Original Article

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General selection criteria for safety and patient benefit [XIII]: Comparing the formulation characteristics of brand-name and generic bifonazole creams

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SUMMARY A comparative evaluation of the brand-name drug Mycospor and six generic drugs (IWAKI, Bifonol, F, YD, Sawai, and TEVA), all comprising a cream formulation containing the antifungal drug bifonazole, was performed based on physicochemical measurements. The pH of the various formulations was significantly higher for the generics Bifonol (pH 7.1), Sawai (pH 6.7), and TEVA (pH 7.3) and significantly lower for YD (pH 4.3) than for the brand-name drug Mycospor (pH 5.5). The viscosity of the various formulations was significantly higher for TEVA (25,011 mPa·s) versus Mycospor (22,376 mPa·s) and significantly lower for IWAKI, Bifonol, F, YD, and Sawai, with Bifonol (8,572 mPa·s) being particularly low. Considering the hysteresis loop area obtained for the shear rate *vs*. shear stress, which represents the thixotropic properties, and using the value of Mycospor as the reference for 100%, YD (179%), Sawai (557%), and TEVA (201%) showed significantly higher values. Furthermore, the membrane permeability of bifonazole at 24 hours was significantly higher for Bifonol (309 μg/mL) and F (182 μg/mL) and significantly lower for Sawai (124 μg/mL) and TEVA (92 μg/mL) than for Mycospor (153 μg/mL). Finally, optical micrographs showed that the dispersion of particles was similar in the various formulations, but the particles of F and TEVA were uniformly dispersed with a smaller particle size than the other formulations. Overall, significant differences were observed in the formulation characteristics between the brand-name drug and generic drugs, which were attributed to differences in the manufacturing process and the types of additives.

Keywords Brand-name drug, generic drug, cream, bifonazole, thixotropy

1. Introduction

In Japan, the overall national healthcare costs have recently been increasing each year, becoming a major social problem (*1*), and generic drugs are being promoted to reduce these healthcare costs (*2*). As of September 2023, the ratio of "generic drugs" to "brand-name drugs with generics + generic drugs" was 80.2%, but considering that the ratio was 79.0% in both 2021 and 2022, further increases are difficult to achieve (*3*). Therefore, as a new measure to increase the ratio, the "selective treatment of brand-name drugs (long-term listed drugs) with generic drugs" came into effect in October 2024 (*4*). This increases the patient's co-payment when a patient requests a prescription for a brand-name drug for which a generic drug is available, which is intended to facilitate the transition to generic drugs. However, awareness of generic drugs among outpatients is low, and many patients are concerned about the side effects and efficacy of generic drugs (*5*). In addition, patients have different preferences when applying topical drugs. One study showed that some patients favored the topical solution that was "not sticky" and "smooth," while some patients reported that "other solutions are better," which were "sticky feeling" and "moist" (*6*). Notably, if pharmacists can inform patients regarding the sense of use characteristics for various products, then they can recommend generic drugs that meet patients' needs.

We have previously reported that the physicochemical

characterization of various dosage forms, mainly topicals with significant differences in the sense of use, including creams (*7,8*), ointments and lotions (*9,10*), ophthalmics (*11,12*), nasal sprays (*13*), and tapes (*14-18*), is necessary to help distinguish the formulations for patients and meet their needs. These reports suggest that differences in the formulation technology and additives used in the manufacturing process affect the sense of use and efficacy of each product among patients.

In this study, a comparative evaluation of brand-name and generic antifungal bifonazole-containing cream formulations was conducted to provide information that may assist patients in selecting the most appropriate product for their needs.

2. Materials and Methods

2.1. Materials

The brand-name bifonazole-containing cream (Mycospor® cream 1%) and the six generic versions used in this study are listed in Table 1.

2.2. pH measurement

The pH of each formulation was measured 10 times using a pH/°C meter designed for dairy and semi-solid foods (HI 99161N, Hanna Instruments Japan, Inc., Chiba, Japan).

2.3. Viscosity measurement

The viscosity of each formulation was measured using a TPE-100H cone-plate viscometer equipped with an integrated temperature control system (Toki Sangyo Co., Ltd., Tokyo, Japan). The measurement temperature was 25°C, the rotational speed of the cone plate (CORD-P1: 1°34' × R24) was set to 1 rpm, and the viscosity (Pa·s) after 90 seconds was recorded. The experiment was conducted 10 times for each formulation.

2.4. Thixotropy measurement

Thixotropy was measured using a TPE-100H cone-plate viscometer with the CORD-04: 3° × R14 cone plate at a constant temperature of 25°C.

Step 1 was shear rate 2 (1/s), Step 2 was shear rate 4 (1/s), Step 3 was shear rate 10 (1/s), Step 4 was shear rate 20 (1/s), Step 5 was shear rate 40 (1/s), Step 6 was shear rate 100 (1/s), Step 7 was shear rate 200 (1/s), Step 8 was shear rate 100 (1/s), Step 9 was shear rate 40 (1/s), Step 10 was shear rate 20 (1/s), Step 11 was shear rate 10 (1/s), Step 12 was shear rate 4 (1/s), Step 13 was shear rate 2 (1/s), and the cone plate was rotated for 90 seconds during each step to obtain the shear stress (Pa). The loop area obtained from the viscosity curve of each formulation was calculated using Visco-chart software (Toki Sangyo Co., Ltd., Tokyo, Japan), and the relative area ratio (%) of the generic drug was compared using the loop area of the brand-name drug as the reference value of 100%.

2.5. Measurement of the membrane permeation volume

A vertical diffusion Franz cell (vertical palm cell) TP-8S (Biocom Systems, Inc., Fukuoka, Japan) was used for membrane permeation volume measurements, and the Strat-M® membrane designed for skin diffusion tests (Merck Ltd., Tokyo, Japan) was used as the membrane. The receptor solution used to fill the vertical diffusion Franz cell was a 1:1 ratio of phosphate buffer saline (pH 7.4) and acetonitrile. After the membrane was mounted in the vertical palm cell, various formulations (0.5 g) were applied to the membrane for measurement at 37°C. The volume of bifonazole that permeated the membrane after 1, 2, 4, 6, and 24 hours was determined by high-performance liquid chromatography (HPLC) using an LC-2000 Plus System (Japan Spectroscopic Corporation, Tokyo, Japan) equipped with an Inertsil ODS-3 column (4.6 × 150 mm, 5 μm; G.L. Science Corporation, Tokyo, Japan). The following HPLC conditions were used: column oven temperature of 40°C, wavelength of 254 nm, flow rate of 1.5 mL/min, analysis time of 4 min, uptake time of 3 min, and a mobile phase consisting of acetonitrile:0.12 M sodium acetate:methanol (84:15:1).

2.6. Visual observation by microscopy

Table 1. List of the creams evaluated in this study

Product name (Former product name)	Abbreviated name	Class	Company name	Lot number
Mycospor® cream 1%	Mycospor	brand name	Bayer Yakuhin, Ltd.	BJ35620
Bifonazol cream 1% "IWAKI" (Bicronol® cream 1%)	IWAKI	generic	Iwaki Seiyaku Co., Ltd.	84065
Bifonol® cream 1%	Bifonol	generic	Toko Pharmaceutical Industries Co., Ltd.	B1101
Bifonazol cream 1% "F"	F	generic	Fuji Pharma Co., Ltd.	AA18A
Bifonazol cream 1% "YD"	YD	generic	Yoshindo Inc.	YAA-1
Bifonazol cream 1% "Sawai"	Sawai	generic	Sawai Pharmaceutical Co., Ltd.	17Z01
Bifonazol cream 1% "TAKEDA TEVA" (Bilmitin® cream 1%)	TEVA	generic	Teva Takeda Pharma Ltd.	CD011

Microscopic observation of the various formulations in the emulsification state was performed using a DMBA310 digital microscope (Shimadzu Rika Corporation, Tokyo, Japan) at 400× magnification. Motic Images Plus 2.2s software (Shimadzu Rika Corporation, Tokyo, Japan) was used to capture images.

2.7. Statistical analysis

The results of each pH measurement, viscosity measurement, flow curve loop area measurement, and membrane permeation volume measurement were tested for significance against the brand-name drug using Dunnett multiple comparison test (*19*). Significance levels are indicated on the graphs for each measurement result using * for $P \leq 0.05$ and ** for $P \leq 0.01$.

3. Results

3.1. pH measurement

The pH measurement results for the various formulations are shown in Figure 1. The generic drugs Bifonol (pH 7.1), Sawai (pH 6.7), and TEVA (pH 7.3) showed significantly higher values than Mycospor (pH 5.5), and YD (pH 4.3) showed significantly lower values.

3.2. Viscosity measurement

Figure 2 shows the viscosity measurement results for the various formulations. The viscosity of TEVA (25,011 Pa·s) was significantly higher than that of Mycospor (22,376 Pa·s), whereas IWAKI (15,301 Pa·s), Bifonol (8,572 Pa·s), F (15,050 Pa·s), YD (20,649 Pa·s), and Sawai (12,347 Pa·s) exhibited significantly lower values. Bifonol had particularly high flowability, with approximately 40% of the viscosity observed for Mycospor.

3.3. Thixotropy measurement

For a dispersion system formulation, the viscosity curve may show hysteresis when the shear rate is reciprocated. This phenomenon is called thixotropy, and the magnitude of thixotropy is determined by measuring the hysteresis area. Therefore, Figure 3 shows the relationship between shear rate (1/s) and shear stress (Pa) obtained by cone-plate viscometry for the various formulations used in this experiment. The shear stress is lower for Bifonol (▲) and YD (○) than for Mycospor (●), whereas IWAKI (■), F (♦), Sawai (□), and TEVA (Δ) have higher shear stress, in that order.

The hysteresis loop areas for the various formulations are shown in Figure 4. The loop area of Mycospor (100%, the reference) was significantly lower than that of YD (179%), Sawai (557%), and TEVA (201%).

3.4. Measurement of the membrane permeation volume

The membrane permeation results at each time point are shown in Figure 5. Membrane permeation continually increased after 2, 4, 6, and 24 hours for all formulations. The permeated volume at 24 hours was significantly higher for F (182 μg/mL) and Bifonol (309 μg/mL) and significantly lower for Sawai (124 μg/mL) and TEVA (92 μg/mL) than that for Mycospor (153 μg/mL).

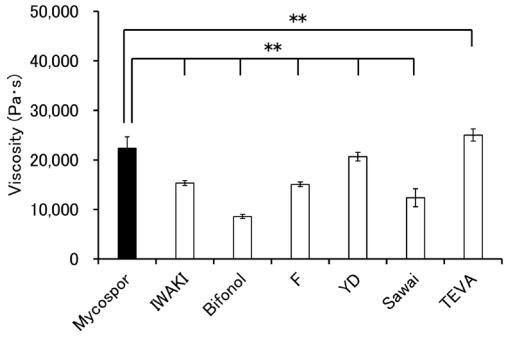

Figure 2. Comparison of viscosity among the various creams. (*n* = 10, *vs*. Mycospor, **$P < 0.01$, *Dunnett*-test) Black bar: brand-name drug, white bar: generic drugs.

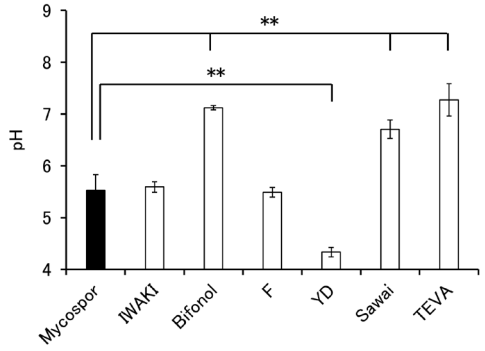

Figure 1. Comparison of pH among the various creams. (*n* = 10, *vs*. Mycospor, **$P < 0.01$, *Dunnett*-test) Black bar: brand-name drug, white bar: generic drugs.

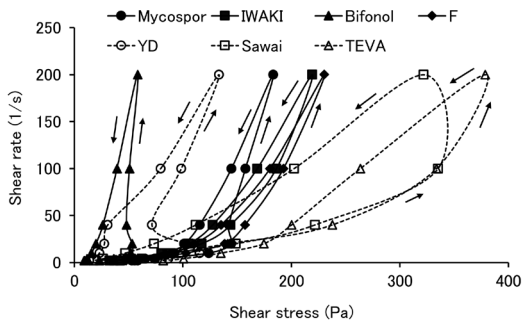

Figure 3. Comparison of thixotropy among the various creams. (*n* = 10) →: direction to strengthen shear stress, ←: direction to weaken shear stress.

3.5. Observation of each formulation in the dispersion state

Figure 6 shows the optical micrographs of each formulation in the dispersion state. Particles were dispersed in all formulations, but IWAKI and Bifonol had the same level of dispersion as Mycospor, YD and Sawai had the largest particles, and F and TEVA had the smallest particles.

4. Discussion

In this study, we comparatively evaluated the formulation characteristics of an antifungal brand-name bifonazole cream (Mycospor® cream 1%) and six generic creams by performing physicochemical measurements.

The pH was significantly higher for Bifonol (pH 7.1), Sawai (pH 6.7), and TEVA (pH 7.3) and significantly lower (pH 4.3) for YD than for Mycospor (pH 5.5) (Figure 1). In general, the pH of the healthy skin surface is reported to be slightly acidic (4.5-6.0) (*20*). However, Bifonol, Sawai, and TEVA may be less irritating to the skin because of their neutral pH range of 6.7 to 7.3. As an antifungal agent, the most common application sites are between the toes and on the soles, including the arch and heel of the foot. Considering that epidermal damage may occur due to pruritus, a low pH may be irritating to the skin, especially in the interdigital area.

The viscosity is an indicator of comfort and is one of the most important factors when applying creams to the affected area. Generally, for ointments and creams, a higher viscosity results in a higher stickiness, and a lower viscosity results in a lower stickiness. The viscosity of TEVA was significantly higher than that of Mycospor, and the viscosities of IWAKI, Bifonol, F, YD, and Sawai were significantly lower (Figure 2). Based on these results, we believe that TEVA can be recommended for patients who do not mind stickiness when using cream formulations containing bifonazole, and Bifonol or Sawai, which have lower viscosity, can be recommended for patients who are concerned about stickiness. Furthermore, YD has a relatively similar viscosity to Mycospor, which may support a smoother changeover from the brand-name drug to the generic formulation.

Next, the hysteresis loop area (the area encompassed by the viscosity curves generated in the direction of the increasing (→) and decreasing (←) shear rate) was calculated for the various formulations (Figures 3 and 4). The larger the hysteresis loop area, the greater the thixotropy. Thixotropy is an indicator of the shear

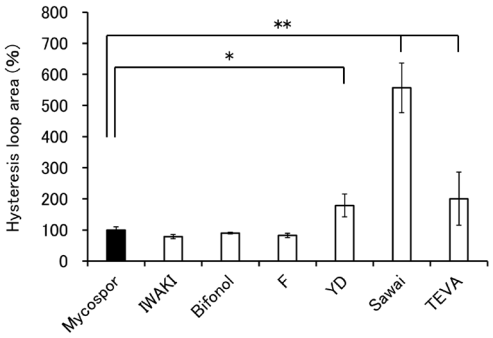

Figure 4. Comparison of hysteresis loop area (%) among the various creams. (n = 10, *vs*. Mycospor, *P < 0.05, **P < 0.01, *Dunnett*-test) Black bar: brand-name drug, white bar: generic drugs.

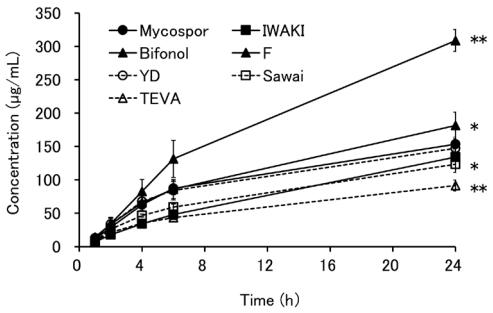

Figure 5. Comparison of membrane permeability of bifonazole after 24 hours among the various formulations. (n = 5, *vs*. Mycospor, *P < 0.05, **P < 0.01, *Dunnett*-test).

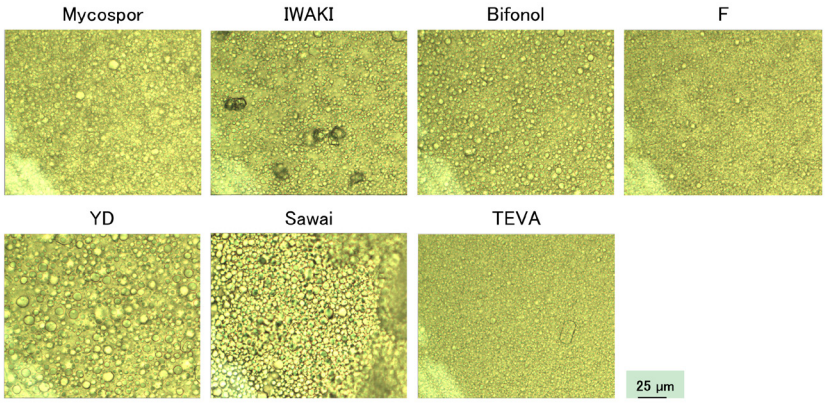

Figure 6. Optical micrographs of the various formulations (400×).

stress that is initially required during application with the fingers. Herein, we compared the formulations using the hysteresis loop area of Mycospor (●) as the reference (100%). Figure 3 shows that Bifonol (▲) and YD (○) have weaker shear stress values, with areas of 91% and 179%, respectively, indicating that they can be spread on the skin with relative ease. In contrast, Sawai (□) and TEVA (Δ) have higher shear stress values and hysteresis loop areas of 557% and 201%, respectively, indicating that they require relatively higher force when spreading them on the skin. These results indicate that the "usability" of Mycospor (●) significantly differed from that of the generic drugs. The formulations with relatively close shear stresses to Mycospor (●) were IWAKI (■) and TEVA (Δ), with loop areas of 79% and 82%, respectively. Therefore, recommending these two formulations may promote a smoother changeover from the brand-name drug to the generic drug.

The membrane permeability of bifonazole was measured for the different formulations using the Strat-M® membrane, an artificial membrane developed as a substitute for animal or human skin in permeability studies. Strat-M® is a multilayer membrane with varying permeability; the upper layer is a double layer of polyethersulfone and the lower layer has a polyolefin structure, which are used to predict the permeation of lipophilic and hydrophilic molecules (*21*). We found that the amount of permeation was significantly higher for Bifonol (309 μg/mL) and F (182 μg/mL) than Mycospor (153 μg/mL), whereas Sawai (124 μg/mL) and TEVA (92 μg/mL) showed significantly lower permeability. According to a questionnaire on generic drugs that was distributed among dermatologists in Kanagawa prefecture, Japan, "Some topicals with different substrates clearly have different efficacy" (*22*). Our results showed that there was approximately a 0.6- to 2-fold difference in permeation compared with Mycospor depending on the formulation, which is consistent with the opinion of the dermatologists, and this may be attributed to the different additives used in the formulations.

Microscopy showed that the dispersion of particles was similar among the various formulations (Figure 6). However, the F and TEVA particles were smaller and more uniformly dispersed than the Mycospor particles, and some YD and Sawai particles appeared to be crystals. The slight differences in dispersion and particle size may reflect the differences in viscosity, thixotropy, and membrane permeability, which may influence the sense of use.

Characteristic differences were observed among the bifonazole-containing cream formulations in terms of viscosity and thixotropy. Furthermore, the amount of drug permeation significantly differed among the formulations, suggesting that the permeation of the drug into the skin, as well as the effectiveness of the drug, is affected by the formulation.

In promoting the use of generic drugs, the differences in the sense of use and efficacy when switching from brand-name to generic drugs may lead to a decrease in adherence and therapeutic efficacy. Providing pharmacists with product-specific information may be critical in selecting or recommending drugs that meet the various needs of patients.

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