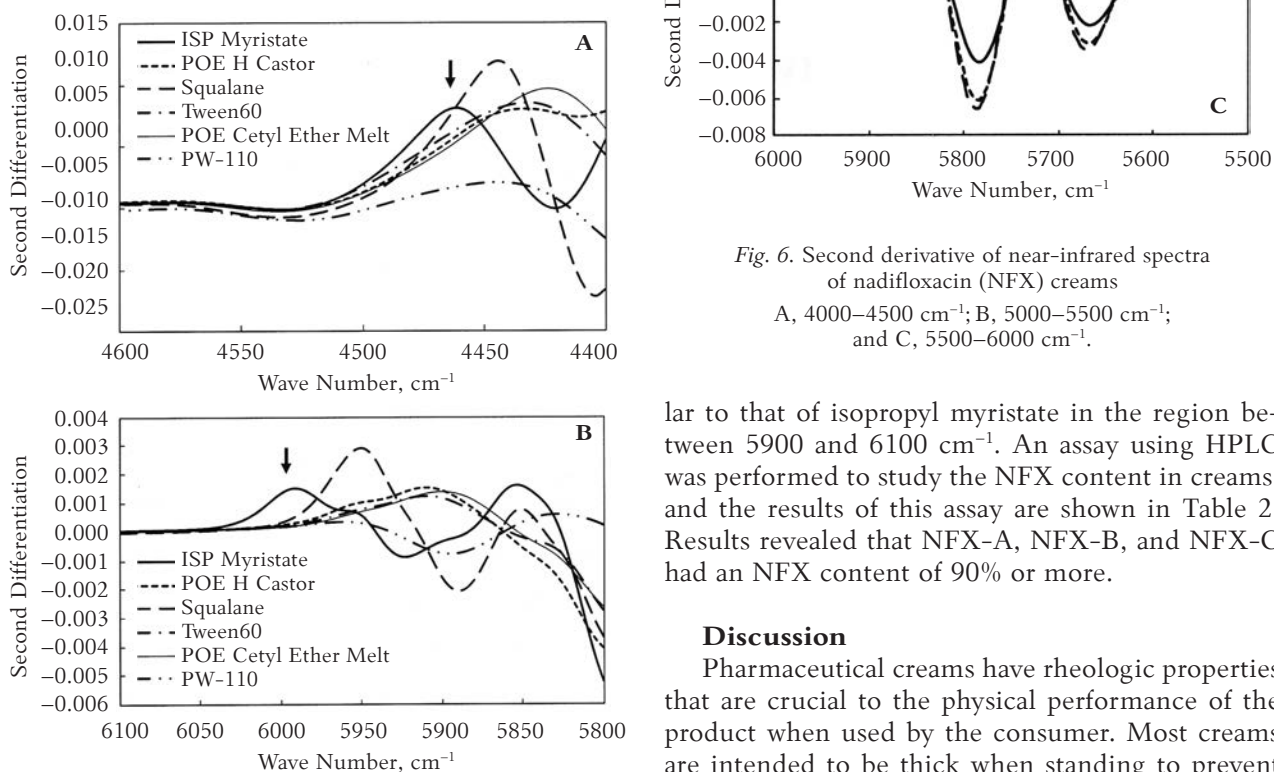


Fig. 6. Second derivative of near-infrared spectra of nadifloxacin (NFX) creams

A, 4,000–4,500 cm⁻¹; B, 5,000–5,500 cm⁻¹; and C, 5,500–6,000 cm⁻¹.

Fig. 7. Second derivative of near-infrared spectra of excipients A, 4,400–4,600 cm⁻¹; B, 5,800–6,100 cm⁻¹.

lar to that of isopropyl myristate in the region between 5,900 and 6,100 cm⁻¹. An assay using HPLC was performed to study the NFX content in creams, and the results of this assay are shown in Table 2. Results revealed that NFX-A, NFX-B, and NFX-C had an NFX content of 90% or more.

Discussion

Pharmaceutical creams have rheologic properties that are crucial to the physical performance of the product when used by the consumer. Most creams are intended to be thick when standing to prevent them from flowing away from the intended area of use. Differences in additives contained in preparations may affect the flattening and adherence of

Table 2. Mean Nadifloxacin (NFX) Content Measured by High-Performance Liquid Chromatography (n=3)

Cream Type	Nadifloxacin Content, mg/mL			
	No. 1	No. 2	No. 3	Total, mean (SD)
NFX-A	0.969	0.969	0.971	0.970 (0.001)
NFX-B	0.899	0.946	0.949	0.931 (0.028)
NFX-C	1.038	1.011	1.021	1.023 (0.013)

creams. Results of comparing the viscosity and flattening of NFX creams in this study indicated that individual preparations had different physicochemical properties. Because of viscosimetry, high viscosity at a near zero shear rate characterizes this behavior; determining the yield stress value quantifies this desired property. Creams are also engineered to be easy to apply when rubbed. Differences in viscosity as were noted here are thought to occur due to differences in the type and amount of additives contained in the preparations. In addition, NFX-C was more likely to have a slightly higher viscosity at about 500 s and 700 s. Typically, when a cream is uniformly emulsified, its viscosity is found to decrease with time. However, determining the viscosity of NFX-C was hampered, so NFX-C is surmised to have a different level of emulsification than that found in NFX-A and NFX-B. From a result of the flattening measurement, NFX-C spread unevenly and not in a concentric fashion. If the preparation were adequately emulsified, viscosity and flattening would be measured consistently. However, determination of viscosity revealed that viscosity temporarily increased approximately 500 s and 700 s for NFX-C, and differences in flattening and the yield values of preparations were noted. Such findings may indicate that differences in additives affected the physical properties of the preparations. When NFX crystals were irradiated with light at a wavelength of 488 nm, they had similar fluorescence, so the NFX-C crystals are surmised to be NFX crystals (Fig. 3). As shown in Fig. 4, the fact that similar powder x-ray diffraction peaks appeared for the 3 preparations may be due to excipients contained in the preparations. The NFX-C was found to produce powder x-ray diffraction peaks at $2\theta=20.4^\circ$. This peak coincides with the peak due to NFX crystals, so results suggested that the NFX-C crystals observed with polarization microscopy are NFX crystals. In terms of the typical changes in viscosity over time, if a certain amount of force is applied and a yield value of the substance is exceeded, then its structure will be disrupted. Its viscosity will decrease and the substance will flatten out. Under conditions where a substance structure is disrupted, its viscosity will seldom increase again. However, NFX-C was found to have a temporary increase in viscosity at 500 s and 700 s. This was potentially caused by the prepa-

ration not being uniformly dispersed since the NFX crystals in NFX-C precipitated. In light of these findings, NFX crystal precipitation and emulsification are surmised to have contributed to differences in the emulsification and viscosity of the creams. Based on these findings of the near-infrared absorption spectroscopy, the small amount of fats and oils and high water content in NFX-B may have been factors that affected the viscosity and flattening of the preparation. In other words, differences in the viscosity and flattening of the creams may reflect differences in the content and quality of fats and oils in additives and differences in water content. The spectrum for NFX-C was found to have its peak in a different location than the peaks of spectra for NFX-A and NFX-B in the regions between 4400 and 4500 cm^{-1} as well as 5800 and 6100 cm^{-1} . This may indicate differences in spectra that arose because of differences in excipients in the preparations. As shown in Fig. 7, neither NFX-A nor NFX-B contained isopropyl myristate as an excipient, so this additive is thought somehow to affect the emulsification of the cream. The properties of individual creams differ, so presumably this would affect an assay of NFX and its stability. Precipitation of NFX crystals in NFX-C was confirmed by microscopy. Since an assay using HPLC was performed by dissolving creams in a solvent and quantitatively measuring NFX, results were converted into the NFX content. Disparities in absorbance by and feel on the skin are thought to occur when creams are actually used clinically despite an assay indicating an NFX content of 90% or more. Clearly, differences among NFX-A, NFX-B, and NFX-C arose because of compounding ratios and manufacturing processes despite the preparations being formulated with the same additives. These differences are expected to affect the emulsification of creams. Thus, differences in the emulsification technique used in the cream may affect the preparation, but differences in emulsification, viscosity, and additives may be reflected in differences in how the preparation feels on the skin in clinical settings. In other words, differences in flattening lead to different amounts applied by patients in clinical settings and different feel on the skin, and these variations may affect the therapeutic effectiveness of the preparation. Near-infrared absorption spectroscopy, a nondestructive method of analysis, is a useful method of identifying differences in preparations (14). As the current study indicated, differences may affect skin penetration since preparations are used on areas with a thin layer of skin, like the face, to treat conditions like acne. In a study using corticosteroids, Stoughton reported that preparations with different additives resulted in different levels of bioavailability despite the preparations having the same active ingredients and the

same amount being applied (6). Near-infrared absorption spectroscopy revealed differences in water content and the type and amount of additives in the NFX preparations studied here. In addition, results suggested differences in emulsification, so these differences may affect the coefficient of drug diffusion across the stratum corneum and lead to disparities in therapeutic effectiveness. The 3 NFX creams examined in this study were found to have different properties, despite having the same active ingredients, due to differences in the type and amount of additives they contained. These differences may affect the feel on the skin and therapeutic effectiveness of the preparation when it is actually used by patients. Studying the physicochemical properties of preparations is a useful way to collect information on a drug.

Elucidating differences in the properties of individual preparations should provide useful information for the assessment and selection of preparations.

Conclusions

Differences in the viscosity and flattening of NFX-A, NFX-B, and NFX-C were noted. In addition, microscopy revealed differences in emulsification and it revealed the precipitation of NFX crystals in NFX-C. Near-infrared absorption spectroscopy revealed that differences in the type and amount of additives and water content in the creams contributed to differences in the preparations.

Statement of Conflicts of Interest

The authors state no conflicts of interest.

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