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EVALUATION OF SILICONE-BASED PRESSURE-SENSITIVE ADHESIVES FOR TRANSDERMAL DRUG DELIVERY [II] EFFECT OF PENETRANT LIPOPHILICITY

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SUMMARY

An adhesive polymer drug dispersion-type transdermal drug delivery (a-TDD) system, consisting of a single drug-loaded adhesive polymer layer sandwitched between a drug-impermeable backing membrane and a detachable release liner, was developed from two silicone-based pressure-sensitive adhesive polymers for the controlled administration of drugs. The effect of variation in penetrant lipophilicity, using a series of testosterone derivatives with an increasing number of methyl groups in the steroid skeleton, on the release kinetics from the a-TDD system and skin permeation rate profiles was investigated. Absence of a methyl group at the

19th position of testosterone increased the flexibility of the steroid molecule and thus yeilded higher diffusivity and greater skin permeation rate. Addition of esters at the 17 ß-position resulted in a reduction in diffusivity with an increase in the alkyl chain length of the ester. These esters were found to be bioconverted to testosterone during permeation through the intact hairless rat skin.

INTRODUCTION

In the past few years, an increasing number of transdermal drug delivery (TDD) system products have been introduced into the market. Several technologies are now in use for the preparation of such products (1), all of which require some kind of adhesive to achieve an intimate contact of drug-releasing surface of TDD systems with the skin. The drug must either permeate through this surface adhesive coating or, in some cases, the drug is directly loaded into the adhesive polymer itself. Thus, the adhesive is a very important component in the TDD systems. Not only must the adhesive be able to perform its functions of adhering to the skin for the required period of time, but must also be able to retain this property when a drug is loaded in it. Pressure-sensitive adhesives are used for this purpose as they can be applied to the skin with slight "thumb" pressure and can be removed without leaving any unwanted residue. At present, there are three classes of pressure-sensitive adhesives which are biocompatible and inert enough to be useful for transdermal applications: polyisobutylenes, polyacrylates and silicones.

Silicone-based pressure-sensitive adhesives are stable, nonirritant and nontoxic and as such the properties of these adhesives can be tailored depending upon the drug that is to be incorporated in the adhesive (2). These adhesives generally consist of a poly(dimethylsiloxane) backbone on which is crosslinked a silicate resin which imparts the tackiness to the adhesive (3). This general structure can be modified by incorporating different chemical groups on the siloxane and silicate backbone, which make the adhesive more compatible with certain functional groups on a drug molecule. For example, Figure 1 shows the general structure of the two silicone adhesives that we used for this investigation : X7-2920 is designed to provide a certain degree of amine resistance, while DC-355 is sensitive to amine groups on the drug molecule.

In the first paper of this series, we investigated the effect of variation in the penetrant hydrophilicity on adhesive polymer drug dispersion-type transdermal drug delivery (a-TDD) systems fabricated from X7-2920 and DC-355 medical adhesives (4). The objective of this second paper is to study the effect of penetrant lipophilicity, using androgens as model drugs, on the release kinetics from a-TDD systems, as well as the subsequent permeation across hairless rat skin. The results are analysed in this report.

The skin is a complex tissue and is far from being a "dead" tissue as earlier scientists had coined it. It has been shown recently that the microorganisms on the surface of the skin as well as the broad range of

enzymes present in the viable epidermis and dermis contribute to a wide variety of extrahepatic metabolism (5,6). During the course of this investigation, we found that the androgen esters we used for the study were completely bioconverted in the skin.

EXPERIMENTAL

MATERIALS :

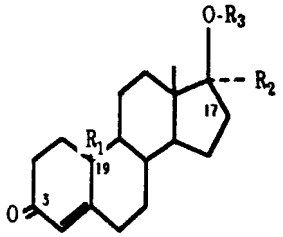
Androgen Derivatives :

A homologous series of androgens with systematic variation in the number and position of methyl groups on the steroid skeleton as well as the chain length of the alkyl group at the 17-ß position (Table 1) were used in this investigation. Testosterone, 19-nor-testosterone, 17-α-methyl testosterone, testosterone acetate and testosterone propionate were purchased (Sigma Chemical Co., St. Louis, MO.), while testosterone pentanoate was custom synthesized (Pioneer Laboratories, Inc., San Francisco, CA.).

Adhesives :

The silicone-based pressure-sensitive adhesives, (Figure 1) i.e., Bio-PSA X7-2920 medical adhesive [35% (w/w) in trichlorotrifluoroethane] and DC-355 medical adhesive [18.5% (w/w) in trichlorotrifluoroethane] were obtained as gift samples from Dow Corning Corp. (Midland, MI) and used as received. The release liner and backing membranes were gifted by 3M Corp.,(St. Paul, MN).

Table 1. Chemical structure of the androgens studied



Testosterone and its derivatives

Drug	R_1	R_2	R_3
19-nor-testosterone(I)	H	H	H
Testosterone(II)	CH_3	H	H
17α-methyl testosterone(III)	CH_3	CH_3	H
Testosterone acetate(IV)	CH_3	H	CH_3CO
Testosterone propionate(V)	CH_3	H	CH_3CH_2CO
Testosterone pentanoate(VI)	CH_3	H	$CH_3(CH_2)_3CO$

Other chemicals and reagents :

The acetonitrile, methanol, methylene chloride, polyethylene glycol (PEG) 400 used for this study were HPLC grade and purchased from Fisher Scientific Co., (Fairlawn, NJ), while deionized water was freshly prepared by a Nanopure system (Sybron/Barnstead, Boston, MA) and filtered through a nylon filter (0.45 μ) before use.

Skin Specimens :

The female fuzzy rats used in this study were purchased from Temple University Health Services, (Philadelphia, PA). The skin was freshly excised

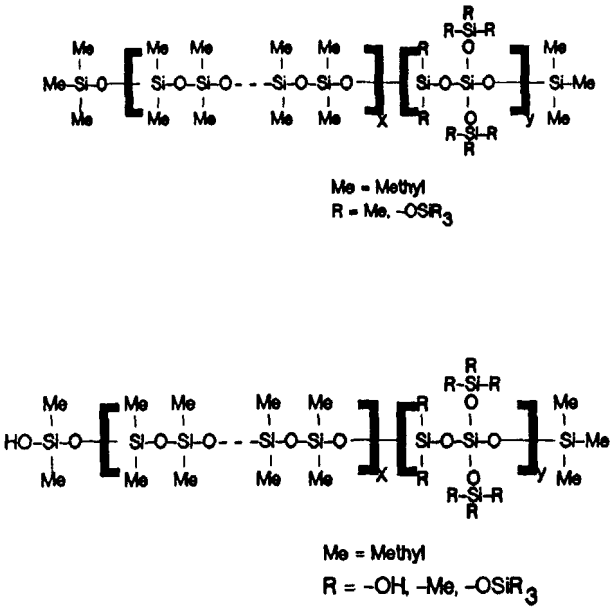


Figure 1 The general structure of X7-2920 (upper panel) and DC-355 (lower panel) silicone medical adhesives.

from the abdomen region of rats (6-8 weeks old) just before the in vitro skin permeation experiments.

METHODS :

Preparation of a-TDD patches :

The androgen was accurately weighed and then dispersed in a small amount of methylene chloride. A known amount of adhesive solution [containing a calculated amount of X7-2920 or DC-355 medical adhesive] was then added and mixed with the drug suspension in a bottle which was gently agitated in a rotator for two hours, followed by standing for 30

minutes to eliminate any entrapped air bubbles. The release liner (8 X 6 inches) was placed on a flat glass plate and secured in place with a tape. The drug-dispersed adhesive solution was poured carefully onto the liner. A K-Bar (300 μ) was then gently passed through the liner to produce a coating of uniform thickness. The solvent was then allowed to evaporate overnight in an exhaust hood. After complete drying, the backing membrane was then placed over the medicated adhesive film, pressed uniformly with moderate pressure and then cut into a-TDD patches of 5 cm^2 each. The patches with monolayer of adhesive polymer matrix, which was loaded with varying doses of one androgen, were evaluated for drug release and skin permeation profiles.

Determination of drug loading in the patches (A) :

Patches of 1-cm^2 in surface area were cut, the release liner was removed and each patch was extracted with 20 ml of methanol, using a mechanical shaker, for 24 hours. The methanolic solution was removed and the patch was extracted once more with another 20 ml of methanol to ensure that all the drug was recovered. The methanolic extracts were combined and the drug concentration in the extracts was then analyzed by the HPLC method described later.

Determination of solution solubility (C_s):

Excess androgen was added to each solution (water, aqueous (40%) PEG 400 solution or silicone fluid) and the suspension was equilibrated at

37°C with gentle shaking for 24 hours. The suspension was filtered through a 0.45 μ teflon filter. The resulting filtrate was diluted appropriately (to be in the concentration range of the standard curve) and analyzed by HPLC. The solubility of each curve was determined by using the appropriate dilution factor.

Determination of adhesive polymer Solubility (C_p):

A saturated solution of each androgen in water was prepared at 37°C, and diluted with water to 50% of the saturation solubility. Placebo a-TDD patches (containing no drug) with surface area of 1 cm^2 each were immersed in the drug solution and equilibrated at 37°C, with gentle shaking in a constant temperature water bath, for 50 hours. The amount of drug taken up by the patch was determined by assaying the amount of androgen in the solution before and after equilibrium as well as by assaying the amount of drug in the patch by extraction with methanol. These data were then used to calculate the solubility of progestins in the adhesive.

In Vitro release of androgens from a-TDD patches :

The Valia-Chien [V-C] skin permeation cell (7), a hydrodynamically well-calibrated skin permeation system, was used for all the in vitro studies. All studies were carried out at 37°C. After removal of release liner, each of the a-TDD patches was mounted between the two half-cells of each V-C cell with the drug-releasing surface facing the receptor half-cell which contained 3.5 ml PEG 400 solution (40% v/v in distilled water) as the

receptor solution. At regular intervals, 1.0 ml receptor solution was withdrawn, which was immediately replaced with the same volume of fresh PEG 400 solution, for a duration of up to 30 hours. The amount of drug released was determined using the HPLC method described later.

In vitro skin permeation studies :

A. Preparation of fuzzy rat skin for permeation studies - Female fuzzy rats were sacrificed just prior to an experiment and the abdominal skin was then carefully excised and all the fatty tissues that adhered to its dermis were completely removed. For the stripped skin studies, the stratum corneum was removed just after sacrificing the animal using a scotch tape (3M, St. Paul, MN). The skin was stripped consecutively for approximately 20 times to completely remove the stratum corneum (8).

B. In vitro studies of androgen permeation from a-TDD patches - The skin was mounted between the two half-cells of each V-C cell with its dermis surface facing the receptor half-cell. A unit of a-TDD system was then placed with its drug-releasing surface in intimate contact with the stratum corneum surface. The receptor solution was then added into the receptor half-cell and samples (0.1 ml each) were taken at regular intervals for up to 36 hours. The drug was assayed using the HPLC method described later.

C. In vitro permeation studies of testosterone esters from saturated solutions - Whole skin or stripped skin was mounted between the two half-cells of each V-C cell. A saturated solution of the testosterone ester (in

aqueous PEG 400 (40%) solution) was added in the donor compartment, while 3.5 ml of drug-free 40% PEG 400 solution was filled in the receptor compartment. The receptor solution was sampled at regular intervals for a duration of upto 40 hours and the drug was assayed using the HPLC method described below.

Analytical Method :

For this investigation, a microprocessor-controlled High Performance Liquid Chromatograph (HP 1084B, Hewlett Packard, Piscataway, NJ) was used. Combinations of acetonitrile and water (at various proportions depending on the type of androgen tested) were used as the mobile phase at a flow rate of 2 ml/min. The drug was resolved using a reversed phase Hypersil column (Hewlett Packard, Piscataway, NJ) and detected at a wavelength of 240 nm. Drug concentrations in the samples was determined by first measuring the peak height of the chromatographic peak for the drug and then computing its concentration from a standard curve.

Data Analysis :

From the concentration profiles of the androgen in the receptor solution, the amount of drug released or permeated (in $\mu g/cm^2$) was calculated and then plotted as a function of time (in hours) or square root of time (in square root of hours). The flux of drug release or the rate of skin permeation was determined from the slope of the linear plots.

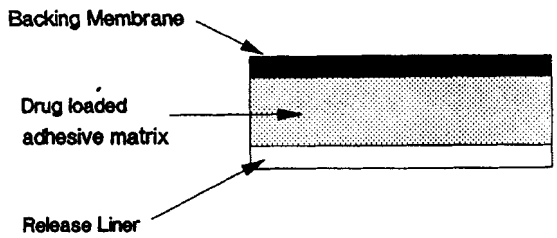


Figure 2 Diagrammatic representation of an a-TDD system.

RESULTS AND DISCUSSION

Table 1 shows the six androgens that were evaluated in this study. Methyl groups are systematically varied in this series of drugs. 19-nor-testosterone is devoid of the methyl group at the 19^{th} position which gives it a flexibility not present in the other androgens (9). Esterification of the 17-ß-OH with various alkanoic acids yields esters of testosterone.

In Figure 2, a schematic representation of an a-TDD system is shown. It consists of a drug-impermeable backing laminate, a drug-loaded adhesive polymer matrix and a detachable release liner. Typically, the drug is loaded, in increasing levels, in the system; so that the effect of drug loading can be determined. The dry adhesive polymer matrix was typically 50 ($\pm$ 6) μ in thickness.

The solubilities (C_s) of androgens in various aqueous media and silicone polymers were determined and the results are compared in Table 2. In general, the aqueous solubility of the androgens decreases with an increase in the lipophilicity as resulted from the addition of methyl groups

Table 2: Solubilities of the androgens in various lipophilic and hydrophilic media and in the silicone adhesives studied.

Androgen	C_S (μg/ml)			C_p[b] (mg/cm^3)[d]	
	Water	PEG soln[a]	Silicone Fluid[c]	X7-2920	DC-355
19-nor-testosterone(I)	275.0	1350	148	3.905	3.907
	(5.42)	(8.52)	(4.56)	(0.42)	(0.57)
Testosterone(II)	46.3	542	170	1.363	2.597
	(2.97)	(6.76)	(5.58)	(0.23)	(0.68)
17α-methyl testosterone(III)	41.4	576	228	7.132	7.355
	(3.52)	(5.48)	(6.42)	(0.58)	(0.72)
Testosterone acetate(IV)	8.5	148	515	8.414	9.380
	(1.02)	(2.43)	(4.58)	(0.79)	(0.71)
Testosterone propionate(V)	3.9	108	604	10.69	13.14
	(0.56)	(3.42)	(8.69)	(0.78)	(0.86)
Testosterone pentanoate(VI)	3.4	56	445	7.859	8.488
	(0.42)	(1.87)	(7.62)	(0.87)	(0.82)

( ) indicates standard deviation, n=4.
(a) 40% (v/v) of polyethylene glycol 400 in water
(b) Both adhesives are not statistically significant (20 cps viscosity)
(c) Dow Corning 360 Silicone Medical Fluid (20 cps viscosity)
(d) Determined from the density of the adhesives

and ester. The use of an aqueous solution of PEG 400 (40%) as a cosolvent improved the aqueous solubility of all the androgens and this cosolvent was thus used as the receptor medium to maintain sink conditions.

The androgens show different solubility behavior in the silicone-based adhesive polymers, which are lipophilic in nature, and behave opposite to that of the aqueous media. The polymer solubility increases with the addition of methyl groups or alkyl ester, with the exception of 19-nor-testosterone and testosterone pentanoate (Table 2). Similar solubility profiles are also observed in the lipophilic silicone fluid. At higher alkyl

chain length of the esters (> C_5), however, there was a drop in both the aqueous and polymer solubilities. The observed reduction in solubility could be due to the increase in the bulk of the alkyl chain on the ester which hinders the solubilization of the steroid. A similar drop in solubility was also observed by Sun et al.,(10) for the ester with higher alkyl chain length. It is interesting to note that the difference in the solubilities of the two silicone adhesives is not statistically significant for all the androgens studied when a students "t" test was performed, suggesting that these silicone-based adhesive polymers were not significantly different in their lipophilicity.

KINETICS AND MECHANISMS OF ANDROGEN RELEASE

The results of in vitro release studies indicated that the intrinsic release of androgens followed a Q vs $t^{1/2}$ relationship. This follows the relationship established by Higuchi (11) for a matrix diffusion-controlled process defined by the following equation :

$$Q = [(2A-C_p)C_pD_pt]^{1/2} \quad (1)$$

where Q is the amount of androgen released, t is the time (in hours), A is the initial loading dose of androgen in the matrix, C_p is the solubility of androgen in the adhesive polymer and D_p is the diffusivity of the androgen in the adhesive matrix. Such profiles are a characteristic of drug-dispersed polymer matrix systems, in which A is much greater than C_p.

One set of typical Q vs $t^{1/2}$ plots are shown in Figure 3 for testosterone. The results indicate that the release flux increases with an

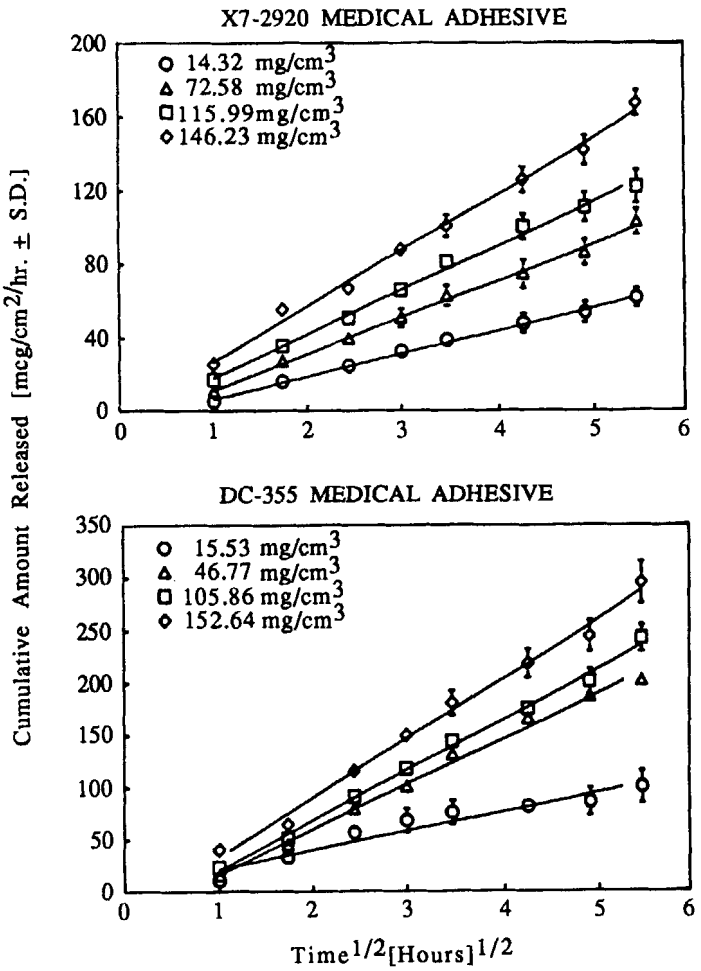


Figure 3 Linear relationship between the cumulative amount of testosterone released from the X7-2920 (upper panel) and DC-355 (lower panel) based a-TDD patches containing varying androgen loadings and the square root of time.

Table 3 : Diffusivity of testosterone and its derivatives in the silicone adhesive matrix.

Androgen	Slope[a] x 10^3 ($cm/hr^{1/2}$)		Diffusivity[b] x 10^5 (cm^2/hr)	
	X7-2920	DC-355	X7-2920	DC-355
19-nor-testosterone(I)	10.70(0.002)	7.55(0.002)	11.45(0.002)	5.70(0.002)
Testosterone(II)	2.06(0.001)	2.27(0.001)	0.43(0.001)	0.52(0.001)
17α-methyl testosterone(III)	2.02(0.002)	2.51(0.002)	0.41(0.002)	0.63(0.001)
Testosterone propionate (IV)	1.41(0.002)	2.42(0.002)	0.20(0.002)	0.59(0.002)
Testosterone propionate(V)	1.41(0.001)	2.43(0.001)	0.20(0.001)	0.59(0.001)
Testosterone pentanoate(VI)	0.54(0.001)	0.54(0.001)	0.03(0.001)	0.03(0.001)

( ) indicates standard deviation

(a) slope = $D_p^{1/2} = Q/t^{1/2}/[2A\text{-}C_p]^{1/2}C_p^{1/2}$

(b) Both adhesives are not statistically significant in regard to the diffusivity of androgens ($p < 0.05$).

increase in the loading dose in the polymer as predicted by equation 2.

$$Q/t^{1/2} = [(2A\text{-}C_p)C_p]^{1/2}D_p^{1/2} \quad (2)$$

Diffusivity of the androgens in the adhesive matrix was determined from the slope of $(Q/t^{1/2})$ vs $[(2A\text{-}C_p)C_p]^{1/2}$ plots and is summarized in Table 3. These diffusivities are plotted as a function of the number of methyl groups on the steroid skeleton in Figure 4. The results indicate that with the exception of 19-nor-testosterone, the diffusivities of all androgens in these two silicone-based adhesive polymer matrices are not statistically significant ($p < 0.05$). It is interesting to note that the 19-nor-testosterone has the highest diffusivity among the androgens tested, indicating that a methyl group at the 19 position is important for the structural and confromational flexibility of the steroid. It has been postulated by Carey and

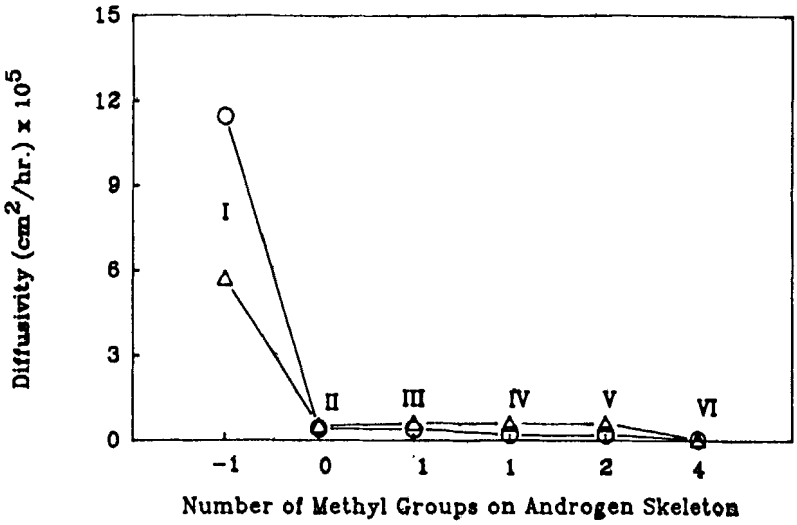


Figure 4 Diffusivity as a function of the number of methyl groups on the androgen skeleton (I,II and III) and alkyl chain length of the ester (IV,V, and VI) for (○) X7-2920 and (△) DC-355 medical adhesive.

Sundberg,(12) that the absence of the 19 methyl group of the steroid increases the flexibility of the trans-trans conformation which has a tendency to shift to a cis-trans conformation with a temperature dependency. Liu et al., (9) reported a change in the slope value of the Arrhenius plots of the diffusivity of 19-nor-testosterone through a silicone membrane occurring at approximately 37°C. Thus, at 37°C, the conformation of the 19-nor-testosterone molecule can alternate and has a much higher diffusivity than the other androgens with the 19 methyl group present. All the 19 methyl-

containing androgens have a substantially lower diffusivity than the 19-nor-testosterone.

The diffusivity of the androgens in the X7-2920 adhesive seemed to decrease with an increase in the number of methyl groups and the alkyl chain length of ester (Table 3), although diffusivity of the androgen molecule in the DC-355 adhesive matrix appears to be independent of the number of methyl groups except for 19-nor-testosterone, and becomes dependent of the alkyl chain length in the ester only for testosterone pentanoate.

KINETICS AND MECHANISMS OF SKIN PERMEATION

A. Skin permeation of androgens from a-TDD systems

The model for drug permeation through the skin from the adhesive polymer matrix system has been described in details in the first paper of this series of investigations (4). As reported earlier for the progestin series, the permeation of the androgens across the intact hairless rat skin was also observed to follow a Q vs t relationship (Figure 5) except that for 19-nor-testosterone. An extremely high skin permeation profile was obtained for 19-nor-testosterone which shows a slight positive curvature. The rate of skin permeation of each androgen can be determined from the steady state portions of these permeation plots. The permeation rates are noted to increase with the increase in the initial loading dose of androgen in the adhesive matrix and then plateau off at a higher loading level (Figures 6). The same profile is also observed for the permeation of testosterone from

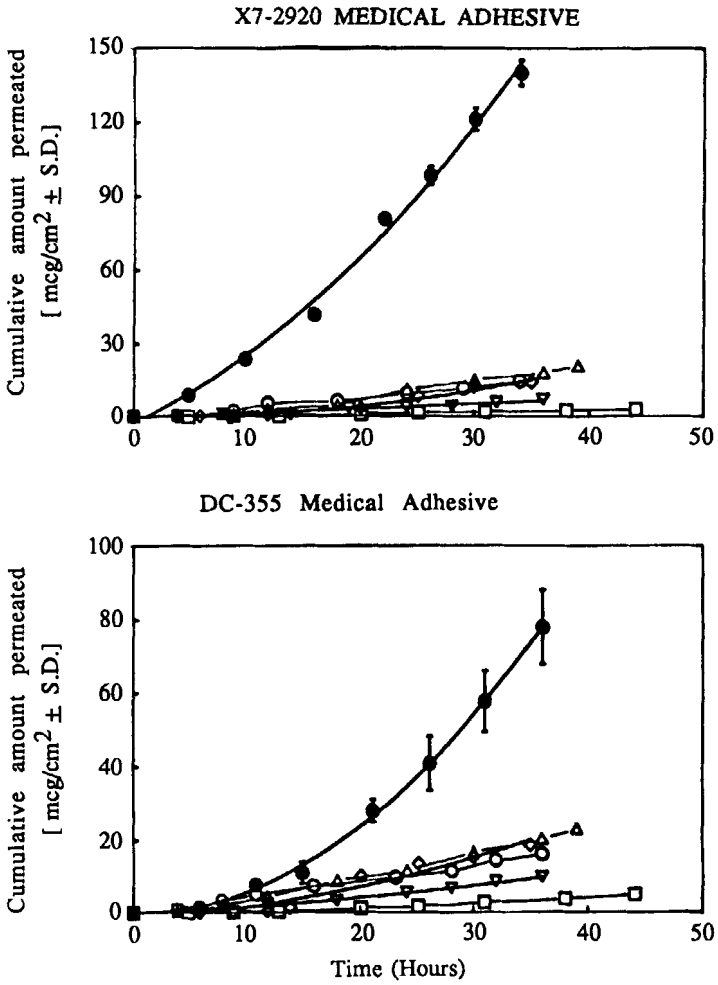


Figure 5 Q vs t relationship for the permeation of various androgens through intact hairless rat skin using a 15% drug loading dose in the X7-2920 (upper panel) and DC-355 (lower panel) medical adhesive. (●) 19-nor-testosterone, (○) testosterone, (△)17α-methyl testosterone, (□) testosterone acetate, (◇) testosterone propionate, (▽) testosterone pentanoate.

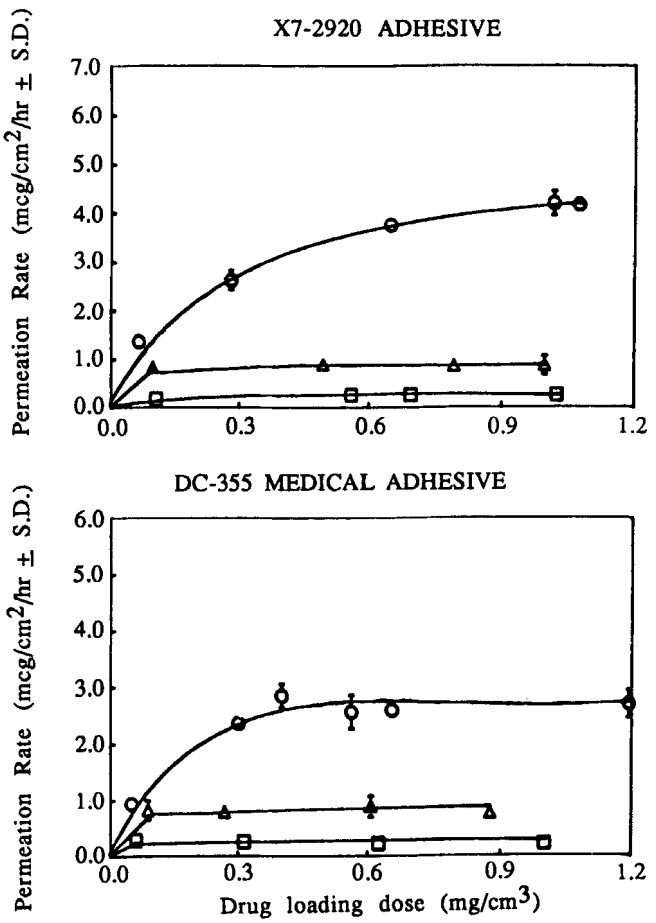


Figure 6 Effect of initial loading dose of androgen in the X7-2920 (upper panel) and DC-355 (lower panel) based a-TDD patches on the skin permeation rate of (○) 19-nor testosterone, (△) testosterone and (□) 17α-methyl testosterone across the intact skin of hairless rats.

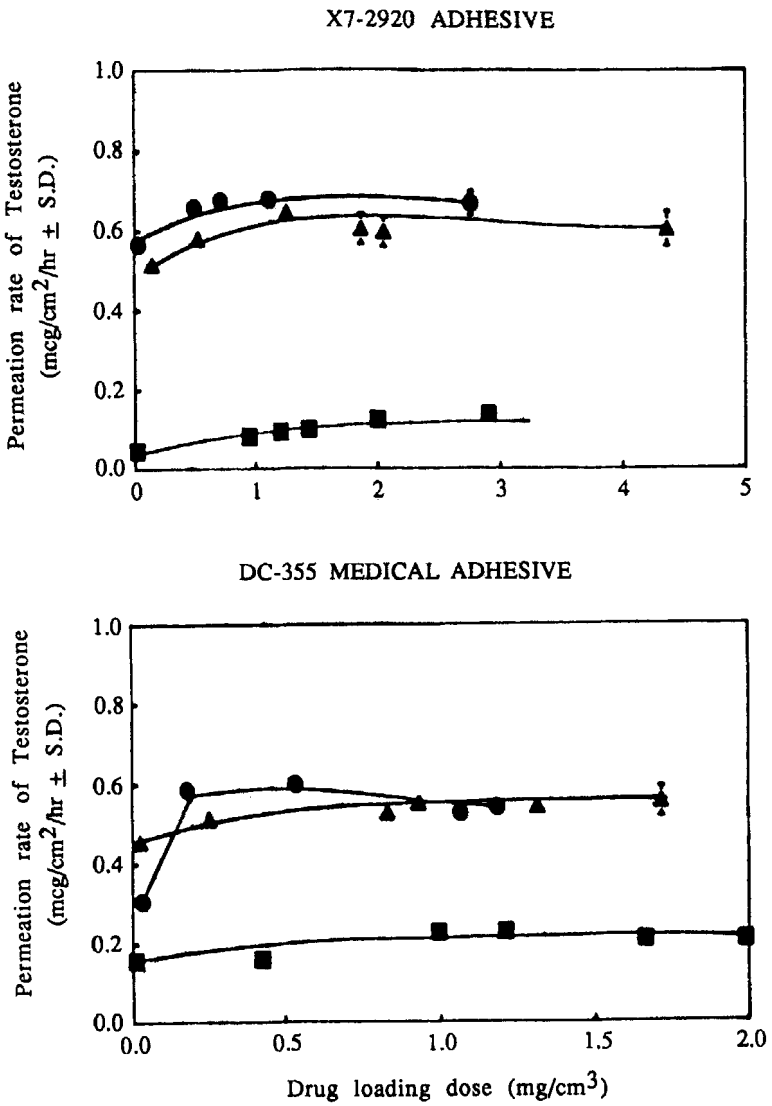


Figure 7 Effect of initial loading dose of testosterone ester in the X7-2920 (upper panel) and DC-355 (lower panel) based a-TDD patches on the skin permeation rate of testosterone from (●) testosterone acetate, (▲) testosterone propionate and (■) testosterone pentanoate.

Table 4 : Plateau permeation rates for the progestins and androgens studied.

Androgen	Plateau Permeation Rates ($\mu g/cm^2/hr.$)	
	X7-2920	DC-355
19-nor-testosterone(I)	4.41(0.61)	2.61(0.17)
Testosterone(II)	0.87(0.08)	0.81(0.06)
17α-methyl testosterone(III)	0.26(0.09)	0.24(0.08)
Testosterone acetate(IV)(a)	0.67(0.01)	0.56(0.03)
Testosterone propionate(V)(a)	0.61(0.02)	0.54(0.01)
Testosterone pentanoate(VI)(a)	0.12(0.02)	0.21(0.01)

( ) indicates standard deviation
(a) Permeation of the native drug testosterone from the testosterone ester.

its esters (Figure 7). Except for 19-nor-testosterone, all androgens plateau off at very low loading levels, suggesting that the skin plays the rate-limiting step in the permeation of androgens even at very low drug loading doses. It should be pointed out that the esters do not permeate through the skin in their native form, but are bioconverted to form testosterone (Figure 7). The plateau permeation rates for the various androgens are compared in Table 4 and the data suggest that the rate is dependent on the number of the methyl groups on the steroid skeleton as well as the chain length of the alkyl ester. There is a significant decrease in the permeation rates from 19-nor-testosterone to testosterone, indicating that the methyl group at the 19^{th} position affects the permeation of androgen molecules through the skin in a similar way as it does to the diffusion through the adhesive matrix (Figure 4).

Esterification of the 17-ß-OH group imparts a "prodrug" type effect and the ester appears to be bioconverted to testosterone in the viable skin layer before it can permeate through the skin. It appears that the bioconversion is also dependent upon the chain length of the alkyl ester; that is, the longer the chain length, the lower the rate of appearence of testosterone. The effect of methyl group and alkyl chain length on skin permeation rate is similar in pattern for both silicone adhesives, but X7-2920 gives a higher plateau permeation rate than DC-355.

B. In vitro bioconversion studies

In order to analyze the biotransformation of testosterone esters to testosterone in further details, studies were carried out in both whole and stripped skin, using a saturated solution of each ester in the donor solution. Control studies were also carried out, using testosterone, for comparison. In all cases, the receptor solution was sampled and monitored for appearance of the ester and testosterone both of which could be analyzed using the same HPLC assay. The appearence rates of testosterone in the receptor solution resulted from the permeation and bioconversion of esters across the whole and stripped skin are compared in Figure 8. In all cases, no ester was detected in the receptor solution in the intact form throughout the 40-hr study. It is interesting to note that the stripped skin permeation rate for testosterone is not significantly higher than that across the whole skin, suggesting that this lipophilic compound could readily permeate through

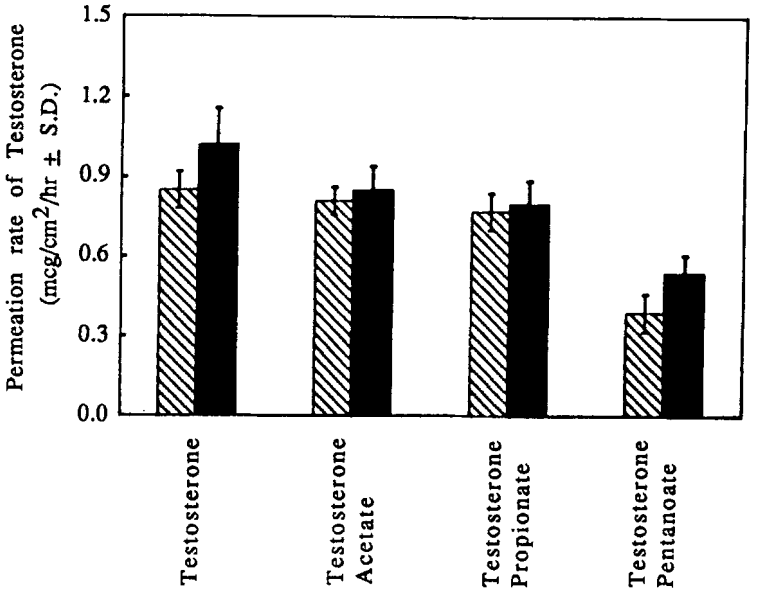


Figure 8 Permeation rate of testosterone across (▨) whole skin and (■) stripped skin of hairless rat for the various androgen esters studied.

the stratum corneum and the permeation through the viable skin becomes the rate-limiting step. Also, the stripped skin permeation rate for the esters was very similar to the whole skin permeation rate. The results lead us to conclude that the bioconversion occurs primarily in the viable skin and not due to any microbial conversion on the stratum corneum surface.

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