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RESEARCH ARTICLE

The 24-hour *in vitro* hairless rat skin permeability study of the 1-day fentanyl transdermal formulations marketed in Japan ü Fentos® Tape and OneDuro® Patch

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ABSTRACT

Context: Two 1-day fentanyl transdermal formulations (FTFs)—Fentos® Tape of gum base and OneDuro® Patch of acrylate base—are marketed in Japan.

Objective: To examine the effects of skin surface temperature and abrasion, as well as adhesive bases on the hairless rat skin permeability of fentanyl.

Materials and Methods: Permeability was examined *in vitro* for 24 hours under the following study conditions: skin surface temperatures (32, 37, and 40°C) and skin abrasion (intact and abraded). The flux (*Js*) rates of fentanyl were calculated. Furthermore, Arrhenius plots were constructed to examine the correlation between skin permeability and skin surface temperature.

Results: We compared the *Js* values of these FTFs in the intact and abraded skin at 32°C. Consequently, FTFs showed the significantly higher ($P < 0.05$) *Js* values in the abraded skin than in the intact skin. The slope was steeper for Fentos® Tape than for OneDuro® Patch.

Discussion and Conclusion: The effects of skin surface temperature on skin permeability were greater for Fentos® Tape than for OneDuro® Patch. Compared to skin intactness, the influences of skin abrasion on skin permeability of fentanyl were greater for both FTFs. Heed needs to be given to skin conditions when using these FTFs in clinical practice.

KEY WORDS: Fentos® , OneDuro® , skin permeability

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INTRODUCTION

Transdermal delivery is an alternative that is useful to the oral delivery of drugs in clinical practice, and the first transdermal drug delivery system (TDDS)—a 3-day patch that delivers scopolamine for the treatment of motion sickness—was approved for use in the United States in 1979.[1] A number of TDDSs of various delivery system designs and delivery mechanisms have been developed thereafter to treat sorts of disorders, e.g., the nitroglycerin, clonidine, and estradiol patches for angina pectoris, hypertension, and menopausal symptoms, respectively.[1]

Among such TDDSs, Duragesic® patch—a 3-day transdermal reservoir patch of fentanyl—was approved for the management of chronic pain in opioid-tolerant patients in the United States in 1990.[2,3] Furthermore, Duragesic® patch was replaced with a new matrix formulation keeping the same brand name in the country in 2009. Fentanyl is a potent, semisynthetic, lipophilic, mu-opioid agonist whose analgesic activity is 75 to 100 times as potent as morphine[4,5] and is one of drugs that are highly useful for the management of moderate to severe cancer pain.[5-7] Duragesic® Patch is composed of the following constituents: the drug release-controlling backing layer of ethyl vinyl acetate (EVA) membrane[8]; the drug reservoir that contains fentanyl as active pharmaceutical ingredient (API) and ethanol as solvent; the adhesive made of hydroxyethyl cellulose; and the protective liner. After its launch, abuse (e.g., extraction of the drug solution from the drug reservoir), content leakage, contact of the leaked solution with the skin, and other problems occurred in association with the use of Duragesic® Patch. Intentional compromise of a fentanyl transdermal formulation (FTF) may result in the uncontrolled delivery of fentanyl and pose a significant risk of overdose and death to the abuser. In 2005, Mylan Technologies, Inc. launched the first generic fentanyl patch "Fentanyl Transdermal System (FTS)"[2,3] (Table 1). Unlike Duragesic® Patch, this matrix FTS contains fentanyl in the silicon-based adhesive and does not control drug release through the EVA membrane.[2,3,5] The Food and Drug Administration gave caution against the possibility that FTFs can be influenced by body temperature elevated by a heated water bed or bathing or by the compromised skin, leading to the increased systemic delivery of fentanyl.[3,9]

Table 1 Characteristics of the 3-day transdermal formulations of fentanyl marketed in the United States of America

Approval year	Manufacturer	Product name	Base polymer	Structure type
1990	Janssen Pharmaceuticals, Inc.	Duragesic	HEC	Reservoir
2009		Duragesic	Acrylate	Matrix
2005	Mylan Technologies, Inc.	FTS	Silicon	Matrix
2006	Lavipharm Laboratories, Inc.		Silicon	Matrix
2007	Actavis Laboratories UT, Inc.		HEC	Reservoir
	Watson Laboratories, Inc.			
	Noven Pharmaceuticals, Inc.		PIB	Matrix
2008	Aveva Drug Delivery Systems, Inc.			
2011	Mallinckrodt, Inc.		HPC	Reservoir

HEC: hydroxyethyl cellulose; FTS: Fentanyl Transdermal System; PIB: polyisobutylene; HPC: hydroxypropyl cellulose

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In Japan, 3-day Durotep® Patch of reservoir type was launched in 2002 but was replaced with 3-day Durotep® MT Patch of matrix type in 2008[6,10] (Table 2). This matrix FTF, which had the advantages of imparting persistent analgesic activity and the stable management of pain relief, was successfully introduced to medical practice in Japan, thus contributing to improvements in the patient's quality of life.

Table 2 Characteristics of the 3-day transdermal formulations of fentanyl marketed in Japan

Approval year	Manufacturer	Product name	Base polymer	Structure type
2002	Janssen Pharmaceuticals, Inc.	Durotep® Patch (cancelled release)	HEC	Reservoir
2008		Durotep® MT Patch	Acrylate (functional)	Matrix
2012	Hisamitsu Pharmaceutical Co., Inc.	3-day application fentanyl tape "HMT"	Acrylate (nonfunctional)	
2013	Yutoku Pharmaceutical Ind. Co., Ltd.	3-day application fentanyl tape "MEIJI"	SIS	
2014	Teikoku Seiyaku Co., Ltd.	3-day application fentanyl tape "TERUMO"		

SIS: styrene-isoprene-styrene; HEC: hydroxyethyl cellulose

On the other hand, nevertheless, the majority of Japanese individuals including cancer patients have a living habit of taking a bath daily. Therefore, Durotep® MT Patch became less adhesive after bathing, and there was an expediential need to develop 1-day FTSs apart from 3-day FTFs.[11,12] In consequence, the following two 1-day FTFs are currently marketed in Japan apart from 3-day matrix FTFs: Fentos® Tape, a matrix FTF composed of the gum-based adhesive, which was launched in 2010; and OneDuro® Patch, another matrix FTF composed of the functional acrylate-based adhesive, which was launched in 2011[12-17] (Table 3).
The pharmaceutical properties thereof are shown in Table 4.

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Table 3 Characteristics of the 1-day transdermal formulations of fentanyl marketed in Japan

Approval year	Manufacturer	Product name	Base polymer	Structure type
2010	Hisamitsu Pharmaceutical Co., Inc.	Fentos® Tape	SIS	Matrix
2011	Janssen Pharmaceutical KK	OneDuro® Patch	Acrylate (functional)	

SIS: styrene-isoprene-styrene

Table 4 Pharmaceutical properties of the 1-day transdermal formulations of fentanyl marked in Japan (Fentos® Tape and OneDuro® Patch)

Manufacturer	Product name	Active ingredient	Excipients	
			Base polymer	Others
Hisamitsu Pharmaceutical Co., Inc.	Fentos® Tape	Fentanyl citrate	Styrene-isoprene-Styrene	Cycloaliphatic saturated hydrocarbon resin, polyisobutylene, liquid paraffin, dibutylhydroxytoluene, synthetic aluminum silicate
Janssen Pharmaceutical KK	OneDuro® Patch	Fentanyl	2-ethylhexyl methacrylate-vinyl acetate-2-hydroxy-ethyl acrylate (functional)	-

Due to its potent opioid nature, clinical concern has arisen about the effects of skin conditions on the skin permeability of fentanyl when applying FTFs to patients with elevated body temperature or compromised skin because of the increased risk of overdose (e.g., respiratory suppression, disturbance of consciousness, somnolence, nausea, and vomiting). However, no head-to-head *in vitro* study of these 1-day FTFs is available that has examined the abovementioned effects. The objective of the present study was to examine the effects of skin surface temperature and abrasion, as well as adhesive bases on the hairless rat skin permeability of fentanyl when using Fentos® Tape and OneDuro® Patch.

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METHODS

MATERIALS

FTFs

Fentos® Tape 1 mg (22.4 × 22.4 mm; Hisamitsu Pharmaceutical Co., Inc., Tokyo, Japan) and OneDuro® Patch 0.84 mg (20.5 × 20.0 mm; Janssen Pharmaceuticals, Inc., Tokyo, Japan) were procured from the market before use.

Animals

Fifteen male WBN/ILA-Ht hairless rats were purchased from Saitama Experimental Animal Supply Co., Ltd. Animals were handled in accordance with the rules established by the Institutional Animal Care and Use Committee at Toko Pharmaceutical Industries Co., Ltd.

Devices

A vertical diffusion cell (Microette™ Plus/Vision Microette™; Hanson Research, Chatsworth, CA, USA) was used to conduct the skin permeation study, and an autosampler (Microette™ Autosampler, Hanson Research) to collect the sample solution for permeation.

Skin treatment

The skin from male WBN/ILA-Ht hairless rats (8 to 9 weeks in age; 180 to 230 g in body weight) was used. General anesthesia was conducted with the 25% solution of urethane, followed by the shaving of abdominal hair with an electric clipper prior to skin resection. The resected skin (35 mm in diameter) was inverted to remove the subcutaneous fat layer with a pair of scissors in order to expose the dermis, followed by still standing of the dermis placed downward onto the filter paper that was impregnated with saline until the attachment of the study formulation.

Fentanyl permeation through the skin

Fentos® Tape and OneDuro® Patch were punched out to round pieces of 15 mm in diameter, and the protective liner was peeled off before attachment to the resected skin. Subsequently, study material was set onto the vertical diffusion cell (Hanson Research), and the upper and lower parts of the cell were fixed with a metallic pinch clamp. The interior of the cell was filled with the receiver solution (30 mM KH_2PO_4; 30 mM Na_2HPO_4 = 1:2, pH 7.0) to remove air bubbles, followed by its passage through the cell at a rate of 1.5 mL/hr. The 1.5-mL aliquots of the solution were collected every 2 hours with Microette™ Autosampler (Hanson Research) up to 24 hours of study. Subsequently, 400 µL of the internal reference solution (4 µg/mL amyl 4-hydroxybenzoate; Tokyo Chemical Industry Co., Ltd., Tokyo, Japan) were mixed with 400 µL of the sample solution collected at each measurement point, and a high-performance liquid chromatograph (10 A series; Shimadzu Corporation, Kyoto, Japan) was then used to measure the fentanyl concentrations in the mixed solution. The drug reservoir was set to temperatures of 32, 37, and 40°C when using the intact skin and to 32°C when using the intact and abraded skin. The flux through the skin (*Js*, µg/cm^2/hr) at steady state was calculated for comparison purposes.[18]

Preparation of the abraded skin and measurement of water content in the skin surface

The resected skin was placed onto an aluminum tray, and the stratum corneum (SC) was stripped off seven times with Scotch Brand BookTape 845 (3M) as described previously.[3] Subsequently, Courage+ (Corneometer® CM 825; Courage+ Khazaka Electronic GmbH,

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Cologne, Germany) was calibrated once before use to measure water content in the skin surface. The probe was cleaned with absorbent cotton impregnated with ethanol and was then applied onto the surface of the removed intact and abraded skin. Water content in the skin surface was measured six times to calculate the mean values.

Conditions for high-performance liquid chromatography

Fentanyl (Mallinckrodt Pharmaceuticals, Dublin, Ireland) was used as reference standard, and amyl 4-parahydroxybenzoate (Tokyo Chemical Industry Co., Ltd.) as internal standard. A high-performance liquid chromatograph (10A series; Shimadzu Corporation) was used to conduct high-performance liquid chromatography (column: ODS cadenza CD-C18; detection wavelength: 205 nm; column temperature at measurement: 40°C; injection volume of sample: 20 μL). The flow rate for the mobile phase [30 mM NaH_2PO_4 + 5 mM SDS: acetonitrile (11:9)] was set to attain the fentanyl measurement peak of 5.6 minutes, with a measurement time of 10 minutes.[7]

Calculation of the flux rates of fentanyl through the intact and abraded skin

Fentanyl content in the sample at each measurement point was calculated from the ratio of fentanyl in the reference standard solution to the internal standard, and *Js* was calculated according to the following equation.[19]

$Js = (VdC/dt)/A \times S$,

where C: drug concentration in the sample, t: measurement time (hr), V: volume (mL) of the receiver in the sample, A: effective diffusion area (cm^2), and S: size of the formulation.

***Js* and maximum flux values of fentanyl through the intact skin**

The *Js* and maximum flux (J_{max}) values of fentanyl from Fentos® Tape and OneDuro® Patch were calculated at measurement temperatures of 32, 37, and 40°C. Furthermore, the increase rates of the J_{max} values of fentanyl at 37°C and 40°C from the values at 32°C were calculated. The *Js* and J_{max} values of fentanyl from Fentos® Tape and OneDuro® Patch at measurement points were compared between the two FTF groups to test a significant difference according to Welch's t-test.

Arrhenius plotting

The natural logarithms of J_{max} for the skin permeation of fentanyl were plotted against the inverse of skin surface temperature to depict linear approximations of skin permeability.

Comparisons of the *Js* and J_{max} values between the intact and abraded skin

The *Js* and J_{max} values of fentanyl through the intact and abraded skin at 32°C when using Fentos® Tape and OneDuro® Patch were compared between the two FTF groups to test a significant difference according to Welch's t-test.

Statistical analysis

All values are expressed as mean ± SE. Microsoft Excel for Windows (version 2003, Tokyo, Japan) was used to perform all statistical analyses according to Welch's t-test. A value of $P < 0.05$, one-tailed, was considered statistically significant.

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RESULTS

Permeability of fentanyl through the intact skin

Time-course changes in the *Js* values of fentanyl from Fentos® Tape and OneDuro® Patch through the intact skin at 32, 37, and 40°C are shown in Figure 1. The J_{max} values of fentanyl from Fentos® Tape and OneDuro® Patch at 32°C were 10.13 ± 6.76 µg/hr/sheet and 10.89 ± 2.13 µg/hr/sheet, respectively. No significant difference was found between the two FTF groups according to Welch's t-test [Figure 1(a)]. The *Js* values of fentanyl from Fentos® Tape and OneDuro® Patch at 37°C were 22.43 ± 2.00 µg/hr/sheet and 20.25 ± 0.47 µg/hr/sheet, respectively. OneDuro® Patch showed the significantly higher ($P < 0.05$) *Js* values at 18, 20, 22, and 24 hours of study [Figure 1(b)]. The *Js* values of fentanyl from Fentos® Tape and OneDuro® Patch at 40°C were 28.12 ± 1.68 µg/hr/sheet and 19.89 ± 2.14 µg/hr/sheet, respectively. Fentos® Tape showed the significantly higher ($P < 0.05$) *Js* values at 6 and 8 hours of study, while OneDuro® Patch exhibited the significantly higher ($P < 0.05$) *Js* values at 18, 20, 22, and 24 hours of study [Figure 1(c)].

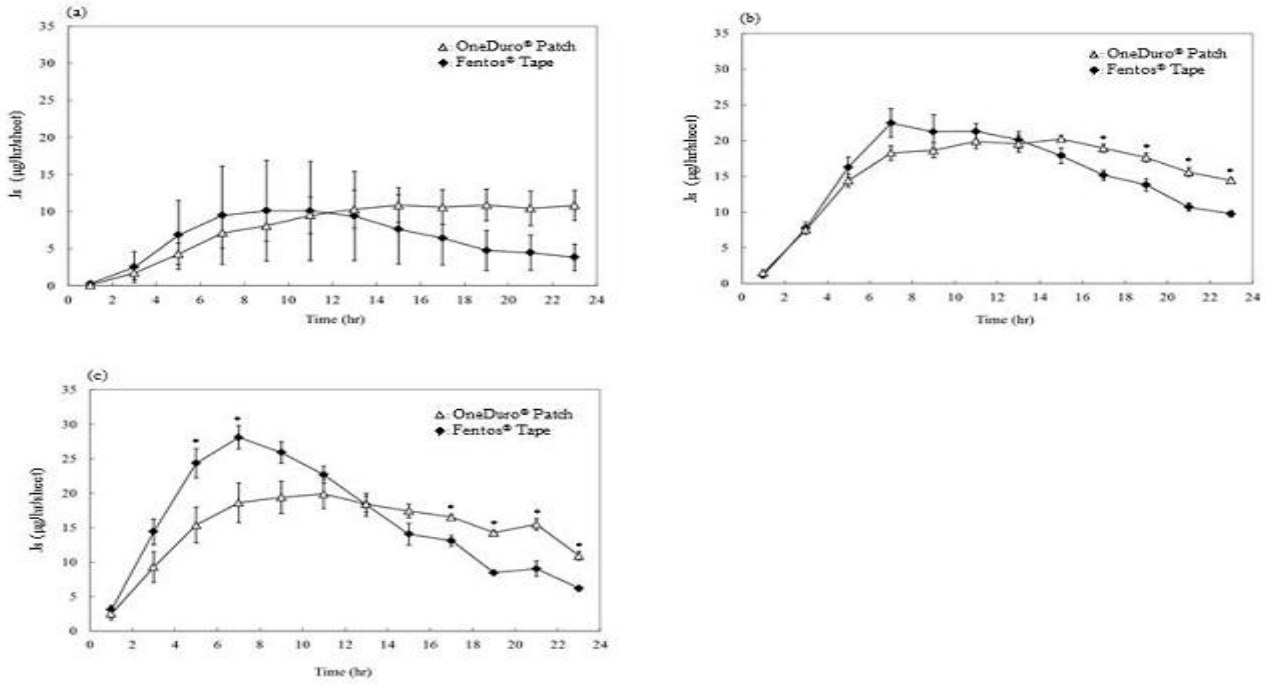

Figure 1 Time-course changes in the *Js* values of fentanyl from Fentos® Tape and OneDuro® Patch through the intact skin in the 24-hour *in vitro* rat skin permeability study (a) 32°C; (b) 37°C; (c) 40°C Values are expressed as mean ± SE (n = 3).

*: $P < 0.05$ (Welch's t-test)

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Through the rat intact skin, both Fentos® Tape and OneDuro® Patch showed increases in the J_{max} values in association with temperature elevations. However, Fentos® Tape exhibited the greater increase rates of the J_{max} values in association with temperature elevations. Namely, Fentos® Tape showed the 2.21- and 2.78-fold increases in the J_{max} values at 37°C and 40°C, respectively, against the J_{max} value at 32°C (Table 5). Arrhenius plots at different measurement temperatures display the steeper slope in the linear approximations of skin permeability for Fentos® Tape than for OneDuro® Patch, suggesting that the former is more prone to be influenced by skin surface temperature (Figure 2).

Table 5 Maximum permeation rates of fentanyl into the intact skin from Fentos® Tape and OneDuro® Patch at 32, 37, and 40°C

Temperature, °C	Fentos® Tape (n = 3)		OneDuro® Patch (n = 3)	
	Mean ± SE, µg/hr/sheet	Scale factor vs. 32°C	Mean ± SE, µg/hr/sheet	Scale factor vs. 32°C
32	10.13 ± 6.76	-	10.89 ± 2.13	-
37	22.43 ± 2.00	2.21	20.25 ± 0.47	1.86
40	28.12 ± 1.68*	2.78	19.89 ± 2.14	1.83

Values are expressed as mean ± SE

*P < 0.05 (Welch's test)

SE: standard error

Fentos® Tape: 5 cm^2/sheet in strength; OneDuro® Patch: 4.1 cm^2/sheet in strength

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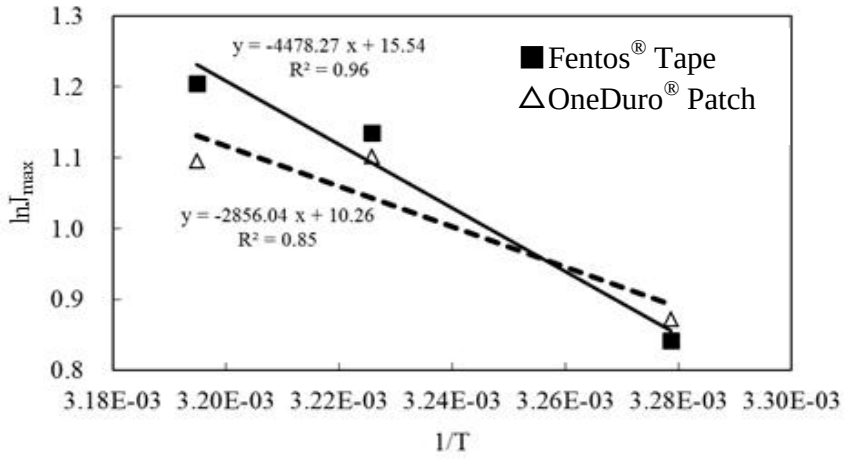

Figure 2 Arrhenius plots displaying the natural logarithms of the steady state rate constant for skin permeation against the inverse of skin surface temperature when using Fentos® Tape and OneDuro® Patch
lnJ_{max}: logarithm of rate constant for skin permeation; T: skin surface temperature

Water content in the intact and abraded skin

The values of water content measured in the intact (n = 6) and abraded (n = 6) skin before application of the study formulations were 15.4 ± 4.4 arb. unit and 32.0 ± 5.5 arb. unit, respectively. A significant difference ($P < 0.05$) was found between these two types of skin, which indicated that the water content in the abraded skin had increased as a consequence of SC stripping. The measured values of water content in the intact and abraded skin when using Fentos® Tape were 13.6 ± 1.5 arb. unit and 31.9 ± 2.3 arb. unit, respectively. A significant difference ($P < 0.05$) was found between the two FTF groups. Furthermore, the measured values of water content in the intact and abraded skin when using OneDuro® Patch were 13.7 ± 1.2 arb. unit and 32.1 ± 1.7 arb. unit, respectively. A significant difference ($P < 0.05$) was found between the two FTF groups.

Permeability of fentanyl through the intact and abraded skin

The *Js* values of fentanyl through the intact and abraded skin at 32°C when using Fentos® Tape and OneDuro® Patch are shown in Figure 3. The *Js* values were 25.30 ± 1.29 μg/hr/sheet and 38.76 ± 1.70 μg/hr/sheet, respectively, when using Fentos® Tape in contrast to 15.33 ± 0.41 μg/hr/sheet and 19.27 ± 0.42 μg/hr/sheet, respectively, when using OneDuro® Patch. Namely, Fentos® Tape exhibited the 1.53-fold *Js* value in the abraded skin against the intact skin, while OneDuro® Patch showed the 1.26-fold *Js* value against the intact skin. The *Js* values of fentanyl for Fentos® Tape and OneDuro® Patch through the intact and abraded skin were compared. Consequently, Fentos® Tape exhibited the significant higher ($P < 0.05$) values at 2, 4, 6, 8, and

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10 hours of study [Figure 3(a)], while OneDuro® Patch showed the significantly higher ($P < 0.05$) *Js* values at 2, 10, 18, 20, and 22 hours of study [Figure 3(b)].

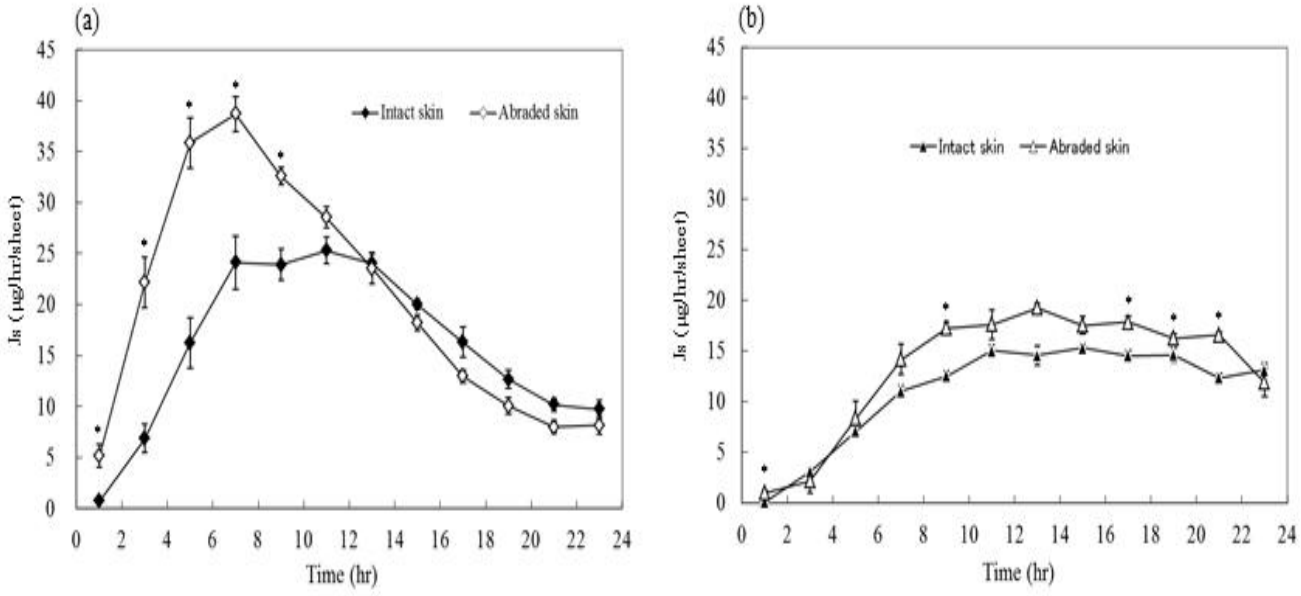

Figure 3 Time-course changes in the *Js* values of fentanyl through the intact and abraded skins at 32°C when using Fentos® Tape and OneDuro® Patch in the 24-hour *in vitro* rat skin permeability study
(a) Fentos® Tape; (b) OneDuro® Patch
Values are expressed as mean ± SE (n = 3).
*: $P < 0.05$ (Welch's t-test)

DISCUSSION

Fentos® Tape has the gum-based adhesive that contains the following components: 1) styrene-isoprene-styrene (SIS) block copolymer that contains polyisoprene as a soft segment which imparts flexibility to the base and polystyrene as a hard segment which imparts cohesion to the base; 2) polyisobutylene and alicyclic saturated hydrocarbon resins as tackifiers; 3) liquid paraffin as a softener; and 4) dibutylhydroxytoluene as an antioxidant. On the other hand, OneDuro® Patch has the acrylate-based adhesive that contains the following components: 1) acrylate 2-ethylhexyl-vinyl acetate-acrylate 2-hydroxyethyl copolymer that contains acrylate 2-ethylhexyl as a soft segment, vinyl acetate as a hard segment, and acrylate 2-hydroxyethyl as the cross-link. Regarding Fentos® Tape, the permeation of fentanyl through the skin is considered to occur due to the action of the carboxyl group that is contained in the adhesive base, which allows the passage of fentanyl into the blood.[20]

The gum base consists of nonpolar polymers. On the other hand, the acrylate base has sorts of pharmaceutical properties and consists of copolymers with or without the functional groups (e.g., polar hydroxyl group and carboxyl group). Drugs made up of copolymers with the

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functional groups (e.g., amine) react especially with the polar acrylate base and are retained in the base.[21,22] The release study of drugs containing the amido, amino, carboxyl, or ester group into the 40% aqueous solution of polyethylene glycol 400 was conducted at 37°C. Consequently, the drug interaction rank order was the amido group > amino group > carboxyl group > ester group based on the values calculated from log D (partition coefficient) and Tg (glass-transition temperature) and on the results from the hydroxyl group wavelength observation by Fourier transition infrared spectroscopy (FTIR).[22] The adhesive base of OneDuro® Patch consists of copolymers that contain the polar hydroxyl group (e.g., acrylate 2-hydroxyethyl copolymer). Therefore, fentanyl with the amido group is considered to interact with the base.

Pressure-sensitive adhesives (PSAs), which had the adhesive of functional acrylate base (e.g., carboxyl and hydroxyl groups) or nonfunctional acrylate base, were used to conduct the 72-hour *in vitro* rat skin permeability study (measurement temperature, 37°C; receiver solution, pH 6.0 phosphate buffer solution).[5] Consequently, the maximum flux, J_{max}, was higher for nonfunctional PSAs than for functional PSAs. This finding was considered attributable to the following facts: 1) fentanyl was retained in the adhesive base because of its reaction with the base containing the amido, carboxyl, or hydroxyl group; and 2) fentanyl was not retained in the nonfunctional acrylate base. Furthermore, double-layered PSAs with the functional or nonfunctional group layers, were used to conduct 72-hour *in vitro* rat skin permeability study. Consequently, the functional group of the acrylate base functioned as the drug release-controlling membrane and the drug reservoir.[5] Based on these results, the acrylate base with the functional group in OneDuro® Patch is considered to retain fentanyl and to suppress drug release into and drug permeation through the skin. Drug release is suppressed by FTFs with the acrylate-based adhesive but is not suppressed by FTFs with the gum-based adhesive that does not interact with the APIs. We consider that these facts led to the greater increase rates of the J_{max} of fentanyl from Fentos® Tape than from OneDuro® Patch.

FTSs, which had the silicon-, acrylate-, or gum-based adhesive that contained 2% fentanyl, were compared with respect to the skin permeation rates of the drug at 32°C and 24 hours of study according to the drug absorption-desorption method.[19] Consequently, the skin permeation rate rank order of fentanyl was the silicon base > gum base > acrylate base, and the solubility of fentanyl from the base was greater for the acrylate base than for the gum base. Furthermore, saturation solubility was reached with 4% fentanyl when adding 1, 2, 4, 6, and 8% fentanyl to the gum base. Drug crystals were formed when adding 6 and 8% fentanyl. The thermodynamic activity of fentanyl in the base increased in FTFs containing not less than 4% fentanyl, and this group of FTFs developed the initial burst effect in water releasability to the phosphate buffer solution (pH, 6.0).[19] Based on these observations, fentanyl is considered to present greater releasability from the gum base than the acrylate base. The 72-hour *in vitro* skin permeability study of the fentanyl reservoir and matrix systems was conducted to compare the rates of permeation through the synthetic membranes at 32°C (skin surface temperature) and 40°C (under the conditions of sauna or hot bating).[3] At 40°C, consequently, the skin permeation rate of fentanyl was twice that seen at 32°C during the first 24 hours of study. When comparing the rates of permeation through the intact and compromised (injury, skin troubles due to sunburn, and hair loss) skin, the skin permeation rates increased for the fentanyl matrix system than for fentanyl reservoir system during the first 24 hours of study; however, the rates became comparable at 25-72 hours of study. The fentanyl matrix system was more prone to be influenced by temperature than the fentanyl reservoir system.[3]

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The values of time to reach maximum concentration (T_{max}) after application to patients were equivalent between Fentos® Tape and OneDuro® Patch, being 20 hours and 18 hours, respectively. [15-17] The values of maximum plasma concentration, C_{max}, for Fentos® Tape (4 mg/sheet) and OneDuro® Patch (3.4 mg/sheet) were comparable, being 0.74 ± 0.55 ng/mL and 0.71 ± 0.25 ng/mL, respectively.[15-17] Daily replacement of a 1-day FTF can sustain plasma fentanyl concentrations equivalent to those obtained with a 3-day FTF. Therefore, Fentos® Tape and OneDuro® Patch became the novel therapeutic options to manage cancer pain in the opioid rotation from oral opioid agents.[14-17] In clinical practice in Japan, therefore, these 1-day FTFs can be used when shifting from 3- to 1-day FTFs.

Body warmers were used to heat the application site of a reservoir FTS to 42°C for the first 4 hours of application to measure plasma fentanyl concentrations and to examine vital signs (blood pressure, heart rate, pulse rate, and respiration rate), and the presence or absence of adverse reactions—saturation, nausea, vomiting, and pruritus.[23] At 4 hours of study, consequently, plasma fentanyl concentrations showed a 4-fold increase in the heating group than in the unheating group. At 24 hours of study, however, plasma fentanyl concentrations were equivalent between the heating group and the unheating group, with no significant differences in vital sign changes and in the incidences of adverse reactions. Furthermore, T_{max} was 23 hours in the unheating group but decreased to 17 hours in the heating group. These observations were considered predominantly attributable to the heat-enhanced skin permeability of fentanyl that had been retained on the skin surface.[23,24] Simulation of plasma fentanyl concentrations indicated a 25% increase when body temperature elevates by 3 degrees from 37°C to 40°C at the time of applying a reservoir FTS to the human skin.[8] Arrhenius plots in the present study, which display the linear approximations of the skin permeability of fentanyl when using Fentos® Tape and OneDuro® Patch, suggest that the former is more prone to be influenced by temperature in concert with the abovementioned findings in the clinical setting.

The *in vitro* skin permeability study of nonsteroidal anti-inflammatory drugs from the gum base was conducted at 2, 25, 37, and 47°C. The natural logarithms of the steady state rate of permeation of felbinac, loxoproprofen, flurbiprofen, and ketoprofen were plotted against the inverse of skin surface temperature to examine the correlations between skin permeability and skin surface temperature.[25] Consequently, drug solubility into the skin increased exponentially in association with temperature elevations, and the *Flux* values increased.[25] The phosphate buffer solution of benzoic acid (BA) was injected into the human skin that had been resected from the abdomen by trypsin treatment. The skin permeability of BA at measurement temperatures of 28 to 40°C was examined by FTIR-mediated observations of wavelengths and by electron microscopy.[26] Consequently, the lamellar layers of the SC disorganized as the consequence that the length of free fatty acids therein shortened in association with temperature elevations, thus exhibiting the increased skin permeability of BA. Based on these findings, we speculate that the permeation of fentanyl through the SC increased as the consequence that the lamellar organization of the SC changed in association with temperature elevations in our study as well, thus leading to increases in the J_{max} of fentanyl.

To date, the only study that directly compared 1-day FTFs—Fentos® Tape and OneDuro® Patch—was conducted by Oshima et al., in which the impression from use and adhesiveness thereof were examined.[12] The releasability and skin permeability of fentanyl differ in FTFs with different adhesive bases.[3,19] Therefore, we conducted the *in vitro* hairless rat skin permeability study using 1-day FTFs with different adhesive bases—Fentos® Tape and OneDuro® Patch—to

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examine the effects of temperature on fentanyl permeation through the skin. On the assumption that differences in the patient's skin conditions would affect the skin permeability of fentanyl, furthermore, we used the intact and abraded skin to examine this profile. Previous studies have indicated that Fentos® Tape rather than OneDuro® Patch is more likely to be influenced by temperature and skin conditions.[3] Variations in skin permeability based on the surface temperature, condition, and other aspects of the skin are predicted to occur not only for 1-day but also 3-day FTFs. Three-day FTFs currently marketed in Japan are made of copolymers that retain the drug by means of 1) the acrylate-based adhesive containing copolymers with the function groups (e.g., hydroxyl and carboxyl groups) and 2) the gum-based adhesive containing copolymers (e.g., SIS). We consider that the fact—changes in the skin permeability of fentanyl due to no retention of the drug by the gum-based adhesive of Fentos® Tape in contrast to fentanyl release and skin permeability that are suppressed by the acrylate-based adhesive of OneDuro® Patch—caused significant differences in the skin permeability of fentanyl between these FTFs.

The skin is composed of the SC, epidermis, and dermis. The SC is the biobarrier that prevents water evaporation and the penetration of foreign matters from the exterior into the body and also functions as the biomembrane that controls drug diffusion in the skin and as the second drug reservoir.[18,27-29] Both Fentos® Tape and OneDuro® Patch showed the higher J_{max} values in the abraded skin than in the intact skin at some time points of measurement. Furthermore, the increase rates of the J_{max} values of fentanyl from Fentos® Tape were greater in the abraded skin (a 1.26-fold increase) than in the intact skin (a 1.53-fold increase). We conjecture that these findings are attributable to the fact that the thinner SC in the abraded skin than in the intact skin resulted to lose its function as the drug reservoir or drug release-controlling membrane.

Based on the results from the present study, we speculate that increased skin temperature, the reduced biobarrier function of the SC, the lowered drug retention in the epidermis, and no suppression of skin permeability by the gum-based adhesive were responsible for the increased J_{max} of fentanyl when using Fentos® Tape and OneDuro® Patch.

CONCLUSIONS

The present study suggests the following: 1) the effects of skin surface temperature on skin permeability were greater for Fentos® Tape with the gum-based adhesive than for OneDuro® Patch with the acrylate-based adhesive; and 2) as compared with skin intactness, the influences of skin abrasion on skin permeability were greater for both FTFs. Therefore, heed needs to be given to skin conditions when using these FTFs in clinical practice.

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Declaration of interest

The authors have nothing to declare.

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