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KINETICS AND THERMODYNAMICS OF DRUG PERMEATION THROUGH SILICONE ELASTOMERS

(I) EFFECT OF PENETRANT HYDROPHILICITY

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ABSTRACT

The hydrophilicity of progesterone, a lipophilic penetrant, was progressively increased by addition of one or more hydroxy substituents at different positions on the steroid skeleton. Effects of these hydrophilic substituents on the kinetics and thermodynamics of permeation of progesterone molecules through polydimethylsiloxane and polytrifluoropropylmethylsiloxane membranes were studied. The addition of OH groups was found to reduce substantially the apparent and intrinsic permeation rates of progesterone. The magnitude

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of this reduction was observed to be dependent upon the number and the position of hydroxy groups and could be attributed to the decrease in the polymer solubility and the increase in the aqueous solubility of progesterone molecules. A remarkable difference was observed between the intrinsic and apparent rates of permeation for progesterone, while no significant difference for the hydroxyl derivatives of progesterone. The rate of permeation increased with temperature as expected from the Arrhenius relationship. The energy required for membrane permeation was noted to be relatively constant and independent of hydroxylation. After normalization, the membrane permeability of progesterone derivatives was found to be higher in polydimethylsiloxane than in polytrifluoropropylmethylsiloxane, which can be attributed to the substitution of methyl group in the polydimethylsiloxane backbone by a more polar and bulkier trifluoropropyl substituent. The substituent effect of trifluoropropyl group is substantial for progesterone but less significant for hydroxy derivatives.

INTRODUCTION

Recently, polymeric membranes have been increasingly used to moderate the rate of drug release. Due to its biocompatibility, the potential of silicone elastomer for the fabrication of drug delivery device was studied by a number of researchers and its potential biomedical applications have been increasingly recognized for the controlled delivery of progestins and other lipophilic steroids (1-15).

The molecular structure was found to play an important role in the release of steroids from silicone elastomer matrix (10, 15-18). Since the diffusivity of steroids varies only slightly, the diverse in release patterns was primarily attributed to the difference in polymer solubilities as well as the partition coefficients, which have been known to be sensitive functions of the structure and substituents on the steroid molecule.

To evaluate the mechanism and kinetics of membrane permeation of steroids, the permeation studies should be conducted in a hydrodynamically well-calibrated diffusion system under a well-maintained sink condition; otherwise, the permeation rate obtained may be distorted to a significant degree by the presence of hydrodynamic diffusion layers on both sides of the membrane. In the literature, the effect of diffusion boundary layer was frequently overlooked. In this laboratory, however, it was constantly observed that the effect of mass transfer in the hydrodynamic diffusion layer is hardly neglected. Experimentally, it has been discovered that using a well-calibrated in vitro system, the apparent rate of membrane permeation obtained can be used to calculate the intrinsic rate of permeation, which is the permeation rate without the effect of hydrodynamic diffusion layer.

In the first report of this series of investigations, the apparent and intrinsic rates of permeation of progesterone and six hydroxyl derivatives (with increasing hydrophilicity) through polydimethylsiloxane and polytrifluoropropylmethylsiloxane membranes were determined and analyzed. This report intends to discuss the effect of variation in drug hydrophilicity and in polymer composition on the kinetics and the thermodynamics of membrane permeation through silicone elastomers.

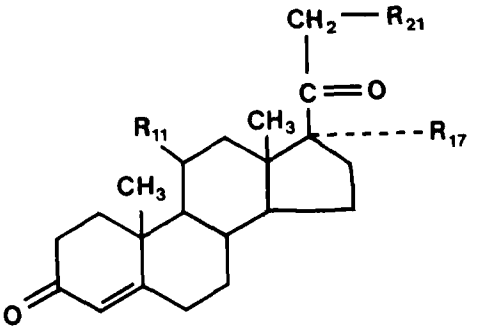
EXPERIMENTAL

A. Materials

(1) Progesterone derivatives - A homologous series of progesterone derivatives with variation in the number and the position of hydroxy groups (Table 1) was used in this investigation: progesterone[1], desoxycorticosterone[1], 11α-hydroxyprogesterone[1], 17α-hydroxyprogesterone[1], cortisone[1], 17α-hydroxycorticosterone[2] and hydrocortisone[2].

(2) Polyethylene glycol (PEG) 400 - A water-miscible liquid polymer[1] which

TABLE 1: Chemical structure of progesterone derivatives investigated



DRUGS	R_{21}	R_{11}	R_{17}
I Progesterone	H	H	H
II Desoxycorticosterone	OH	H	H
III 11α-Hydroxyprogesterone	H	OH	H
IV 17α-Hydroxyprogesterone	H	H	OH
V Corticosterone	OH	OH	H
VI 17α-Hydroxydesoxycorticosterone	OH	H	OH
VII Hydrocortisone	OH	OH	OH

was blended with different volume fractions of distilled water to increase the aqueous solubility of progesterone derivatives.

(3) Silicone elastomers - polydimethylsiloxane and polytrifluoropropylmethylsiloxane membranes (Figure 1) were custom made[3].

B. In Vitro membrane permeation system:

The well-calibrated Ghannam-Chien System[4] (Fig. 2) described previously (19, 20) was used.

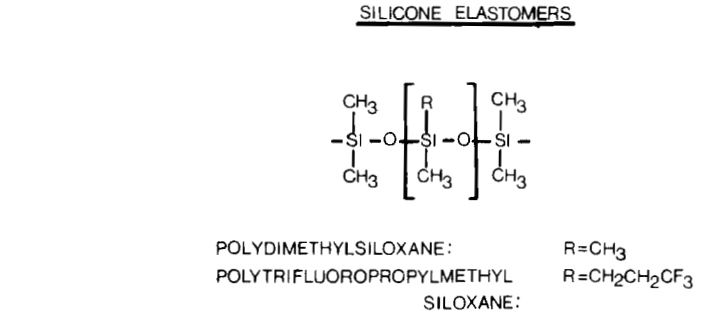


Figure 1: The types of silicone membranes investigated.

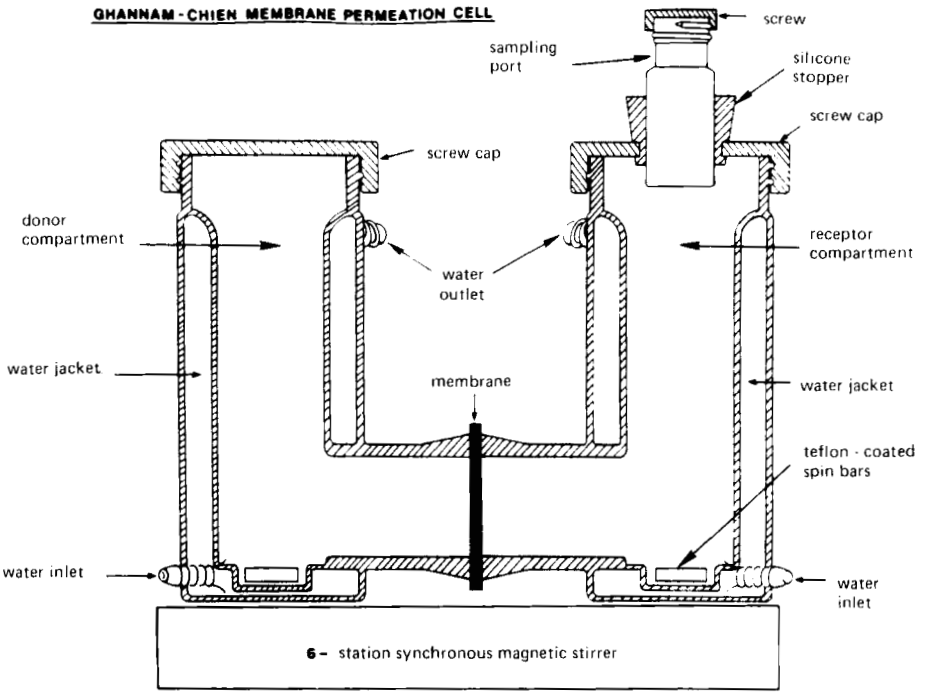


Figure 2: The membrane permeation system used in the investigation.

C. Procedures:

(1) Membrane permeation studies:

Saturated solution of a progesterone derivative was prepared by suspending an excess amount of steroid crystals in 40% aqueous PEG solution and used as the donor solution. Excess solid is presented to assure that the solution is maintained at a constant drug concentration (at saturation solubility) throughout the course of the experiment. The same aqueous solution (with no steroid added) was filled to the receptor compartment as the desorbing medium under sink condition.

At each predetermined time interval, 10 ml of the receptor solution was sampled and, quickly, an equivalent volume of the drug-free aqueous solution was added into the receptor solution to maintain a constant solution volume in the receptor compartment. The concentration of the progesterone derivative in the samples was then analyzed spectrophotometrically[5].

(2) Determination of solubility:

a) Aqueous solubility - An excess amount of a progesterone derivative was equilibrated with 40% (v/v) aqueous PEG 400 solution for 24 hours with constant shaking in a water bath at 37°C. The saturated solution was quickly filtered and the drug concentration in the filtrate was then determined spectrophotometrically.

b) Polymer solubility - An excess amount of a progesterone derivative was equilibrated in silicone fluid for 24 hour with constant shaking in a water bath at 37°C. The saturated solution was then quickly filtered. The filtrate was extracted with methanol and the drug concentration in the methanol was then determined spectrophotometrically.

(3) Determination of partition coefficient:

The partition coefficient was determined by dividing the solubility of the drug in the aqueous solution over its solubility in the silicone fluid.

THEORETICAL ANALYSIS

Permeation of drug molecules across a unilayer membrane from the donor solution to the receptor solution can be described by the physical model as shown in Figure 3. This model suggests that the rate of membrane permeation (dQ/dt) is mathematically expressed by (19, 20):

$$\frac{dQ}{dt} = \frac{C_s}{\frac{\ell}{K_1 D_m} + \frac{K_2}{K_1}\frac{1}{K_R} + \frac{1}{K_D}} \qquad (1)$$

where C_s is the saturation solubility in the donor solution; D_m is the diffusivity in the membrane with thickness of ℓ ; K_1 and K_2 are the partition coefficients for the interfacial partitioning between the donor solution and the membrane and between the receptor solution and the membrane, respectively; K_D and K_R are mass transfer coefficients across the diffusion boundary layers on the donor side and receptor side of the membrane.

Determination of Intrinsic Rate of Membrane Permeation:

If the agitation of fluid is so vigorous that the diffusional resistance across the hydrodynamic diffusion layers on both sides of the membrane becomes negligibly small, Eq. 1 is then reduced to:

$$\left(\frac{dQ}{dt}\right)_\infty = \frac{C_s}{\ell/(K_1 D_m)} = \frac{C_s K_1 D_m}{\ell} \qquad (2)$$

where $(dQ/dt)_\infty$ is the intrinsic rate of membrane permeation.

The correction factor (γ) for the calculation of the intrinsic permeation rate from the apparent permeation rate (dQ/dt), which was experimentally obtained under a non-ideal mixing condition, can be determined by the following relationship:

$$\gamma = \frac{dQ/dt}{(dQ/dt)_\infty} = \left[1 + (\alpha + \beta)\frac{K_1}{Sh}\frac{d}{\ell}\frac{D_p}{D_R}\right]^{-1} = 1 - \frac{(\alpha+\beta)}{Sh}\frac{(dQ/dt)}{D_R C_s/d} \qquad (3)$$

where $\alpha = K_R/K_D$, $\beta = K_2/K_1$, and $Sh = K_m d/D$

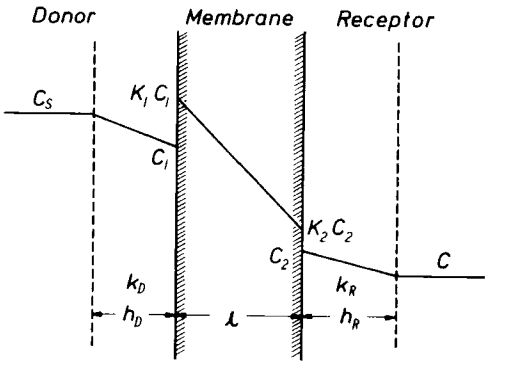


Figure 3: Multilayer Model proposed. C_S is the equilibrium solubility in the donor solution, C is the bulk concentration in the receptor solution, h_D and h_R are the hydrodynamic diffusion layers on the donor and receptor sides of the membrane, K_D and K_R are the mass transfer coefficients, C_1 and C_2 are the drug concentrations at the solution/membrane interface of the donor-side and receptor-side boundary layers.

where Sh is the Sherwood number and d is the length of the stirring magnet. After rearrangement:

$$\gamma = 1 - \frac{(\alpha + \beta)}{Sh} \frac{(dQ/dt)}{DC_S/d} \tag{4}$$

In the present study, the same solution medium and same agitation speed were used in both the receptor and donor compartments, Equation (4) can be simplified to:

$$\gamma = 1 - \frac{2}{Sh} \frac{(dQ/dt)}{DC_S/d} \tag{5}$$

In this case

$$\alpha = \beta = 1$$

The intrinsic rate of permeation $(\frac{dQ}{dt})_\infty$ is then given by:

$$(\frac{dQ}{dt})_\infty = (dQ/dt)/\gamma \tag{6}$$

Determination of Normalized Permeability:

To account for the variation in saturation solubilities among steroidal drugs and the difference in thickness from one membrane to another, membrane permeability should be normalized. Normalized permeability can be obtained from the following treatment:

Ficks's first Law of diffusion can be written as:

$$J = dm/Adt = D(C_1 - C_2)/\ell \quad (7)$$

where C_1 and C_2 are the concentrations in the membrane at the donor and receptor sides, respectively; ℓ is the thickness of the membrane, A is the surface area, dm/dt is the amount of drug permeated per unit time. This equation assumes that the aqueous boundary layers on both sides of the membrane do not have any significant effect on the total transport process. The concentration C_1 and C_2 can be determined from the (polymer/solution) partition coefficient K and the concentration C_d in the donor solution or C_r in the receptor solution as follows:

$$\frac{dm}{Adt} = \frac{DK\,(C_d - C_r)}{\ell} \quad (8)$$

and since sink conditions are maintained in the receptor solution, i.e., C_r=0; so

$$\frac{dm}{Adt} = \frac{dQ}{dt} = \frac{DKC_d}{\ell} \quad (9)$$

$$\text{Normalized Permeability} = \frac{(dQ/dt) \times \ell}{C_d} = DK \quad (10)$$

RESULTS AND DISCUSSION

Apparent and Intrinsic Rates of Permeation:

The *in vitro* permeation profiles of progesterone derivatives across polydimethylsiloxane (PDS) and polytrifluropropylmethylsiloxane (PTPM) are shown, respectively, in Figure 4 and 5. Apparently, the permeation of progesterone and its hydroxy derivatives across the two types of silicone

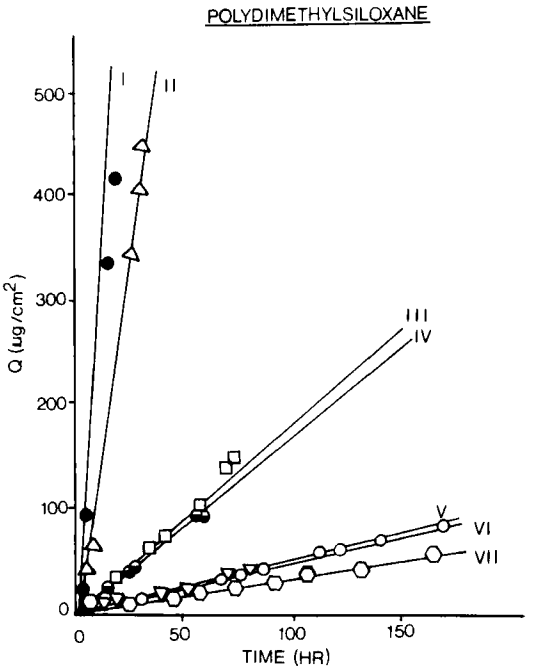


Figure 4: Linear relationship between the cumulative amount of progesterone derivatives permeating through a unit surface area of polydimethylsiloxane membrane (Q) and time (t) at 37°C (membrane thickness = 0.0127cm).

membranes followed the membrane permeation-controlled process (15). As expected from Eq. 9, the cumulative amount of progesterone derivative permeated (Q) is a linear function of the time. The results in Figures 4 and 5 suggest that progesterone has the highest permeation profile across the PDS and PTPM membranes; and following the addition of OH groups, the permeation profile of progesterone decrease. The magnitude of reduction appears to be dependent upon the number and position of OH groups added.

The rate of permeation can be estimated from the slope of Q vs.t plots (Fig. 4 and 5). The rates of permeation so obtained are the apparent permeation rates and they can be converted to the intrinsic permeation rates

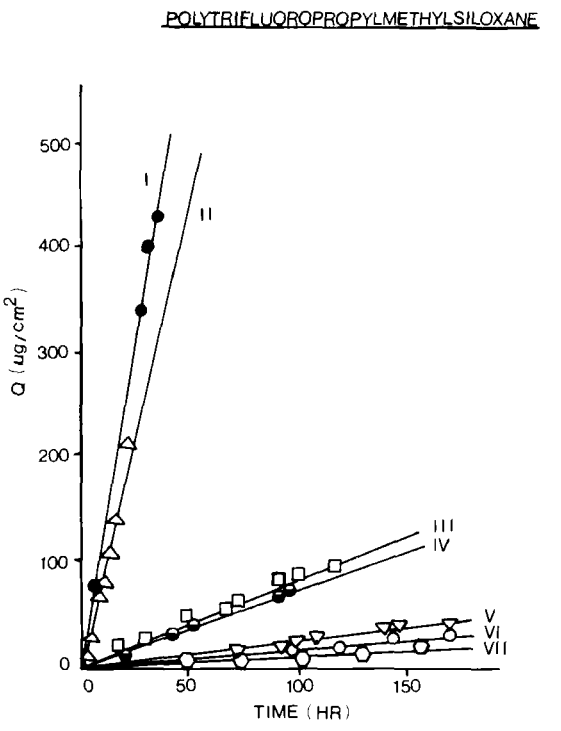


Figure 5: Linear relationship between the cumulative amount of progesterone derivatives permeating through a unit surface area of polytrifluoromethylsiloxane membrane (Q) and time (t) at 37°C (membrane thickness = 0.0254cm).

by using Eq. 6. The deviation of the apparent permeation rate from the intrinsic rate of permeation was found to be mostly significant for progesterone with a correction factor of 0.35 (Figure 6), while it became less significant for the hydroxyl derivatives of progesterone (Table 2), especially when two or more OH groups were added. The reason for this apparently lies in the fact that progesterone is a lipophilic molecule with high permeability across the hydrophobic silicone membrane, so its mass transfer process across the hydrodynamic diffusion layer on the membrane surface plays a significant rate-limiting role. By addition of OH groups, the progesterone molecule becomes more hydrophilic in nature, so the rate-

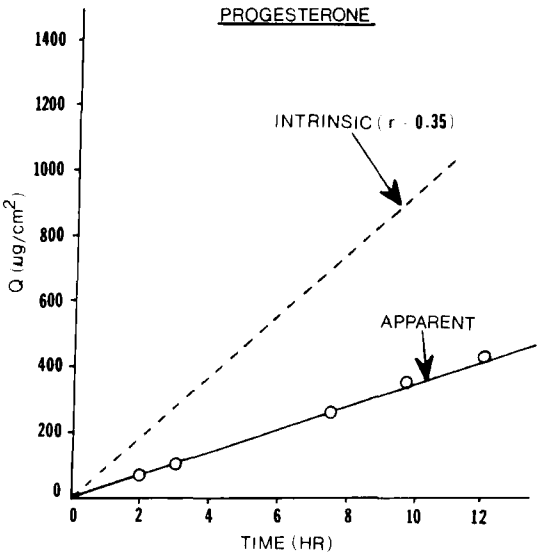


Figure 6: Linear relationship between the cumulative amount of progesterone permeating through polydimethylsiloxane membrane (Q) and time (t) at 37°C. It compares the intrinsic and apparent permeation profiles, which have a correction factor (γ) of 0.35.

limiting role of mass transfer process becomes smaller in the whole process of membrane permeation.

Effect of hydroxy groups

The data in Table 2 show that as more hydroxy groups are added to the progesterone molecule, the rate of permeation decreases. This reduction was observed to be a function of the number and the location of hydroxy groups. A hydroxy group at either the 11α- or 17α-position has the most drastic effect on the permeation rate of progesterone across silicone membrane. Addition of two hydroxy groups further reduced the rate of membrane permeation. When a third hydroxy group was added, the rate of permeation was decreased furthermore. This reduction in the rate of

TABLE 2: *Effect of hydroxy group on correlation between apparent and intrinsic rates of membrane permeation*

Progesterone Derivatives	RATE OF PERMEATION ($\mu g/cm^2/hr$)	
	Apparent	Intrinsic
I	33.70	96.3
II	18.07	19.1
III	1.66	1.68
IV	1.50	1.56
V	0.55	0.55
VI	0.47	0.47
VII	0.32	0.32

permeation can be explained by examining Eq. (11), which is integrated from Eq. (2) followed by substitution with $C_s K_1 = C_p$.

$$\left(\frac{Q}{t}\right)_{\infty} = \frac{C_p D_m}{\ell} \tag{11}$$

Equation 11 suggests that the reduction in $(Q/t)_{\infty}$ in response to the addition of hydroxy groups could be a result of the changes in polymer diffusivity (D_m) or polymer solubility (C_p). In theory, the addition of hydroxy groups increases the hydrophilicity and modifies the stereochemical configuration of progesterone. In the present study, the addition of hydroxy groups to progesterone is expected to decrease both D_m and C_p values, while the solubility in the aqueous PEG solution (C_s) will be increased. The increase in C_s and the decrease in C_p are apparently related to the increased hydrophilicity of progesterone molecule due to the addition of hydrophilic hydroxy groups.

The partition coefficient of most drugs can be predicted reasonably well by using the group contribution approach (21, 22). Theoretically, there should be a progressive increase in the partition coefficient toward aqueous solution in response to the addition of more hydroxy groups to the progesterone molecule. Since partitioning is a process involving molecular equilibrium at interface, a partition coefficient is, therefore, an equilibrium constant directly related to the standard free energy (ΔF_d) of desorption (15). K_{OBS} (partition coefficient of progesterone and its hydroxyl derivatives) is theoretically related to ΔF_d for a molecule as partitioning from the polymer phase into the aqueous elution solution:

$$\Delta F_d = -RT \ln K_{OBS} \tag{12}$$

It is assumed (15) that ΔF_d can be expressed additively in terms of the individual contributions of the nonpolar progesterone skeleton (ΔF_p) and the polar hydroxy group (ΔF_{OH}); then,

$$\Delta F_d = \Delta F_p + n\ (\Delta F_{OH}) \tag{13}$$

It is also known that:

$$\Delta F_p = - RT \ln K_p \tag{14}$$

where K_p is the (solution/polymer) partition coefficient for progesterone itself. Combining Equations (12) - (14) yields:

$$\log K_{OBS} = \log K_p - \frac{n\ (\Delta F_{OH})}{2{,}303\ RT} \tag{15}$$

Equation 15 suggests that K_{OBS} values are first order dependent upon the number of hydroxy groups (n) on the progesterone molecule. Figure 7 shows that this is the case.

K_{OBS} for monosubstituted hydroxy progesterone is also dependent on the substituent hydroxy group position (Table 3) from the following relationship:

$$\Delta F_{OH} = -2.303\ RT\ (\text{Log}\ K_{OBS} - \text{Log}\ K_p) \quad (16)$$

The ΔF_{OH} values for 21-OH, 17α-OH, and 11α-OH were estimated to be -1.362, -1.830, -2.993 Kcal/mole, respectively, at 37°C.

A linear relationship exists between the intrinsic rate of permeation and the polymer solubility of progesterone derivatives (Figure 8). This is consistent with the theoretical treatment in Equation 11.

Effect of silicone structure

The physical and mechanical properties of silocone polymers affect their permeability. The energy of activation of viscous flow, which is defined as the energy required to make a hole for the polymer segment,

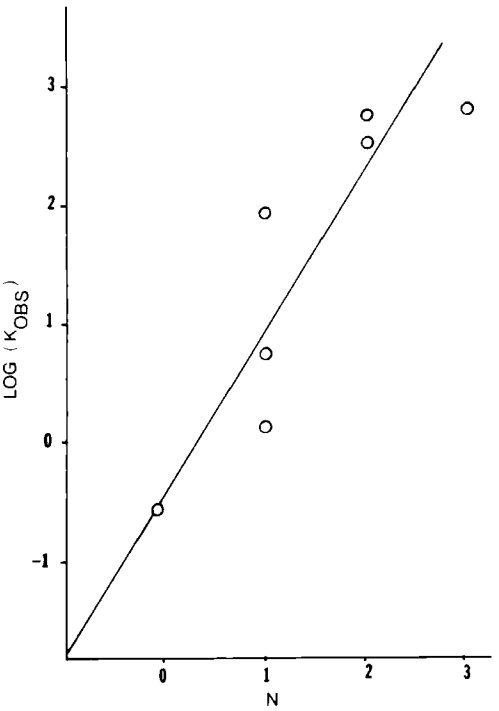


Figure 7: Dependence of Log K_{obs}, (solution/polymer) partition coefficient, on the number of hydroxy groups (N) on progesterone molecule.

TABLE 3: Effect of hydroxy group on solubility in 40% PEG 400 solution (C_s), solubility in silicone fluid (C_p), and solution/polymer partition coefficients (K_{OBS}) of progesterone

Progesterone Derivatives	N[2)]	SOLUBILITY[1)], (μg/ml ± SD) Cs	Cp	K_{OBS}
I	0	198 ± 16.8	606.9 ± 9.9	0.33
II	1	1192 ± 26.8	197.9 ± 12.5	6.02
III	1	813.2 ± 10.2	10.4 ± 0.74	78.19
IV	1	336.7 ± 5.4	29.7 ± 1.05	11.34
V	2	899 ± 45.1	1.63 ± 0.21	551.53
VI	2	460.4 ± 29.1	1.13 ± 0.12	407.43
VII	3	2271 ± 63.1	4.57 ± 0.25	496.94

(1) At 37°C

(2) Number of hydroxyl groups

varies from one type of silicone elastomer to another. It was found that as the alkyl chain increases in length, the energy values would increase (23). This means that as the pendant side group increases in size and/or polarity, the cohesive energy density increases. PDS and PTPM have different polarities: PTPM has a higher polar component arising from the very polar $CF_3CH_2CH_3$. This polarity makes it relatively more hydrophilic. Results indicated that the permeation of progesterone derivatives through PDS membrane is higher than through PTPM membrane (Table 4). The most significant effect was observed for progesterone since it is the most

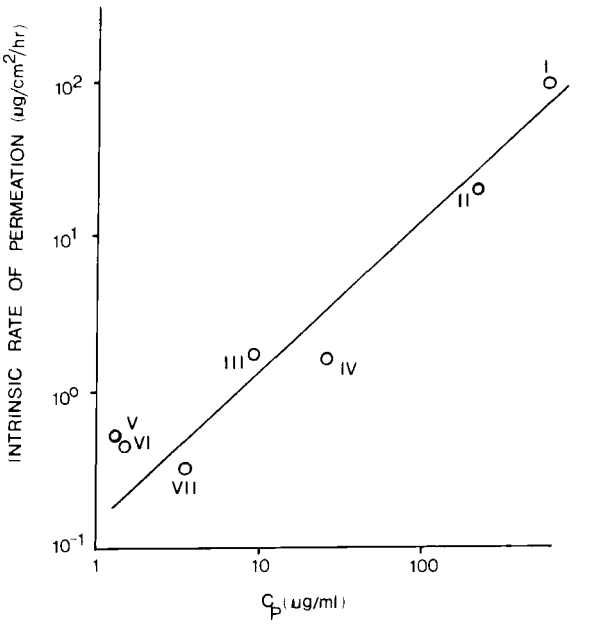


Figure 8: Dependence of intrinsic rate of permeation on the polymer solubility (C_p) of progesterone derivatives in the silicone fluid at 37°C.

TABLE 4 - Effect of polymer composition on normalized permeability*

Progesterone Derivatives	PDS (cm^2/hr)	PTPM (cm^2/hr)	Ratio
I	30.4×10^{-3}	2.57×10^{-3}	11.97
II	3.30×10^{-4}	1.99×10^{-4}	1.66
III	2.91×10^{-5}	2.60×10^{-5}	1.12
IV	6.97×10^{-5}	5.39×10^{-5}	1.29
V	9.15×10^{-6}	7.49×10^{-6}	1.22
VI	1.94×10^{-5}	1.53×10^{-5}	1.27
VII	2.64×10^{-6}	1.70×10^{-6}	1.55

*Permeabililty coefficient x membrane thickness

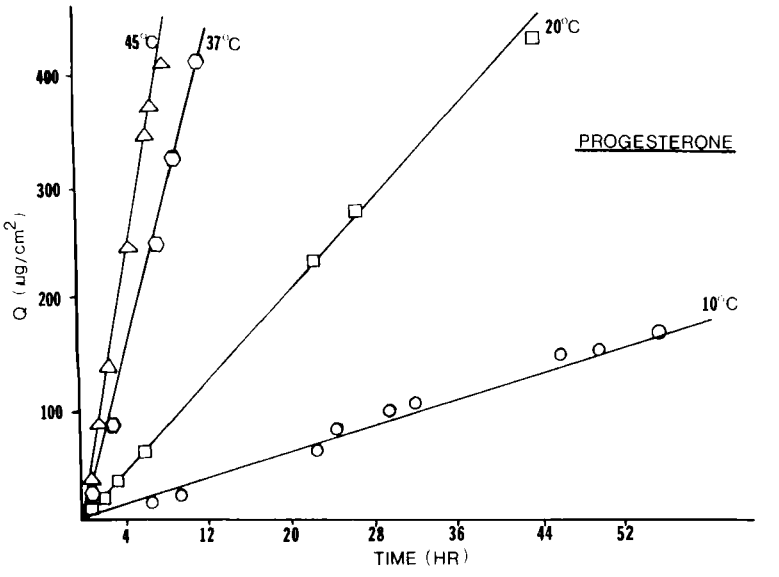


Figure 9: Effect of temperature on the permeation profiles of progesterone across polydimethylsiloxane membrane.

non-polar in this series of compounds investigated. The data in Table 4 also show that the effect of hydroxy group follows the same pattern in both types of membranes, i.e., the rate of permeation depends on the location of hydroxy group and decreases with the number of hydroxy groups.

Effect of temperature

The rate of permeation through membranes was observed to increase with temperature. The temperature dependence of Q/t values is, theoretically, linked to two energy-activated processes: solvation and diffusion of drug molecules and is defined by the following relationship (15):

$$\text{Log } (Q/t) = \text{constant} - \frac{E_h + \Delta H_{T,S}}{2.303R} \frac{1}{T} \qquad (17)$$

where E_h is the activation energy of diffusion and $\Delta H_{T,S}$ is the energy of solvation. Figure 9 shows that the rate of permeation increases with

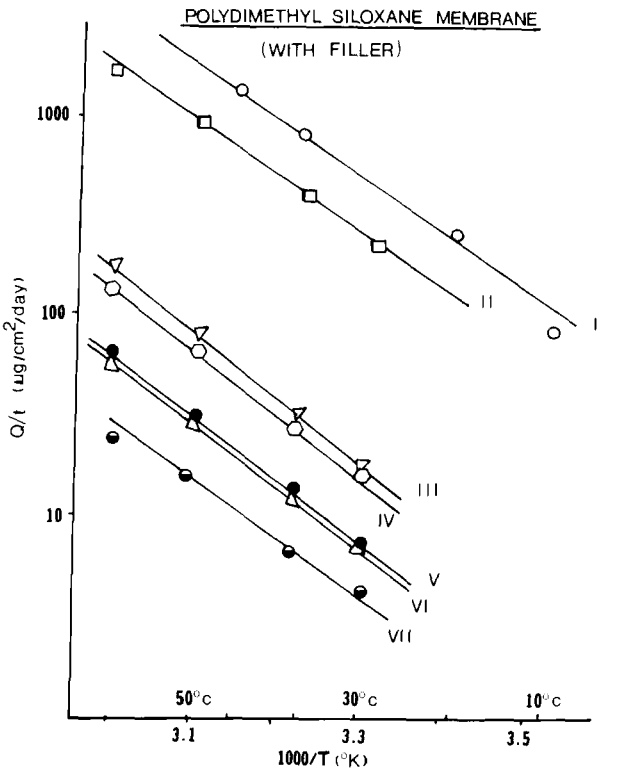


Figure 10: Linear relationship between the rate of permeation of progesterone derivatives (Q/t) across the polydimethylsiloxane membrane and the reciprocal of absolute temperature (1/T).

temperature and Figure 10 demonstrates that all the rate profiles follow the Arrhenius relationship. Results indicate that the energy requirements for various progesterone derivatives lie in the range of 12.5-15.7 Kcal (Table 5).

CONCLUSION

The apparent and intrinsic rates of permeation through polydimethylsiloxane and polytrifluoropropylmethylsiloxane for different progesterone derivatives was determined. It was found that the intrinsic rate of perme-

TABLE 5 - Energy required for the permeation of progesterone and its hydroxy-substituted derivatives through polydimethylsiloxane

Progesterone Derivative	$(E_H + H_{T,S})$ (Kcal/Mole)
I	14.43
II	12.94
III	15.72
IV	14.95
V	13.85
VI	14.40
VII	12.48

ation for progesterone was most significantly affected by the mass transfer process in the hydrodynamic diffusion layer and less significant in the hydroxyl derivatives. This can be explained by the fact that the rate-limiting steps for the intrinsic permeation are the rate of membrane permeation and aqueous solubility of the drug. Progesterone has the highest rate of permeation among the steroids studied and has the lowest aqueous solubility.

Hydroxylation was found to reduce the permeation of progesterone substantially. The magnitude of this reduction depended on the number and position of hydroxy groups and could be attributed to decreased polymer solubility and increased aqueous solubility.

Rates of permeation increase with temperature and follow the Arrhenius relationship. The overall energy requirements were found to be relatively constant and showed no dependence on the extent of hydroxylation.

Rates of permeation were found to be higher in polydimethylsiloxane than in trifluoropropylmethylsiloxane. The most significant effect was observed in progesterone. This can be attributed to a higher polarity of polytrifluoropropylmethylsiloxane.

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FOOTNOTES

1. Fisher Scientific, Fairlawn, New Jersey
2. Upjohn Co., Kalamazoo, Michigan
3. Dow Corning Corp., Midland, Michigan
4. Bellco Glass, Vineland, New Jersey
5. UV/VIS Spectrophotometer, Model 559A, Perkin Elmer Corp., Chicago, Illinois

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