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RESEARCH PAPER

The Effects of Pressure-Sensitive Adhesives and Solubilizers on the Skin Permeation of Testosterone from a Matrix-Type Transdermal Delivery System

Hong Zhao,[1,*] Dong-Woo Park,[2] Soo-Kyun Kim,[2] Chi-Ho Lee,[1] and Dae-Duk Kim[1,†]

[1]*College of Pharmacy, Pusan National University, Pusan 609-735, South Korea*
[2]*Il Yang Pharm Co., Ltd., Seoul 449-900, South Korea*

ABSTRACT

Matrix-type transdermal delivery systems of testosterone (TS) were formulated with three different pressure-sensitive adhesives (PSA). The effects of PSA, skin permeation enhancers, and solubilizers on the rat skin permeation rate of TS were systematically investigated. Without a solubilizer, the skin permeation rate of TS reached its maximum value when only 2% of TS was loaded in the matrix and the crystal formation in the matrix was very rapid and severe. Two surfactants differing in their hydrophile–lipophile balance (HLB) number were, therefore, considered. Span 80, which was of the lower HLB number, was more effective than Tween 80 in increasing the solubility, and thereby increasing the permeation rate of TS. Moreover, the concentrations of both the solubilizer and the skin permeation enhancer affected the skin permeation rate. Thus, the highest skin permeation rate (4.14 μg/cm^2/hr) was achieved when 2% TS was loaded in DuroTak® 87-2516 together with 10% Span 80 and 3% dodecylamine, the permeation enhancer. In vivo study showed that the application of an experimental patch on rat abdominal skin resulted in a prompt and significantly higher plasma concentration of TS than that of a commercial product (Testoderm®) designed to

*Present address: LG Chem Investment, Ltd./Life Science R&D, Research Park, Taejon 305-380, South Korea.
†Corresponding author. Fax: +82-81-510-2800; E-mail: ddkim@pusan.ac.kr

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apply on the scrotal skin. The area under the curve (AUC) increased linearly as the loading dose of TS increased up to 6%. Thus, based on these results, a non-scrotal matrix-type transdermal delivery system of TS could be developed.

Key Words: *Matrix-type; Non-scrotal; Testosterone; Transdermal delivery*

INTRODUCTION

Testosterone (TS) is clinically used for substitutional therapy in men with hypogonadism. Since TS undergoes extensive first-pass metabolism after oral administration, conventional treatments for hypogonadal men consist of periodic intramuscular injections of chemically modified TS or oral administration of methyl TS. Recently, many alternative formulations have been developed for TS administration, including the transdermal delivery system (TDS),[1] topical spray and topical aerosol,[2,3] sublingual tablets,[4] and subcutaneous implants.[5] Among these, TDS is considered to be safer and more effective than injection methods. Currently, reservoir-type non-scrotal TDS (Androderm®) and matrix-type scrotal TDS (Testoderm®) of TS are commercially available.

Matrix-type scrotal TDS must be applied on the scrotal skin because of its low skin permeation rate.[6] Also, it undergoes transdermal first-pass metabolism due to the high level of 5α-reductase present in scrotal skin, which may result in enlargement of the prostate. Non-scrotal reservoir-type TDS is often related with skin irritation due to high ethanol concentration,[6] and its preparation process is costly and complex.

The development of a non-scrotal matrix-type TDS of TS is expected to achieve an effective, safe, and convenient TS replacement therapy. However, low solubility of drug in the pressure-sensitive adhesive (PSA) has always been a typical problem, resulting in the crystal formation in the matrix and the reduction of the skin permeation rate.[7–9] In this study, the effect of PSA and additives on the skin permeation rate of TS was systematically investigated. In vivo plasma concentration profiles were also investigated after applying the experimental TDS on rat abdominal skin.

MATERIALS AND METHODS

Materials

Testosterone and dodecylamine were supplied by Sigma Chemical Co. (St. Louis, MO). Span 80 and Tween 80 were purchased from Yakuri Pure Chemical Industry Co. (Osaka, Japan). Three polyacrylate PSA (DuroTak® 87-2516, 87-2620, 87-2852) were kindly supplied by National Starch & Chemical Company (Bridgewater, NJ) as gifts. Release liner (Scotchpak 1022) and backing layer (CoTran 9722) were obtained from 3M (St. Paul, MN). All other chemicals were reagent grade or higher, and used as received.

Preparation of Matrix-Type TDS

The weighed amounts of TS and other solid additives (i.e., skin permeation enhancer) were first dissolved with the minimum amount of ethanol, and then mixed with PSA and other ingredients (i.e., Span 80 or Tween 80) using a mechanical stirrer at 800 rpm for 15 min until a clear solution was obtained. The mixture was degassed using an ultrasonicator, and then casted on the release liner using a micrometer adjustable casting knife (R.K. Coat Instruments Ltd., U.K.), which was set at 100 μm. After drying overnight at ambient temperature, the PSA was covered with the backing laminate. The TDS was cut into 4 cm × 5 cm sizes and sealed in a pouch until used for future studies.

Preparation of Rat Skin

The animals used for the preparation of skin were male Sprague Dawley (220–250 g) rats purchased from Dae-Han Laboratory Animal Research Center Co. (Taejon, Korea). The rats had free access to food and water until they were used for experiments. The rats were humanely sacrificed in a CO_2 chamber right before the experiments. The dorsal hair was removed with a clipper and full-thickness skin (about 16 cm^2) was surgically removed from each rat. The fat and connective tissue were carefully removed from the skin. The skin specimens were cut into appropriate sizes after washing with normal saline.

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In Vitro Skin Permeation Study

A Valia-Chien skin permeation system (diffusion area 0.64 cm^2 and volume 3.5 mL) was used at 37°C to investigate the in vitro permeation of TS through the freshly excised rat skin. The receptor solution was composed of 40% PEG 400 in isotonic phosphate buffer (pH 7.4) solution to maintain the sink condition. After applying TDS on the stratum corneum side of the skin, samples (400 μL) were withdrawn from the receptor medium at predetermined time intervals and immediately refilled with an equal volume of fresh solution. The concentration of TS in the samples was determined by high-performance liquid chromatography (HPLC).

HPLC Analysis of TS

A HPLC system equipped with a binary pump (Gilson Model 305 and 306) and an autoinjector (Gilson Model 234) was used to determine the concentration of TS. A Merck C_{18} LiChroCAT 125×4 column (5 μm particle size, Merck, Darmstadt, Germany) was used as an analytical column at ambient temperature. The mobile phase was an acetonitrile–acetate buffer (50 mM, pH 4.0) combination (60:40) at a flow rate of 1.0 mL/min. The variable wavelength UV detector (Gilson Model 118) was set at 242 nm. All solutions to be analyzed were injected at a volume of 20 μL. There was no interference from the matrix or skin, and TS yielded a single peak at approximately 6 min.

In Vivo Study

Abdominal hair of rats was carefully removed using a clipper one day before the experiments. The rats were fixed in a supine position under light ether anesthesia. The femoral artery of the rats was cannulated with a polyethylene tube (PE-45 Intramedic, BD Clay Adms, Sparks, MD, USA) for blood sampling. An experimental TDS or Testoderm® was cut to 4 cm×5 cm size, and applied on the abdominal skin of rats. Blood samples (150 μL) were withdrawn at predetermined time intervals for 48 hr, and centrifuged for 10 min at 4000 rpm. Blood samples without TDS application were also taken to determine the basal TS concentration. The plasma was separated and kept at −20°C until analyzed by radioimmunoassay (RIA).

The plasma concentration of TS was determined using a commercially available RIA kit supplied by the Diagnostic Products Corporation (Los Angeles, CA).

The area under the TS plasma concentration curve (AUC_{0-48}) was calculated using the linear trapezoidal rule for the time interval from 0 to 48 hr.

Evaluations of the Degree of Crystallization

The severity of crystallization of TS in the PSA matrix was quantified by visual observation using a 0–5 scoring system. Score 0 means that no crystal was observed and score 5 means that the matrix was fully covered with crystal.

RESULTS AND DISCUSSION

Effect of TS Loading Dose and PSA on the Skin Permeation

Various concentrations of TS were loaded in three different PSA, after which the effect of loading dose and PSA on the skin permeation rate of TS was investigated. As shown in Fig. 1, the highest flux (1.59 μg/cm^2/hr) was observed when 4% TS was

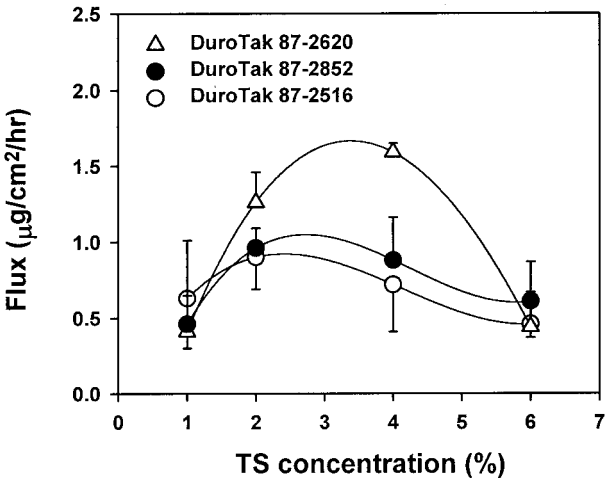

Figure 1. Rat skin permeation rate of testosterone loaded in three different pressure-sensitive adhesives at various concentrations. Data indicates mean (±SD) of triplicate experiments.

Table 1

Physicochemical Properties of Various DuroTak® Adhesives[a]

Product Number	87-2516	87-2620	87-2852
Copolymer Type	Acrylate-vinylacetate	Acrylate	Acrylate
Functional group	–OH	–COOH	–COOH
Total solid (%)	42	38	34
Theoretical T_g (°C)	−48	−47	−44
180° Peel adhesion (oz/in width)			
20 min bond time	35	50	50
24 hr bond time	40	60	60
1 week bond time	80	70	75
Shear (holding power: 8 psi at 72°F)	20 hr	100 hr	50 hr
Water vapor transmission (g/cm^2/24 hr)	430	290	340
Tack (loop) (oz/in^2)	30	65	40

[a]Data from National Starch & Chemical Company, USA.

loaded in DuroTak® 87-2620. In DuroTak® 87-2516 and 87-2852 formulations, however, the flux already reached its highest value when the TS loading dose was 2%. It can be speculated that the physicochemical properties of the PSA affected the solubility of TS in the matrix, and thereby affected the permeation rate of TS. Table 1 shows the properties of three PSA used in this study. DuroTak® 87-2516 is an acrylate–vinylacetate copolymer type with a hydroxy group, while DuroTak® 87-2620 and 87-2852 are acrylate copolymer type with carboxylic acid groups. In the case of primaquine, a higher permeation rate could be achieved with PSA containing a hydroxy group than those with an acidic side chain, since the hydroxy group is more compatible with primaquine.[10] However, in this study it was not possible to observe any relationship between TS flux and the functional group of PSA. Although DuroTak® 87-2620 and 87-2852 had the same functional group, a higher skin permeation rate of TS was achieved with DuroTak® 87-2620 than with DuroTak® 87-2852, probably due to the higher adhesion to the skin (Table 1).

According to Fick's diffusion law, the permeation rate is related to the solubility of the drugs in the adhesives. Crystals began to appear in the matrix when the TS loading dose was higher than 2%, which implies that TS reached its saturated solubility in the PSA. The skin permeation rate of TS showed a decreasing tendency at higher TS loading dose, since the polymer resistance and/or polymer inner structures may have been changed when TS is saturated in the PSA.

Effect of Solubilizer on the Skin Permeation Rate of TS

Several incidences of crystallization of drugs in the matrix-type TDS have been reported during storage.[7,8] The presence of crystals in the adhesives can cause problems in the performance of TDS. In order to increase the solubility and thermodynamic activity of TS in the PSA, Span 80 (HLB = 4.3) or Tween 80 (HLB = 15.0) was added as a solubilizer. Addition of 10% Span 80 significantly enhanced the skin permeation rate of TS in all three PSA (Fig. 2). Visual crystallization scores also decreased from 5, 4, 2 to 2, 2, 1 in DuroTak® 87-2516, 87-2620 and 87-2852, respectively. However, as expected, Tween 80 was not as effective as Span 80 in increasing the skin permeation rate of TS and in decreasing the crystallization. Since TS is a relatively lipophilic compound ($\log P = 3.4$),[11] a solubilizer with lower HLB number, such as Span 80, should be more effective in increasing the solubility of TS.

Figure 3 shows the relationship between Span 80 concentration and the TS skin permeation rate. In all three adhesives, the permeation rate showed a linear increment with the addition of up to 10% Span 80, and then decreased with further increase in Span 80 concentration. The maximal permeation rate of TS was 2.83, 2.72, and 2.17 $\mu g/cm^2$/hr in DuroTak® 87-2516, 87-2620, and 87-2852, respectively. As the Span 80 concentration increased, the score of crystallization showed a decreasing tendency (Table 2). This indicates that Span 80 increased the

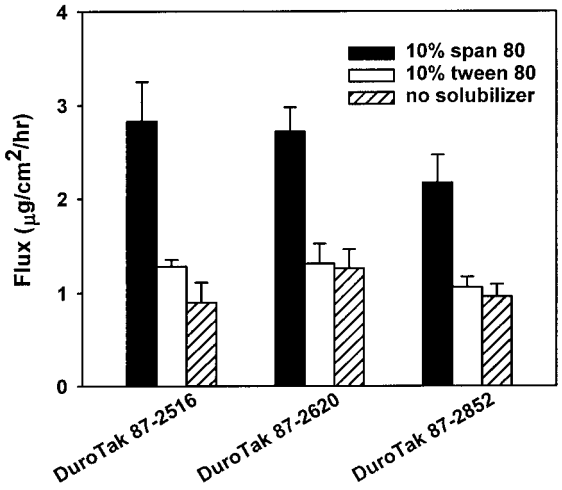

Figure 2. Effect of solubilizer (Span 80 and Tween 80) on the rat skin permeation rate of testosterone. Various pressure-sensitive adhesives were formulated to contain 2% testosterone and 10% solubilizer. Data indicates mean (±SD) of triplicate experiments.

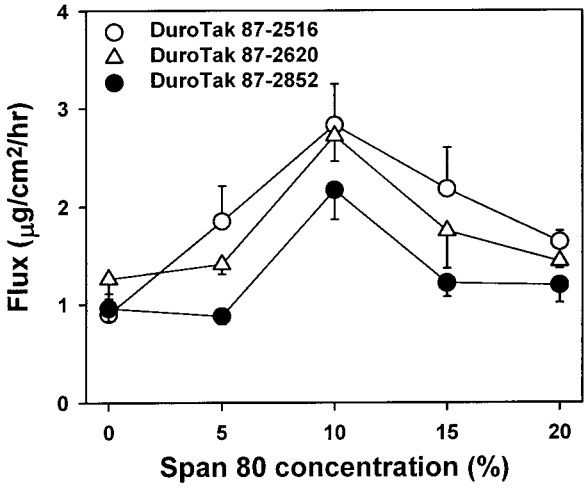

Figure 3. The effect of Span 80 concentration on the rat permeation rate of testosterone. Various pressure-sensitive adhesives were formulated to contain 2% testosterone and various concentrations of Span 80. Data indicates mean (±SD) of triplicate experiments.

permeation rate of TS by increasing the TS solubility in the adhesive polymers. However, Span 80 seemed to change the inner structure of adhesive polymers in higher than 10% concentration, thereby decreasing the diffusivity of TS by trapping it in the adhesives.

Table 2

The Degree of Crystallization of Testosterone in Various DuroTak® Adhesive Polymers Containing 2% Testosterone and Various Concentrations of Span 80 After One Year of Fabrication

	Scores of Crystallization in DuroTak® Adhesives		
Span 80 (%)	87-2516	87-2620	87-2852
0	5	4	2
5	5	5	0.5
10	2	2	1
15	1	2	0.5
20	1	1	0

Effect of Dodecylamine on the Skin Permeation Rate

As shown in Fig. 3, although Span 80 increased the skin permeation rate of TS by enhancing the solubility of TS in DuroTak® 87-2516, higher than 10% of Span 80 decreased the permeation rate of TS. Based on the observation that the adhesive polymer changed into a gluelike state, it was speculated that the inner structure of the adhesive polymer was changed at higher than 10% Span 80. Thus, the synergistic effect of dodecylamine on the skin permeation rate of TS was investigated using 5% and 10% Span 80 in the DuroTak® 87-2816 adhesive. Like our previous studies,[11,12] the skin permeation of TS significantly increased with the addition of up to 3% dodecylamine (Fig. 4). However, higher than 3% dodecylamine also changed the adhesive polymer into a gluelike state, and decreased the permeation rate of TS. The highest skin permeation rate of TS (4.14 μg/cm^2/hr) was achieved with 10% Span 80 and 3% dodecylamine in DuroTak® 87-2516. Along with the skin permeation-enhancing effect of dodecylamine, it also seemed to synergistically increase the solubility of TS in the adhesive polymer, since no crystal formation was observed when up to 6% TS was incorporated in this formulation (data not shown).

In Vivo Study

Figure 5 shows the TS plasma concentration profiles after applying an experimental TDS or

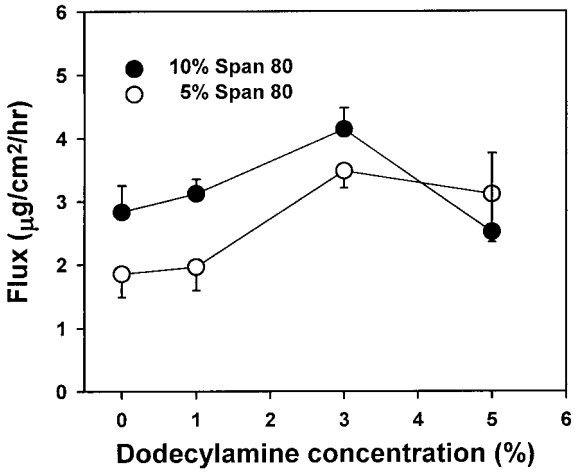

Figure 4. Effect of dodecylamine concentration on the rat skin permeation rate of testosterone. Various concentrations of dodecylamine were added in DuroTak® 87-2516 containing 2% testosterone and Span 80 (5% or 10%). Data indicates mean (±SD) of triplicate experiments.

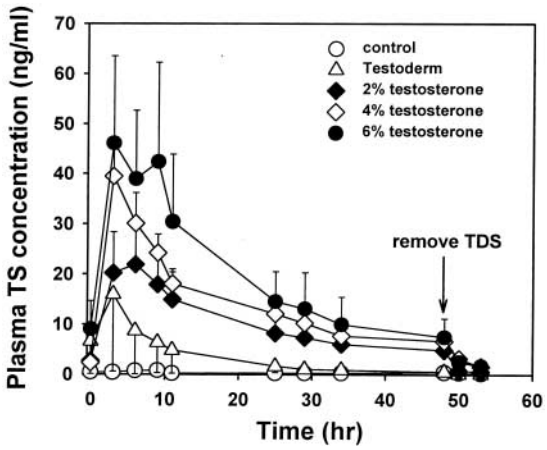

Figure 5. Plasma concentration profiles of testosterone after applying an experimental TDS or Testoderm® on rat abdominal skin (20 cm^2). Experimental TDS was formulated to contain various concentrations of testosterone in DuroTak® 87-2516 containing 10% Span 80 and 3% dodecylamine. Control means basal plasma concentration of testosterone without applying TDS. Data indicates mean (±SD) of four to ten rats.

a commercially available matrix-type product (Testoderm®) on rat abdominal skin. In all formulations, plasma TS concentration began to rise abruptly, and reached peaks at 3–6 hr after application. When the TDS was removed after 48 hr, plasma TS concentration rapidly fell to the basal level within 5 hr. It is interesting to note that the experimental TDS containing as low as 2% TS already showed a higher plasma TS concentration profile than that of Testoderm®, which is designed to apply on the scrotal skin. Moreover, as the TS concentration in the experimental TDS increased up to 6%, the plasma TS concentration increased accordingly. Figure 6 shows a good linear relationship between the TS concentration in the adhesive polymer and AUC_{0-48} calculated by the trapezoidal rule.

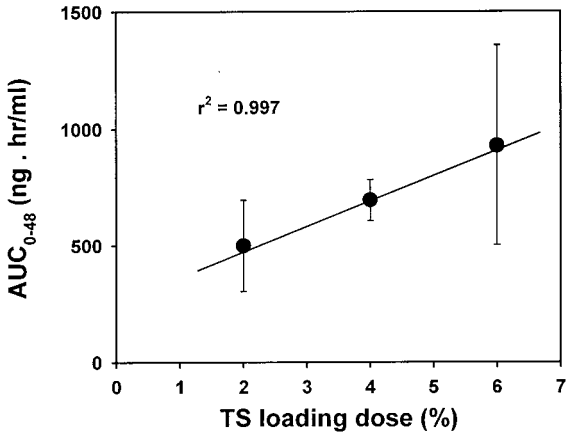

Figure 6. Relationship between testosterone loading dose and AUC_{0-48} calculated by the trapezoidal rule. Experimental TDS was formulated to contain various concentrations of testosterone in DuroTak® 87-2516 containing 10% Span 80 and 3% dodecylamine. Data indicates mean (±SD) of four rats.

In conclusion, a matrix-type transdermal delivery system composed of DuroTak® 87-2516 (adhesive polymer), Span 80 (as a solubilizer), and dodecylamine (as a skin permeation enhancer) could incorporate up to 6% TS without crystal formation. Since this system showed significantly higher plasma TS concentration profiles than those of Testoderm® for 48 hr, clinical studies are under way in this laboratory to further develop this non-scrotal matrix-type transdermal delivery system of TS.

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