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Effect of physicochemical properties of adhesive on the release, skin permeation and adhesiveness of adhesive-type transdermal drug delivery systems (a-TDD) containing silicone-based pressure-sensitive adhesives

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Summary

Adhesive dispersion-type transdermal drug delivery (a-TDD) systems consisting of a monolayer of drug-loaded adhesive matrix were developed from three types of silicone-based pressure-sensitive adhesives. The adhesive polymers were tailored such that two of them were lipophilic (Bio-PSA® X7–2920 and Dow Corning® -355 Medical Adhesive) and one was relatively hydrophilic (E8086® adhesive) in nature. Three steroids viz., progesterone, testosterone and hydrocortisone, were used as model penetrants and their release from the a-TDD systems and permeation through skin were investigated. The adhesive properties of these systems were also studied. The partial and total solubility parameters of these adhesive polymers were also determined. The release of steroid molecules was observed to be a complex function of the physicochemical properties of the drug and polymer. The adhesiveness as determined from a standard peel test indicated that incorporation of the drug in higher drug loading doses results in a loss of adhesiveness. The results suggest that the chemical nature of the polymer is an important consideration when studying such adhesives for transdermal drug delivery.

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Introduction

The adhesive is a major component of a transdermal drug delivery (TDD) system and plays an important role in maintaining intimate contact of

the delivery system with the skin. A wide variety of TDD systems, including membrane permeation-controlled, matrix diffusion-controlled and microreservoir-controlled TDD systems, currently on the market or under investigation, contain a pressure-sensitive adhesive (PSA) to achieve adherence to the skin (Chien, 1987; Baker and Heller, 1988; Hsieh, 1988). More recently, some systems contain the drug dispersed directly in the adhesive. For the purposes of this paper, such systems will be called adhesive-type transdermal drug delivery systems (or a-TDD systems). Many medical-grade silicone-, polyacrylic- and polyisobutylene-based PSAs are available in the market and are suitable for the preparation of TDD systems (Musolf, 1987; Govil, 1988).

Silicone-based PSAs are non-irritating, nontoxic, non-sensitizing, possess sufficient tack and peel properties and can be customized to accommodate specific requirements of TDD systems (Musolf, 1987; Pfister, 1989). This paper investigates three of these PSAs, viz. Bio-PSA® X7–2920, Dow Corning® -355 Medical Adhesive and E8086®. These all consist of a similar polymer backbone of polydimethyl siloxane crosslinked with a silicate resin. The backbone or the end groups of the polymer, however, are modified to provide specific properties for lipophilic or hydrophilic drugs. Depending on the nature of the substituent on the polymer chain, these adhesives vary in their physical and mechanical properties. This paper investigates some of these properties and correlates them with the release rate of various steroids incorporated in these adhesive polymers in the form of a-TDD systems.

Three steroids (progesterone, testosterone and hydrocortisone), with varying physicochemical properties were studied as model transdermal penetrants. The drug-related effects on the release and skin permeation from a-TDD systems have been previously discussed with special emphasis on the solubility and diffusivity of the drug (Toddywala and Chien, 1990, 1991). Also discussed were the effects of penetrant lipophilicity and hydrophilicity on the release and skin permeation. In this paper, we investigated the effect of variation in the polymer structure (and thus its properties) of the three silicone-based adhesives on properties such as release, skin permeation and adhesiveness of a-TDD systems containing these steroids. The effect of the physicochemical properties of penetrant and polymer was studied using uni-layered a-TDD systems and mathematical relationships were proposed between the release rate and physicochemical properties of drug and polymer. The adhesiveness of these polymers using a model peel test with and without the presence of drug was also studied and is reported.

Experimental

Materials

Penetrants

Three steroidal drugs, progesterone, testosterone and hydrocortisone, were studied as model penetrants in this investigation. These were purchased from Sigma Chemical Co., St. Louis, MO.

Adhesives

The silicone-based pressure-sensitive adhesives, i.e., Bio-PSA® X7–2920 (35% (w/w) in trichlorotrifluoroethane), Dow Corning® -355 Medical Adhesive (18.5% (w/w) in trichlorotrifluoroethane) and E8086® Adhesive (50% (w/w) in hexane) were obtained from Dow Corning Corp. (Midland, MI) and used as received. Hereafter, these adhesives will be referred to as X7–2920, DC-355 and E8086, respectively. The release liner and backing membranes were obtained from 3M Corp (St. Paul, MN).

Other chemicals and solvents

All the solvents used in this study were of HPLC grade (Fisher Scientific Co., Fairlawn, NJ). The deionized water used in the HPLC analysis was freshly prepared by a Nanopure system (Sybron/Barnstead, Boston, MA) and filtered through a 0.45 μm pore size filter (Fisher Scientific, Fairlawn, NJ) before use.

Skin specimens

Female hairless rats used in this series of studies were purchased from Walter Reed Institute of

Pathology (Washington, DC). The abdominal skin of rats (6–8 weeks old) was freshly excised just before the in vitro skin permeation experiments.

Methods

Determination of solubility parameter

Solubility parameters of steroids The value of the solubility parameter (δ_s) was calculated using the following relationship (Fedors, 1974)

$$\delta_s = \Sigma G / V_s = (\Delta E / V_s)^{1/2} \quad (1)$$

where ΣG is the sum of the molar attraction constants, calculated based on the structure of the steroid, ΔE is the energy of vaporization and V_s is the molar volume of each steroid.

Solubility parameters of adhesive According to theory (Hansen, 1967), the solubility parameter of a polymer (δ_p) can be characterized by a set of three partial solubility parameters: δ_{dis} (non-polar or dispersion forces), δ_{pol} (dipolar forces) and δ_{hyd} (hydrogen bonding and other strong permanent dipole forces) as follows:

$$\delta_p = \left(\delta_{dis}^2 + \delta_{pol}^2 + \delta_{hyd}^2\right)^{1/2} \quad (2)$$

There are several methods available for the determination of the solubility parameters (Fedors, 1974). These include measurement of turbidity, swelling ratios and intrinsic viscosity. For a polymer consisting of a low crosslink density, the measurement of swelling ratios becomes difficult since the polymer film tends to break apart upon solvent treatment. Turbidity measurements were also not used in this study since they require use of pure solvents and are very sensitive to impurities such as dust. Thus, the solubility parameter of the silicone polymers was determined using intrinsic viscosity measurements. A polymer typically exhibits its highest intrinsic viscosity at the solubility parameter value. The solvent systems used in this study were chosen by a

TABLE 1

Solvent combinations used for the determination of the solubility parameters of the adhesives

Solvent system	Ratio (w/w)	Solubility parameter			
		δ_{dis}	δ_{pol}	δ_{hyd}	δ_p
Isopentane : 1,4-dioxane	82.1 : 17.9	7.00	0.10	0.64	7.02
Isopentane : acetone	61.0 : 39.0	7.00	1.70	1.32	7.32
n-Heptane : diethyl ether	45.4 : 54.6	7.29	0.75	1.36	7.45
Isopentane : acetonitrile	56.8 : 43.2	7.00	3.33	1.29	7.85
n-Heptane : cyclohexane	45.7 : 54.3	7.86	0.00	0.00	7.86
Cyclohexane : 1,4-dioxane	74.2 : 25.8	8.43	0.19	0.92	8.48
Diethyl ether : ethyl acetate	17.7 : 82.3	7.57	2.34	3.32	8.59
Methylene chloride : diethyl ether	72.1 : 27.9	8.14	2.38	2.86	8.95
Diethyl ether : acetonitrile	51.1 : 48.9	7.29	4.84	2.74	9.16
Diethyl ether : ethanol	66.7 : 33.3	7.29	2.30	5.56	9.29
Cyclohexane : 1,4-dioxane	22.0 : 78.0	9.00	0.65	2.51	9.36
1,4-Dioxane : acetone	71.4 : 28.6	8.71	2.35	3.54	9.69
Methylene chloride : acetone	29.5 : 70.5	7.86	4.70	3.28	9.72
Methylene chloride : 1,4-dioxane	79.5 : 20.5	9.00	2.55	3.12	9.86
Methylene chloride : acetonitrile	77.0 : 23.0	8.43	5.02	3.00	10.25

half-factorial design using a computer program designed in our laboratories (Bogner et al., 1988). Table 1 lists the solvent systems used, their ratios and their partial and total solubility parameters. The solvent systems were selected such that they consisted of a range of partial and total solubility parameters.

Viscosity was determined in a U-tube viscometer (Schott Instruments, Germany), which was jacketed and maintained at 25°C. The solvent originally present in the adhesive solution was first evaporated until it was completely free of solvent. A known quantity of each adhesive was weighed out in a bottle, then 0.4% (w/v) solution of each adhesive was prepared in each solvent system outlined in Table 1 as the stock solution. The stock solution was then diluted serially to concentrations of 0.2, 0.1 and 0.05% (w/v). Approx. 3 ml of each solution were placed in the wide mouth of the viscometer and equilibrated at 25°C for 10 min. The time required for the solution to travel between two predetermined points on the viscometer was recorded using an accurate stop watch. Blank measurements were made using the solvent systems devoid of the adhesive.

The reduced viscosity was determined from the following relationship

$$\text{Reduced viscosity} = [\eta/\eta_0 - 1]/c \qquad (3)$$

where η is the viscosity of solvent system with adhesive concentration at c, while η_0 is the viscosity of the solvent system itself (without the adhesive).

The intrinsic viscosity was determined by plotting the reduced viscosities vs the adhesive polymer concentrations and extrapolating to reduced viscosity at zero concentration.

The intrinsic viscosity value obtained for each adhesive solution in a solvent system was fitted into an X-stat program (X-Stat Version 1, Softpower Inc., 1984) to yield the partial and total solubility parameter of that adhesive.

Determination of the physical properties of steroids

Properties such as melting point and heat of fusion were determined using a differential scanning calorimeter (Perkin Elmer Delta series 7, Perkin Elmer, Piscataway, NJ). A known amount of each steroid was placed in a pan and scanned over a wide range of temperatures. The melting point and the heat of fusion were obtained, respectively, from the peak and the area under the curve of each DSC thermogram (Table 2). Other properties such as molecular weight, volume, density and the Gibbs free energy change were either calculated from the structure of the steroid or obtained from literature (Windholtz, 1983).

TABLE 2

Physicochemical properties of the steroids studied

	Progesterone	Testosterone	Hydrocortisone
Melting point (T_m) (°C)	132.6	149.2	221.1
Mol. Wt. (g/mol)	314	288	362
Density (ρ) (g/cm^3)	1.17	1.20	1.23
Volume (V_s) (cm^3/mol)	269	240	295
Solubility parameter (δ_s) (cal/cm^3)$^{1/2}$	8.60	8.3	8.54
Heat of fusion (ΔH_f) (kcal/mol)	6.06	5.48	8.41
ΣG (cal cm^3)$^{1/2}$	2313	1993	2515
Solubility in adhesive polymer (mg/cm^3)			
X7-2920	1.57 (0.20)	1.36 (0.23)	0.08 (0.01)
DC-355	2.64 (0.07)	2.59 (0.68)	0.11 (0.01)
E8086	2.73 (0.06)	3.14 (0.45)	0.26 (0.01)
Solubility in water (μg/ml)	11.9 (0.97)	46.3 (2.97)	421 (10.4)
Solubility in PEG 400 : water (40 : 60) (μg/ml)	210 (18)	542 (6.76)	2679 (131)

V_s, Mol. Wt./ρ; δ_s, $\Sigma G/V_s$.

Preparation of a-TDD patches

The steroid was accurately weighed and then dispersed in a small amount of methylene chloride. A known amount of adhesive in solution was added and mixed well with the steroid suspension in a bottle, with constant agitation, for 2 h, followed by standing for 30 min to eliminate any entrapped air bubbles. A sheet of release liner (8 × 6 inches) (Scotchpak® low adhesion polyester film no. 1022, 3M Corp, St. Paul, MN) was placed on a flat glass plate and secured in place with a tape. The adhesive suspension was poured carefully onto the liner. A K-Bar (300 μm) was then gently passed through the suspension to produce a coating of uniform thickness. The solvent was then allowed to evaporate off overnight in an exhaust hood. After complete drying, the medicated adhesive film was covered with a sheet of backing membrane (Scotchpak® heat sealable polyester film no. 1009, 3M Corp, St. Paul, MN) of equal size and pressed uniformly with thumb pressure.

In vitro drug release studies

The Valia-Chien (V-C) skin permeation cell (Chien and Valia, 1984), a hydrodynamically well-calibrated skin permeation system, was used for both drug release and skin permeation studies. All studies were carried out at 37°C. For the in vitro drug release studies, each of the a-TDD patches prepared, after removal of release liner, was mounted between the two half-units of the V-C cell with the drug-releasing surface facing the receptor solution (3.5 ml of a 40% (v/v) aqueous PEG 400 solution). At predetermined intervals, a 1.0 ml aliquot of receptor solution was withdrawn (which was replaced immediately with the same volume of a fresh PEG 400 solution) for a period of up to 30 h. The amount of drug in the samples was then determined using the HPLC method described later. The cumulative amount of drug released was then calculated and plotted against the square root of time according to the Higuchi relationship (Higuchi, 1963).

In vitro skin permeation studies

Preparation of skin for permeation studies Female hairless rats were killed just prior to the experiment. The abdominal skin was then carefully excised and all the fatty tissues adhering to its dermis were completely removed.

In vitro permeation studies using a-TDD patches The skin was mounted between the two half-units of the V-C cell with the dermis surface facing the receptor half-unit. A unit (5 cm^2) of the a-TDD system was then mounted with the drug-releasing area in intimate contact with the stratum corneum surface. The receptor solution was then added into the receptor half-cell. Samples (0.1 ml each) were taken at appropriate intervals for up to 36 h and the drug concentration in each sample was assayed using the HPLC method described below under Analytical method. The a-TDD patches containing several loading doses of each steroidal drug were tested and the permeation rates were calculated from the steady-state portion of the cumulative amount of drug permeated vs time plots (Toddywala and Chien, 1990).

Analytical method

A microprocessor-controlled high performance liquid chromatograph (Hewlett Packard, HP 1084B, Palo Alto, CA) was used. Combinations of acetonitrile and water (in varying proportions) were used as the mobile phase at a flow rate of 2 ml/min. Each of the steroids was resolved using a reversed-phase Hypersil column (Hewlett Packard, Palo Alto, CA) and detected at a wavelength of 240 nm. Drug concentration in each of the samples was determined by first measuring the peak height of the chromatographic peak for each steroid and then computing the concentration from a standard curve.

180° peel test for adhesive properties

The adhesive properties of the a-TDD system were determined using a standard 180° peel test. The test was performed using a Slip/Peel tester (model SP-102B-3M90, Instrumentors Inc., Strongsville, OH). Strips of 1 × 6 inch each were cut out for this test. The release liner was removed and the strips were placed on stainless-steel plates and passed through an autoroller (8 lb) for uniform pressure. Each sample was then allowed to stand on the plate for exactly 10 min before peeling. The platen speed was adjusted to

3 inch/min. Each sample was then peeled off at an angle of 180° for 25 s. The average peel force was monitored and reported as the mean and standard deviation of six measurements.

Results and Discussion

The chemical composition of the three silicone-based adhesives used for this investigation is shown in Fig. 1. These silicone adhesives contain the poly(dimethyl siloxane) crosslinked with a silicate resin (usually at a polymer : resin crosslinking ratio of 40% : 60%), which give adhesives of varying molecular weight and properties. While DC-355 contains a silanol (-OSiOH) functionality, X7–2920 has a third $-CH_3$ group to replace the -OH group in the silanol functionality and thus eliminates the sites for potential hydrogen bonding and crosslinking reaction. X7–2920 adhesive is thus expected to be useful for drugs having amine groups where hydrogen bonding could occur and affect the physical and mechanical properties of drug-adhesive blends. The E8086 adhesive, on the other hand, consists of a poly(dimethyl siloxane) backbone in which some of the methyl groups have been replaced by polyethylene oxide groups, thus making this polymer relatively hydrophilic. Thus, the three adhesives used are composed of different chemical substituents on the polymer backbone, which makes them vary

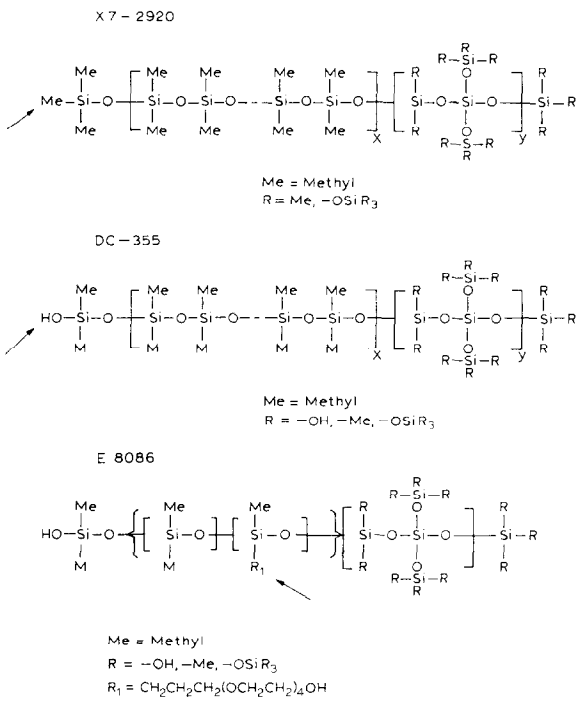

Fig. 1. Schematic illustration of the chemistry of the three silicone-based pressure-sensitive adhesives used in this study.

TABLE 3

Intrinsic viscosities of the adhesives

Solvent system	Intrinsic viscosity		
	X7-2920	DC-355	E8086
Isopentane : 1,4-dioxane	0.340 (0.032)	0.108 (0.004)	0.098 (0.003)
Isopentane : acetone	1.020 (0.097)	0.679 (0.056)	0.079 (0.008)
n-Heptane : diethyl ether	1.282 (0.095)	0.623 (0.079)	0.857 (0.126)
Isopentane : acetonitrile	0.222 (0.008)	0.487 (0.077)	0.128 (0.076)
n-Heptane : cyclohexane	1.147 (0.196)	0.165 (0.061)	0.673 (0.053)
Cyclohexane : 1,4-dioxane	0.476 (0.054)	0.158 (0.007)	0.132 (0.022)
Diethyl ether : ethyl acetate	0.368 (0.022)	0.125 (0.066)	0.798 (0.005)
Methylene chloride : diethyl ether	0.458 (0.087)	0.128 (0.054)	0.154 (0.003)
Diethyl ether : ethanol	0.575 (0.072)	0.576 (0.027)	0.608 (0.052)
Diethyl ether : acetonitrile	0.129 (0.009)	0.201 (0.049)	0.409 (0.185)
Cyclohexane : 1,4-dioxane	0.000 (0.000)	0.000 (0.000)	0.056 (0.007)
1,4-dioxane : acetone	0.102 (0.004)	0.056 (0.003)	0.106 (0.001)
Methylene chloride : acetone	0.124 (0.012)	0.167 (0.060)	0.198 (0.006)
Methylene chloride : 1,4-dioxane	0.000 (0.000)	0.000 (0.000)	0.046 (0.006)
Methylene chloride : acetonitrile	0.000 (0.000)	0.097 (0.002)	0.145 (0.023)

Values in parentheses indicate standard deviation, $n = 3$.

in their physical and mechanical properties. These polymers typically have a glass transition temperature of −123°C. This imparts a degree of chain flexibility (Pfister, 1989). They are stable at the normal processing temperatures and have good flow properties. Finally, they are known to possess good tack and skin adhesion making them good candidates for a-TDD systems.

Solubility parameter of the adhesives

The solubility parameter of a polymer can be useful in characterizing the polymer. Solubility parameters of polymers have been described in the literature and tables have been published for the more commonly used polymers (Burrell, 1975). Table 3 lists the intrinsic viscosity values for the three silicone-based adhesives determined in the solvent systems shown in Table 1. Using these intrinsic viscosity values, response surface was created to determine the partial and total solubility parameters. Fig. 2 shows some representative contours obtained for the three adhesives studied. The square region in these contours represents the maximum intrinsic viscosity values and thus is an indirect measure of the solubility parameter. The values of the partial solubility parameters are calculated by use of appropriate mathematical equations. For our case, a quadratic equation fitted the given data and was used to calculate the partial solubility parameters. Table 4 shows the equation and its coefficients for all three adhesives. Table 5 lists the partial and total solubility parameters determined for the adhesives used. The values obtained for the total solubility parameter of X7–2920 and DC-355 adhesives compare well with those of Ghosh et al. (1988). The partial solubility parameter is known to be a good indicator of the nature of the adhesive and would be a useful parameter in the formulation of drugs in an a-TDD system. Apparently, the solubility parameter of the X7–2920 adhesive is composed of only the non-polar (or disperse) component and is thus a lipophilic adhesive. The DC-355 adhesive consists of a relatively large contribution from a polar component and a smaller non-polar and hydrogen bonding component. Review of the structure of X7–2920 and DC-355 adhesives indicates that the difference between these adhesives is the presence of a silanol functionality in DC-355, which could be responsible for the existence of the polar component in DC-355 and the absence thereof in X7–2920. Thus, the polar and hydrogen bonding components of the solubility parameter could be attributed to this silanol functionality. The E8086 adhesive, on the other hand, consists of larger non-polar and hydrogen bonding components than those of DC-355, but a smaller polar component. The polyoxyethylene groups on the E8086 adhesive could account for both of these properties. An intimate knowledge of such interactions

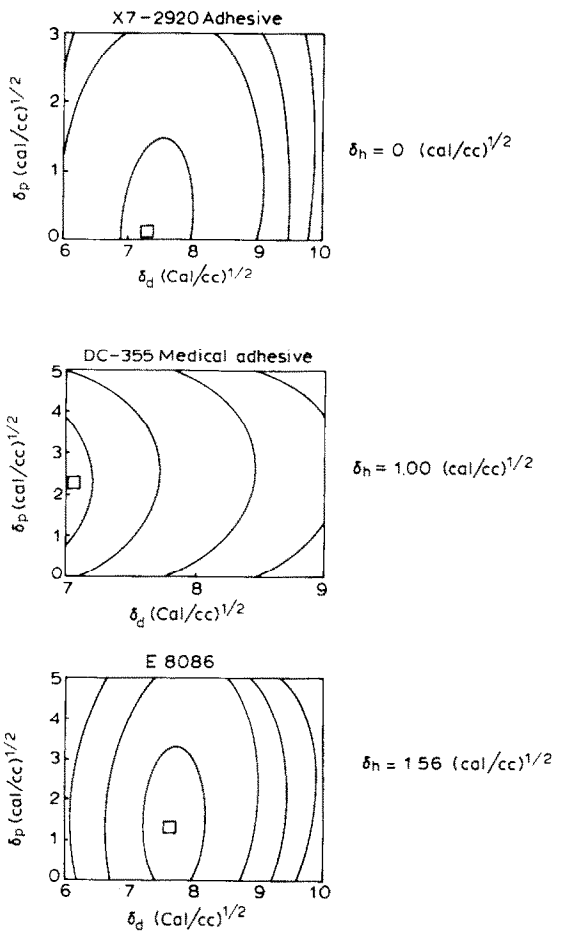

Fig. 2. Response surface contours of the non-polar and polar solubility parameters for the three adhesives studied. The box in the contours represents the region of highest intrinsic viscosity and thus the total solubility parameter of the adhesive.

TABLE 4

Equation and coefficients used for calculation of the partial solubility parameters of silicone-based adhesives

Intrinsic viscosity = $A + B\delta_{dis} + C\delta_{pol} + D\delta_{hyd} + E\delta_{dis}^2 + F\delta_{dis}\cdot\delta_{pol} + G\delta_{pol}^2 + H\delta_{dis}\cdot\delta_{hyd} + I\delta_{pol}\cdot\delta_{hyd} + J\delta_{hyd}^2$

Coefficient	X7-2920	DC-355	E8086
A	−10.21	7.49	−20.38
B	2.73	−1.91	5.33
C	−0.07	0.10	0.13
D	1.15	1.05	0.36
E	−0.17	0.12	−0.34
F	0.02	0.01	−0.04
G	−0.07	−0.02	0.01
H	−0.16	−0.13	−0.02
I	0.09	−0.01	0.02
J	−0.05	−0.02	−0.03

could assist the study of drug-polymer compatibility.

Physicochemical properties of steroids

The physicochemical properties of these steroids are summarized in Table 2. These physicochemical properties appear to be dependent upon the type, number and position of the substituent on the steroid. The molecular weights of these compounds were almost equal, ruling out most molecular weight effects. The solubility parameters thus calculated are an important characteristic of each compound. The diversity of physicochemical properties (especially the solubilities) of these three steroids makes them good candidates for studying effects of minor structural variations on properties such as release of drug from the adhesive polymer, skin permeation and adhesiveness.

TABLE 5

Partial and total solubility parameters of the adhesives

Adhesive	Partial solubility parameter			Total solubility parameter
	δ_{dis}	δ_{pol}	δ_{hyd}	δ_p
X7-2920	7.38	0.00	0.00	7.38
DC-355	7.00	2.18	1.00	7.39
EC8086	7.77	1.47	1.56	8.06

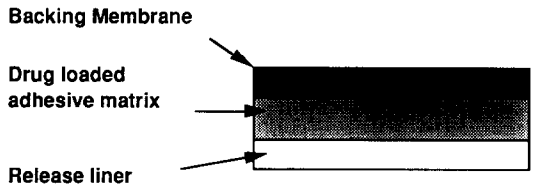

Fig. 3. Schematic illustration of an a-TDD system.

The solubility of these compounds in water ranges widely from 11.9 μg/ml for progesterone to 421 μg/ml for hydrocortisone. The solubility of the steroids in relatively lipophilic adhesive polymers has been reported in our earlier publications (Toddywala and Chien, 1990, 1991). These show the opposite behavior, i.e., progesterone displays the highest while hydrocortisone shows the lowest solubility. The solubility of the steroids is least in X7–2920 adhesive and greatest in the E8086 adhesive. The reasoning for this becomes clear when comparing the various solubility parameters of the adhesive polymers. The X7–2920 adhesive is the most lipophilic and is devoid of hydrogen bonding sites. DC-355 adhesive, on the other hand, contains end hydroxy groups which allow some hydrogen bonding, while the E8086 adhesive is relatively more hydrophilic due to the presence of oxyethylene groups on its skeleton.

Preparation of the a-TDD system

Fig. 3 shows a schematic representation of the a-TDD system which consists of a drug-impermeable backing membrane, drug-loaded adhesive layer and a detachable release liner. In an ideal situation, the release liner is removed and discarded and the patch is applied to the skin for required period of time. Thus, the adhesive material must not stick to the release liner and must stick over extended periods of time to the skin. In addition, the adhesive must be compatible with the drug and must not lose its adhesive properties. Finally, additives such as preservatives, humectants, chemical enhancers, etc., should not reduce the system efficacy.

Release of steroids from a-TDD systems

The release of the steroids studied all followed a Q vs $t^{1/2}$ relationship as described by the

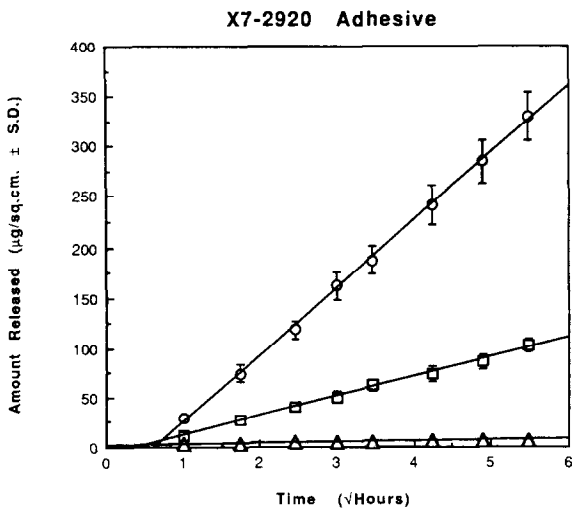

Fig. 4. Q vs $t^{1/2}$ profiles for the release of progesterone (○), testosterone (□) and hydrocortisone (△) from X7-2920 based a-TDD systems containing a 5% drug loading.

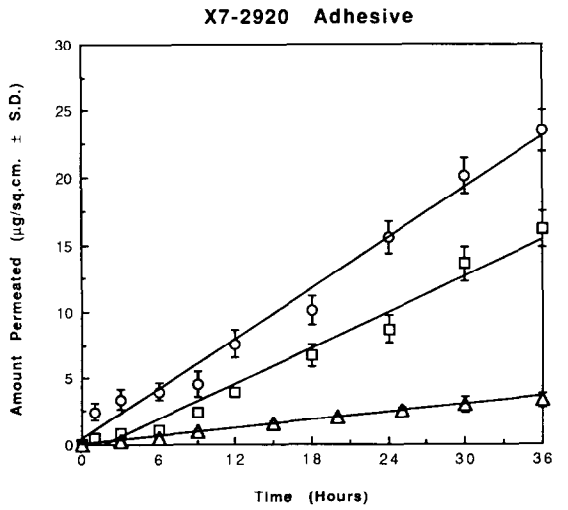

Fig. 5. Q vs t profiles for the skin permeation of progesterone (○), testosterone (□) and hydrocortisone (△) from X7-2920 based a-TDD systems containing a 5% drug loading.

Higuchi relationship (Higuchi, 1963). Fig. 4 shows the release of progesterone, testosterone and hydrocortisone from a-TDD systems fabricated with a 5% loading dose. In the two previous papers, we reported that the kinetics of release of steroids is dependent upon the solubility, diffusivity and dose of the drugs in the adhesives (Toddywala and Chien, 1990, 1991). An increase in the loading dose in the adhesive polymer results in an increase in release flux. The solubility and diffusivity are both dependent upon the functional groups on the steroid molecule.

Table 6 compares the release rates of the steroids from the three adhesives studied. It is apparent that the term 'release rate' mentioned here is the slope of the plot of amount released vs the square root of time and may not represent the instantaneous release rate at a given time point. However, it serves as a good value for comparison of the release potential of these polymers. The three steroids all show a similar release pattern in the three adhesives with the general trend: progesterone > testosterone > hydrocortisone. However, being close in structure and lipophilic in nature, no correlation could be made between the structure of these adhesives and the release rates. It thus appears that for these silicone polymers, the structure of the drug (and not the adhesive) is predominant in predicting the release rates.

TABLE 6

Comparison of release rates of progesterone, testosterone and hydrocortisone from a-TDD systems prepared with various silicone adhesives and containing a 5% drug loading dose

Adhesive	Release rate ($\mu g/cm^2$ per $h^{1/2}$) ± S.D.		
	Progesterone	Testosterone	Hydrocortisone
X7-2920	67.68 (±1.58)	19.81 (±0.46)	0.85 (±0.04)
DC-355	37.56 (±3.43)	35.77 (±3.39)	0.71 (±0.04)
E8086	83.01 (±5.96)	47.57 (±5.96)	0.65 (±0.02)

Skin permeation of steroids from a-TDD systems

The permeation of the steroids through hairless rat skin followed a Q vs t profile characterized typically by a time lag and a steady-state permeation profile (Fig. 5). The rate of permeation, determined from the slope of the steady-state portion of the Q vs t plots, increases with the increase in loading dose and then reaches a plateau level at higher drug loading doses. Such plateaus are reached at steroid drug loading doses as low as 3%. The plateau permeation rate for steroids is a function of the number of hydroxy or methyl/methylene groups on the steroid skeleton

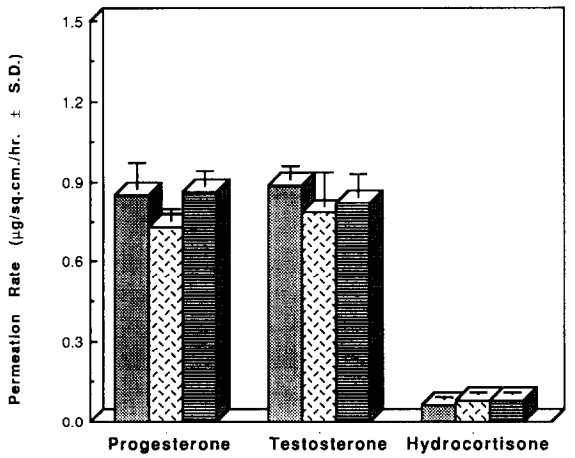

Fig. 6. Bar graph comparing the permeation rates of the steroids studied from X7-2920 (▨), DC-355 (▩) and E8086 (▤) adhesives.

(Toddywala and Chien, 1990). Fig. 6 compares the different adhesives for their permeation rates. It appears that there is no significant difference in the permeation rates of these steroids when delivered using different silicone polymers as the matrix material. It is thus apparent that the skin, not the a-TDD system, is the rate-limiting step in determining the plateau permeation of the steroids.

Effect of physicochemical properties of steroid and adhesive

According to Michaelis et al. (1975), the solubility of a drug in a polymer can be expressed in terms of its physicochemical properties as:

$$C_p = \rho \exp\left[-\left\{\frac{\Delta H_f}{R}\left[\frac{1}{T}-\frac{1}{T_m}\right] + 1 + \frac{V_s}{RT}\left[\delta_s - \delta_p\right]^2\right\}\right] \quad (4)$$

where ρ is the density of the steroid with heat of fusion ΔH_f, T is the absolute temperature under which the experiments were carried out, T_m is the melting point of the steroid, V_s is the molar volume of the steroid, δ_s is the solubility parameter of the steroid and δ_p is the solubility parameter of the polymer.

The release flux of a steroid can be expressed by the Higuchi Equation (Higuchi, 1963) as:

$$Q = \left[(2A - C_p)C_p D_p t\right]^{1/2} \quad (5)$$

when $2A \gg C_p$ Eqn 5 is reduced to

$$Q = \left[2AC_p D_p\right]^{1/2} t^{1/2} \quad (6)$$

where Q is the amount of steroid released from the a-TDD system at time t, A is the amount of steroid present in the drug matrix and D_p is the diffusivity of the steroid in the polymer matrix.

By substituting Eqn 4 for solubility (C_p) in the Higuchi Equation (Eqn 6), the release flux can be expressed as a function of the physicochemical properties as:

$$\frac{Q}{t^{1/2}} = \left[2AD_p\rho\right]^{\frac{1}{2}} \exp\left[-\frac{1}{2}\left\{\frac{\Delta H_f}{R}\left[\frac{1}{T}-\frac{1}{T_m}\right] + 1 + \frac{V_s}{RT}\left[\delta_s - \delta_p\right]^2\right\}\right] \quad (7)$$

In Table 7, the experimentally obtained solubilities of progesterone, hydrocortisone and testosterone are compared with those calculated using the physicochemical properties in Table 2. It appears that the calculated solubilities obtained using the physicochemical properties are

TABLE 7

Predicted and experimental solubilities of progesterone, testosterone and hydrocortisone in the silicone-based adhesives

Steroid	X7-2920	DC-355	E8086
Experimental			
Progesterone	1.57 (0.20)	2.64 (0.07)	2.73 (0.06)
Testosterone	1.36 (0.23)	2.59 (0.68)	3.14 (0.45)
Hydrocortisone	0.08 (0.01)	0.11 (0.01)	0.26 (0.01)
Predicted [a]			
Progesterone	2.21	2.09	3.44
Testosterone	2.98	2.87	3.91
Hydrocortisone	0.14	0.14	0.23

Values in parentheses indicate standard deviation, $n = 4$.
[a] Predicted from Eqn 7 using the data in Table 2.

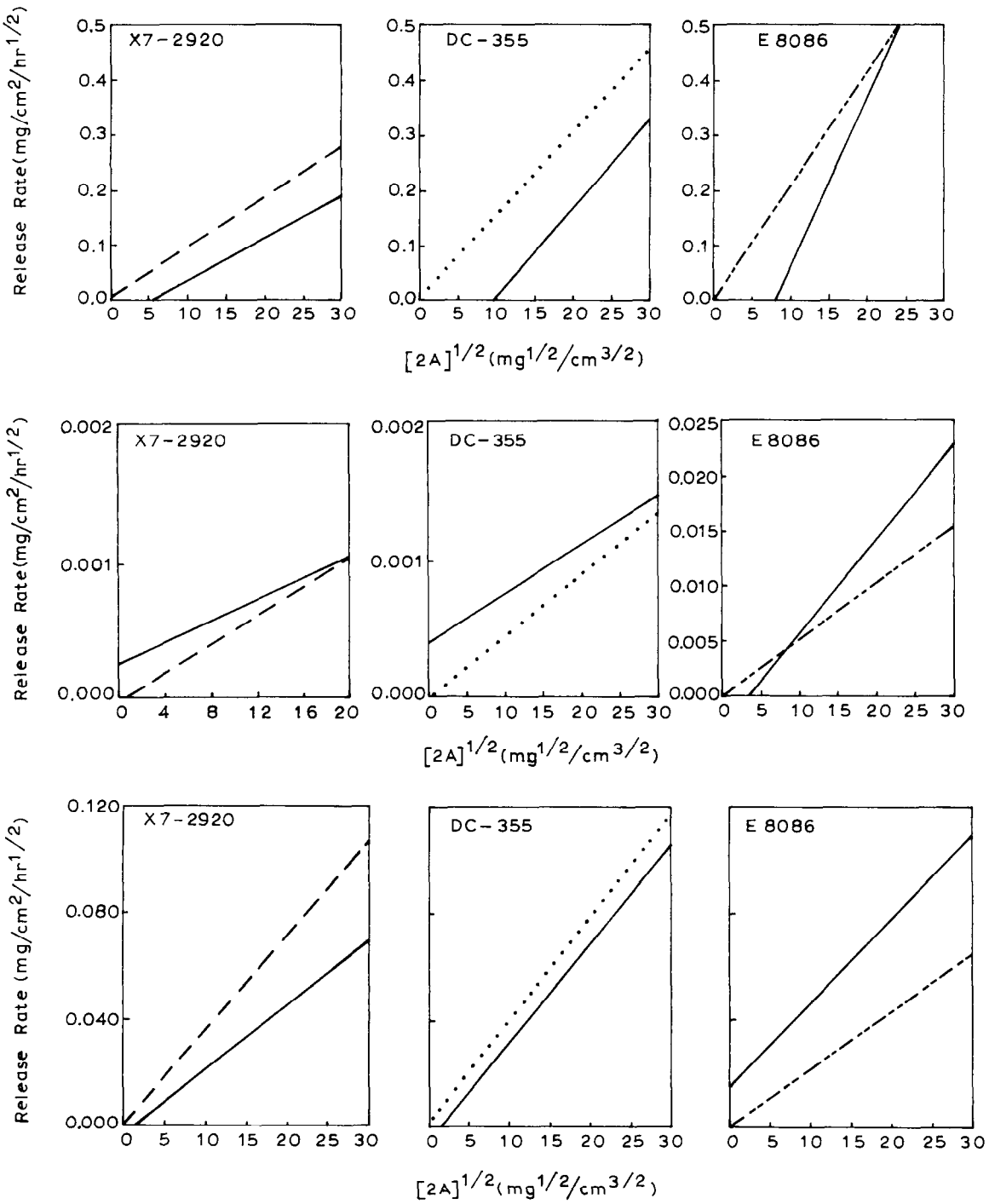

Fig. 7. Predicted (- - -) and experimental (———) $Q/t^{1/2}$ vs $(2A)^{1/2}$ plots for progesterone (upper panels), testosterone (middle panels) and hydrocortisone (lower panels) in the adhesives studied.

slightly higher than those determined experimentally. In Fig. 7, the predicted and experimental $Q/t^{1/2}$ vs $(2A)^{1/2}$ plots for progesterone, hydrocortisone and testosterone are compared for all three adhesives. The results indicate that there is a fairly good correlation between the predicted and experimental lines. There are, however, two important observations to be made regarding each of these lines – the intercept and the slope. The predicted lines all show an intercept value of zero, while the experimental lines show a positive or negative intercept. Such intercepts indicate that at a low drug loading dose, the Higuchi Equation may not be valid since the delivery system is no longer a dispersion-type matrix (the matrix at low doses is a subsaturated dissolved matrix). The slope, on the other hand, is a function of the solubility and the diffusivity of the drug in the polymer. Changes in the experimental and theoretical solubilities could account for differences in the slope values. These results lead us to believe that the physicochemical properties of the drug and adhesive are an important determinant in controlling the release of drug from the adhesive. According to Eqns 4 and 7, it appears that the properties of the steroid play a greater role than those of the polymer, in predicting the release. An intimate knowledge of all these properties would help in the design of optimal transdermal therapeutic systems since the adhesive could be tailored according to the drug specifications.

Adhesive properties of the a-TDD systems

One of the important considerations in designing a transdermal system is its adhesive properties. The adhesive properties of a polymer may change due to presence of other ingredients in the formula. Thus, for membrane-type systems, the adhesiveness may decrease due to the migration of drug or other excipients from the reservoir layer to the adhesive layer. Similarly, in a-TDD systems this parameter may be of the utmost importance since the drug/excipients are directly dispersed in the adhesive. There are several methods available to measure the adhesiveness of a-TDD systems. These include probe tack and peel tests. Each of these tests measures a different aspect of adhesion. For this investigation, we used the 180° peel test, which is a standard ASTM method (ASTM D1000–82a) for measuring adhesiveness of pressure sensitive adhesives. It essentially measures the force required to peel off the a-TDD system from a standard substrate. Fig. 8 shows a bar graph comparing the peel force of the silicone adhesives. The following trend was observed: X7–2920 > DC-355 > E8086. Addition of the steroid in these adhesives results in a drastic reduction of the peel force even at low drug loading doses. Table 8 shows some of these changes taking X7–2920 adhesive as an example.

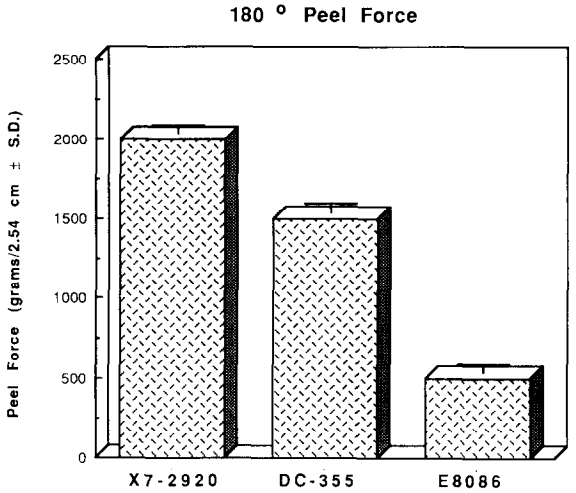

Fig. 8. Bar graph comparing the adhesiveness of the three silicone adhesives.

TABLE 8

Effect of drug loading dose on the 180° peel force for the steroids studied using X7-2920 adhesive

% Drug loading dose	Peel force (g/2.54 cm)		
	Progesterone	Testosterone	Hydrocortisone
0	2000 (27)	2000 (27)	2000 (27)
1	1940 (35)	1900 (39)	550 (25)
2	1050 (42)	1650 (39)	500 (25)
3	100 (35)	1000 (50)	455 (30)

Values in parentheses indicate standard deviation.

Conclusions

The release, permeation and adhesive properties are three properties of paramount importance in the design of optimal a-TDD systems. The choice of the appropriate drug and adhesive combination depends greatly on their individual physicochemical properties and these need to be determined and optimized.

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