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KINETICS AND THERMODYNAMICS OF DRUG PERMEATION THROUGH SILICONE ELASTOMERS III. EFFECT OF ALKYL SUBSTITUENT (R) IN $(MeRSiO)_x$ POLYMER

Chi-long Lee, Katherine L. Ulman and Kent R. Larson

Silicone Research Department
Dow Corning Corporation
Midland, Michigan 48686

ABSTRACT

The effect of silicone polymer structure on the permeability of drug through silicone membranes was investigated in the capsule-type drug delivery system. The permeability, diffusivity and solubility of progesterone and testosterone through polymethylalkylsiloxane membranes, $(MeC_nH_{2n+1}SiO)_x$, where n = 1, 2, 3, 6 and 8, were determined at 25, 37 and 50°C respectively.

As the size of the alkyl substituent was increased from methyl to octyl, the diffusivity decreased, whereas the solubility increased. As a result, the permeability of progesterone decreased initially but increased gradually thereafter, going from $(Me_2SiO)_x$ to $(MeOctSiO)_x$, in this series of polymer. The same results were obtained with testosterone; however, permeabilities of testosterone were found to be one order of magnitude lower than those of progesterone. This was attributed to the lower solubilities of testosterone in $(MeRSiO)_x$ polymers when compared to those for progesterone. The activation energies of permeation for

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progesterone in these polymers were found to be in the range of 13-15 Kcal/mol.

INTRODUCTION

Silicone polymers are known for their high permeability towards gases and drugs[1-14]. Permeability of progesterone through polydimethylsiloxane membranes, for example, is 2-3 orders of magnitude greater than that through several synthetic organic membranes[9]. This high permeability coupled with good biocompatability and physiological inertness[15,16] makes silicone polymers suitable for novel drug delivery applications.

The permeability of drugs through silicone polymers, like other physical properties, depends markedly on the structure of the polymer. In order to select a suitable silicone membrane to deliver a specific drug at a desired rate, it is necessary to know exactly how the structure of the silicone polymer affects the drug permeability. Similarly, for a given specific silicone membrane, the release rate of drug depends not only on the size and shape of the drug molecule, but also on the type, number and position of any functional group in the drug molecule. Quantitative information on the relationships between the structure of both silicone polymer and drug molecule on the drug permeability are therefore very useful in designing a device for the controlled release of bioactive material.

The objective of the work reported in this paper was to systematically investigate the effect of alkyl substituent in $(MeC_nH_{2n+1}SiO)_x$, where n is 1, 2, 3, 6, and 8, on the permeability of drug, using progesterone and testosterone as

model drug compounds. This work represents the first of a series of studies undertaken at Dow Corning Corporation aimed at establishing the relationships between silicone polymer structure and drug permeability. It is hoped that the results of such an effort will eventually lead to a mathematical model for predicting the delivery rate of any drug through any silicone membrane. Preliminary experimental results obtained to this date are reported in this paper.

EXPERIMENTAL

A. Materials

1. Progesterone, testosterone (both purchased from Sigma Chemical Co.), and polyethylene glycol, PEG 400 (purchased from Fisher Scientific), were used as received.

2. Silicone Polymers

Polydimethylsiloxane and polymethylethylsiloxane were prepared by the base catalyzed ring-opening polymerization of the respective cyclotetrasiloxane in the presence of an endblocker, $ViMe_2SiOSiMe_2Vi$, using potassium silanolate as a catalyst. After the polymer had been fully equilibrated, carbon dioxide was added and the polymer was fractionally precipitated to remove the low molecular weight linear and cyclic species. For $(MeRSiO)_x$, where R is propyl, hexyl and octyl, the polymer was made by ring-opening polymerization of the respective cyclotrisiloxane using lithium silanolate as a catalyst. Acetic acid was added to terminate the polymerization. Dimethylvinylchlorosilane was then added to convert the terminal hydroxyl group to a vinyldimethylsiloxyl group.

3. Membrane Fabrication

The polymers thus prepared were crosslinked with an organic peroxide to give the desired membranes. It was found

that if the membrane was flexible and too thin, it had a tendency to bow in the permeation cell, thus changing its surface area during the experiment. The data thus generated were found to be erratic. To avoid this problem, the thickness of the membrane was kept above 0.146 cm.

B. Drug Permeability Measurements

The drug permeability was investigated in a capsule-type drug delivery system using the apparatus developed by Ghannam-Chien[17,18]. The apparatus consisted of two concentric cells separated by a silicone membrane as shown in Figure 1. Experiments were carried out in 40/60 v/v PEG 400/water solution by the procedure described below.

After the membranes had been mounted into the apparatus, the receptor compartment was loaded with 170 ml of the 40% aqueous PEG solution. The system was then warmed to 37°C (to simulate body temperature) using the water jacket that completely surrounded the apparatus. The donor compartment was then loaded with a saturated drug solution which had been prepared by dissolving an excess amount of drug (progesterone or testosterone) in 40% aqueous PEG solution and stirred overnight at 37°C. Excess solid was suspended to assure that a constant drug concentration (i.e., saturated solution) would be maintained during the entire course of an experiment.

Exactly 10 ml of the solution were withdrawn from the receptor compartment at pre-determined time intervals followed by the addition of 10 ml of fresh 40% aqueous PEG solution to the receptor solution to maintain a constant volume in the receptor compartment. The concentration of the steroid in the samples from the receptor compartment was then analyzed with a Bausch & Lomb Spectronic® 2000 Spectrophotometer.

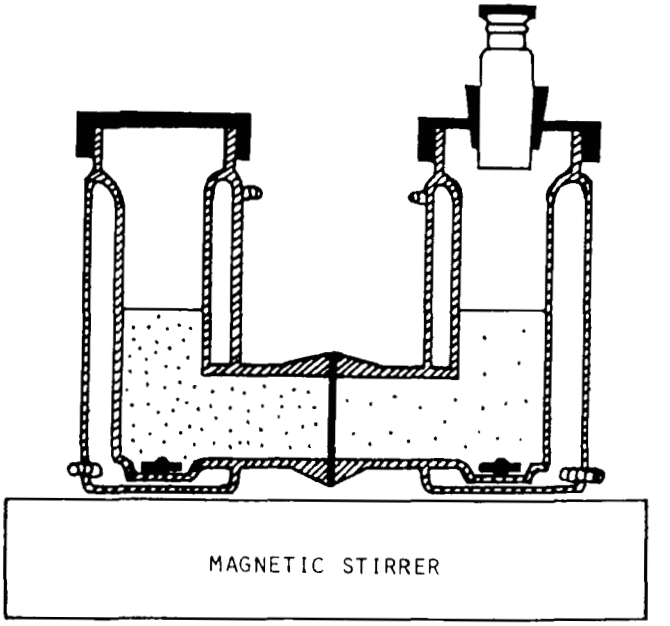

FIGURE 1

Ghannam-Chien membrane permeation apparatus.

Absorption peaks at 245.8 nm and 245.7 nm were used to determine the concentration of progesterone and testosterone, respectively.

C. Determination of the Intrinsic Rate of Permeation, $(dQ/dt)_\infty$

To determine the $(dQ/dt)_\infty$, the amount of drug permeated through the membrane (Q) was plotted against time, t, to give a straight line. The apparent rate of permeation, $(dQ/dt)_a$, was determined from the slope and $(dQ/dt)_\infty$ was calculated from the following equation[17,18]:

$$(dQ/dt)_\infty = (dQ/dt)_a/\gamma \quad (1)$$

where $\gamma = 1 - 2d\,(dQ/dt)_a/Sh_R D_R C_s$

D_R = diffusion coefficient of drug in the receptor phase (9.81×10^{-7} cm²/sec. for both progesterone and testosterone in 40/60 v/v PEG 400/water at 37°C)

C_s = concentration of saturated drug solution in the donor phase (204 µg/ml for progesterone and 432 µg/ml for testosterone at 37°C in 40/60 v/v PEG 400/water)

d = length of the magnetic stir bar (2.54 cm)

Sh_R = Sherwood number (379 at 425 r.p.m. stir rate in 40/60 v/v PEG 400 water at 37°C)

To correct for the difference in thickness from one membrane to another, the $(dQ/dt)_\infty$ thus obtained was multiplied by the membrane thickness, ℓ.

D. Determination of Diffusion Coefficient, D_p

Diffusion coefficients of the polymer, D_p, were determined by the following methods:

1. Capsule-Type Delivery System

In this delivery system, a plot of Q vs. t gave a straight line as described above. Extrapolating the line to the X-axis gave the time-lag, t_1. D_p was then calculated from the following equation[19]:

$$D_p = \ell^2/6t_1 \quad (2)$$

where ℓ is the membrane thickness

2. Matrix-Type Delivery System

A slab of silicone rubber (1.5 cm x 1.5 cm x .3 cm) was immersed in a saturated drug solution for 2 days at 37°C. The sample was then removed from the solution and wiped with a tissue paper to remove the excess fluid and drug. The sample was then immersed in a 40% aqueous PEG solution with constant stirring and the amount of drug released, Q, as a function of time, t, was determined spectrophotometrically as described in the previous section. D_p was calculated from the following equation[20]:

$$D_p = \left(\frac{Q/Q_\infty}{\sqrt{t}}\right)^2 \cdot \frac{\pi \ell^2}{16} \qquad (3)$$

where: Q = Amount of drug permeated/unit area of membrane at time, t

Q_∞ = Total amount of drug permeated/unit area of membrane

ℓ = membrane thickness

Equation (3) can be applied only when $0<Q/Q_\infty<0.6$.

E. Determination of Solubility

The solubility of progesterone and testosterone in 40% aqueous PEG was determined by equilibrating an excess amount of the steroid in a 40% aqueous PEG solution in the membrane permeation cell for 24 hours at 37°C under constant stirring. An aliquot of the solution was withdrawn, filtered and the drug concentration determined spectrophotometrically.

The solubility coefficient of polymer, C_p, was calculated from the following equation:

$$C_p = (dQ/dt)_\infty \cdot \ell / D_p \qquad (4)$$

F. Determination of Glass Transition Temperature

Glass transition temperatures (Tg) were determined using a DuPont® 910 Differential Scanning Calorimeter (DSC). Samples were rapidly cooled with liquid nitrogen and heated at a rate of 8.0°C/min. in a helium atmosphere.

G. Determination of Compressibility

The apparatus employed in this work consisted of a cylindrical precision bore cavity in a steel shell. The cavity was filled with the polymer, then entrapped air was removed by application of high vacuum and a precisely fitted ram-rod was inserted into the cavity. Force was applied to the ram-rod which compressed the polymer. The ram-rod movement was plotted as a function of applied pressure. Since the diameter of the cavity and the initial length of the cavity occupied by polymer were known, the volumetric change of the polymer was determined from the ram-rod movement. The compressibility was calculated by the equation $\beta=(\Delta V/V)/p$ where p was the applied pressure and V was the volume. There were two limitations to this method. First, the polymer must be of sufficiently low molecular weight so that it flows under its own weight in order to fill the cavity, requiring each polymer to be prepared exclusively for compressibility testing. Second, since compressibility was not a linear function of pressure, the values had to be averaged over the experimental pressure range. In order to obtain meaningful data, the experiment had to be carried out to at least a pressure of 1,500 psi.

RESULTS AND DISCUSSION

A. Progesterone

Plots of the amount of progesterone permeated through polymethylalkylsiloxane membrane, Q, vs. time, t, gave

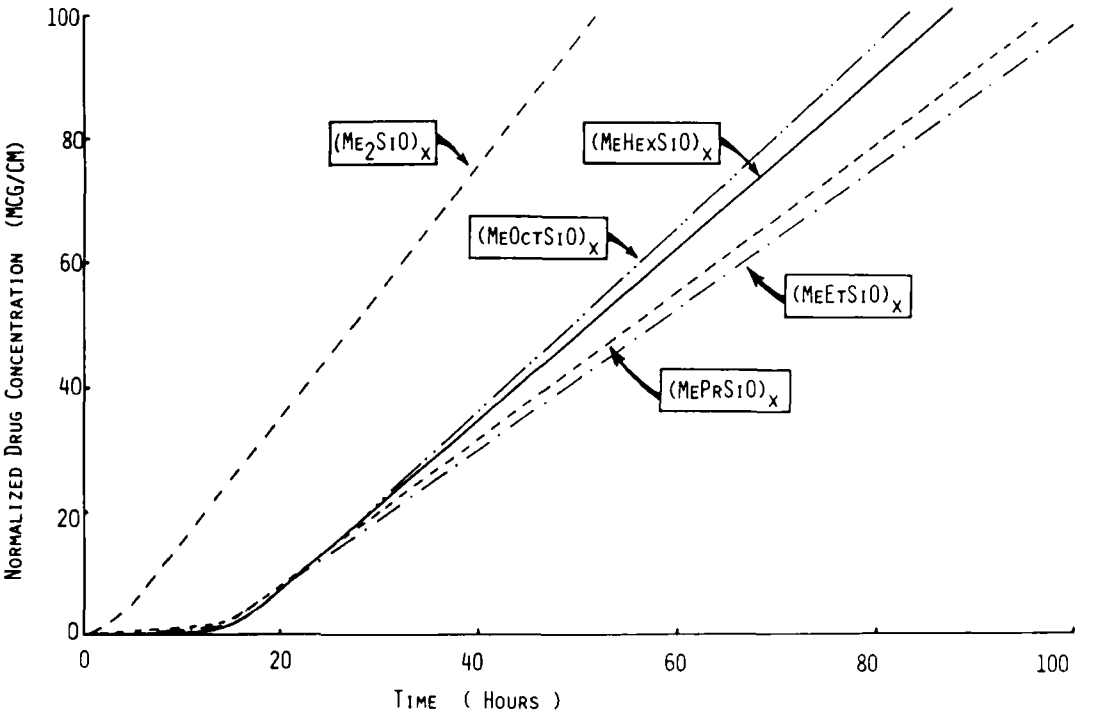

FIGURE 2

Progesterone flux rate at 37°C.

straight lines indicating that Fickian diffusion was followed. These are shown in Figure 2. From the slope of the line the apparent rate of permeation, $(dQ/dt)_a$, was calculated. The intrinsic rate of permeation was then calculated from equation (1). Normalized values of the intrinsic rate of permeation, $(dQ/dt)_\infty \cdot \ell$, are listed in the first column of Table 1.

The polymer diffusion coefficients, D_p, were calculated from time-lag, t_l, using equation (2). The D_p was also determined independently using the matrix-type delivery system and equation (3). Reasonable agreement between the two methods was obtained. Average values of D_p, obtained by these

TABLE 1

Rate of Permeation, Diffusion Coefficient, Solubility Coefficient and Partition Coefficient of Progesterone Through $(MeRSiO)_x$ Membranes at 37°C

$(MeRSiO)_x$	$(dQ/dt)_\infty \cdot \ell$ (X 10^4) (mcg/cm-s)	D_p (X 10^7) (cm^2/s)	C_p (mcg/cm^3)	K*
R = Me	5.67	9.03	628	.325
Et	3.34	3.23	1034	.197
Pr	3.37	3.35	1006	.203
Hex	4.20	3.09	1359	.150
Oct	4.23	2.43	1741	.117

*$K = C_s/C_p$, C_s = 204 mcg/cm^3

two methods, are listed in Table 1 and were used to calculate the solubility coefficients, C_p. Results are summarized in Table 1.

The data show that polydimethylsiloxane gave the highest rate of permeation for progesterone. As the size of the alkyl group was increased from methyl to ethyl, the rate of permeation decreased significantly. As the size of alkyl group was increased further from ethyl to octyl, however, the rate of permeation increased gradually. This trend was attributed to the change in the diffusion coefficients (D_p) and solubility coefficients (C_p). That is, as the size of the

alkyl group was increased from methyl to octyl, D_p decreased, whereas C_p increased. As a result, the permeability of progesterone decreased initially but increased gradually thereafter, going from $(Me_2SiO)_x$ to $(MeOctSiO)_x$.

The increase in C_p as a function of the number of carbons in the alkyl group was found to be linear as shown in Figure 3. Thus C_p was expressed by:

$$C_{p,n} = C_{p,o} + An$$

where $C_{p,n}$ was the solubility coefficient of progesterone in the nth congener of polymethylalkylsiloxane, $C_{p,o}$ was the solubility coefficient of progesterone in the hypothetical zero chain length and 'A' was the constant whose magnitude was dependent upon the type of drug molecule. The empirical equation for progesterone in $(MeC_nH_{2n+1}SiO)_x$ derived from Figure 3 is shown below:

$$C_{p,n} = 460 + 128n$$

Similar effects of alkyl chain length on the solubility of penetrant, with the alkyl groups in an aqeuous solution, C_s, has been reported for p-aminobenzoate esters[21,22] and testosterone esters[23].

B. Testosterone

The intrinsic rates of permeation, $(dQ/dt)_\infty \cdot \ell$, diffusion coefficients, D_p, and polymer solubilities, C_p, obtained for testosterone at 37°C are summarized in Table 2. Permeabilities of testosterone through polymethylalkylsiloxane membranes were found to be about one order of magnitude lower

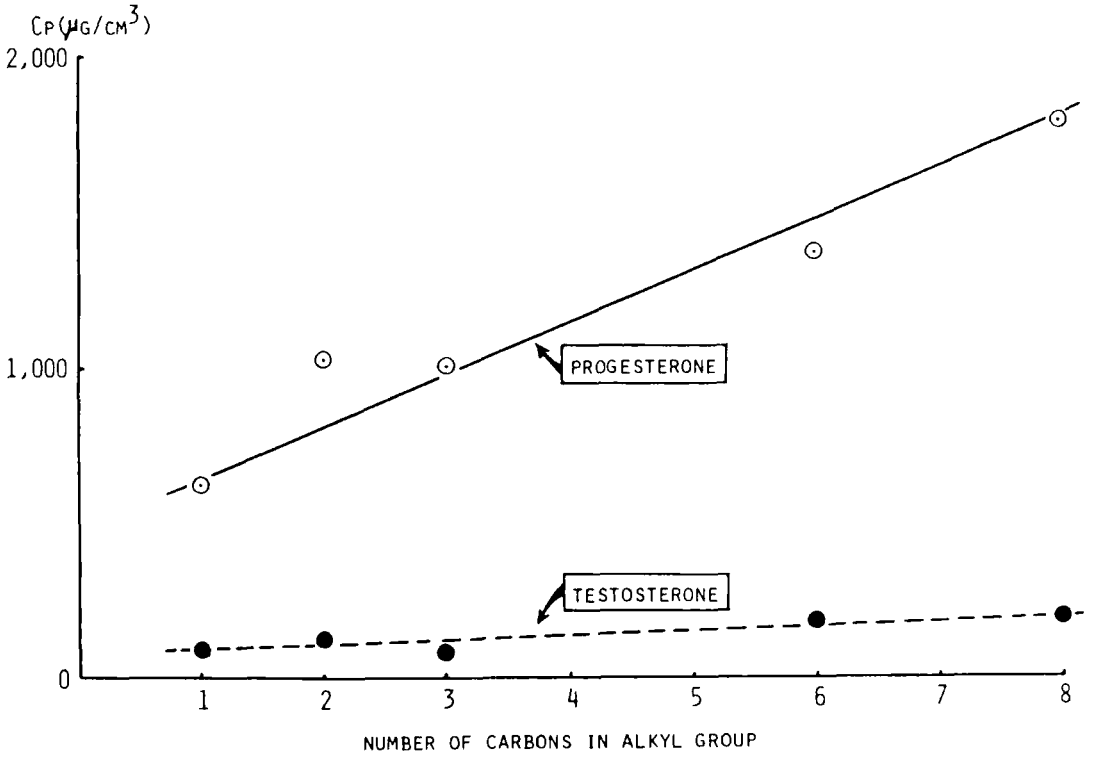

FIGURE 3

Effect of number of carbons in R group of $(MeRSiO)_x$ on C_p

than those of progesterone. This was attributed to the lower C_p values for testosterone compared to those of progesterone. Replacement of the acyl group at C-17 in progesterone by the hydroxyl group in testosterone produced a marginal change in D_p but a very significant decrease in C_p values and increase in C_s values, resulting in an almost 20 fold increase in the partition coefficients, defined here as $K = C_s/C_p$.

The effect of the alkyl group substituent on $(dQ/dt)_\infty \cdot \ell$, D_p and C_p of testosterone appears to follow the same pattern as was observed with progesterone. A plot of C_p vs. number of

TABLE 2

Rate of Permeation, Diffusion Coefficient, Solubility Coefficient and Partition Coefficient of Testosterone Through $(MeRSiO)_x$ Membranes at 37°C

$(MeRSiO)_x$	$(dQ/dt)_\infty \cdot \ell$ $(X\ 10^5)$ (mcg/cm-s)	D_p $(X\ 10^7)$ (cm^2/s)	C_p (mcg/cm^3)	K*
R = Me	5.55	6.55	85	5.08
Et	2.19	1.81	129	3.35
Pr	2.64	3.26	81	5.33
Hex	3.62	2.84	181	2.39
Oct	4.22	2.22	191	2.26

*$K = C_s/C_p$, C_s = 432 mcg/cm^3

carbons in alkyl group, n, is shown in Figure 3. The empirical $C_{p,n}$ as a function of n was found to be:

$$C_{p,n} = 80 + 15n$$

C. Effect of R on D_p

An attempt was made to interpret the dependence of D_p on the size of R group in terms of the free volume model. According to this model, the process of diffusion was assumed to proceed by the movement of molecules into a void which was formed by redistribution of free volume[24]. The diffusion

coefficient was expressed in terms of the fractional free volume, V_f, as follows[25]

$$D_p = RT\, A_d \exp(-B_d/V_f) \quad (5)$$

where R is the gas constant, T is the absolute temperature, and A_d and B_d are characteristic parameters. The fractional free volume depends on the temperature, the hydrostatic pressure and the penetrant concentration. At a reference temperature T_s and pressure P_s, V_f was represented by the following equation[26,27]:

$$V_f(T,P,V) = V_{fs}(T_s, P_s, 0) + \alpha(T-T_s) - \beta(P-P_s) + \gamma V \quad (6)$$

where $V_{fs}(T_s, P_s, 0)$ was the fractional free volume of pure polymer at T_s and P_s, α was the thermal expansion coefficient, β was the compressibility, and γ was the concentration coefficient. By choosing the reference state at the glass transition temperature, T_g, of the polymer and at 1 atm. pressure, equation (6) was rewritten as:

$$V_f(T.P.V) = V_f^*(T) - \beta P + \gamma V \quad (7)$$

where $V_f^* = V_{fs}(T_g, 1\text{ atm.}, 0) + \alpha(T-T_g) + \beta(1\text{ atm.})$, which is the fractional free volume of pure polymer. The choice of Tg as a reference state was consistent with the argument of Fox and Flory[28] that the glass was an iso-free volume state, i.e., $V_{fs}(Tg, 1\text{ atm. } 0) = 0.025$[29].

Equation (7) suggests that the polymer with a lower T_g should have a higher free volume and hence a higher D_p at room temperature. In the case of $(MeRSiO)_x$, as the size of R group was increased, T_g was expected to increase, thus decreasing D_p accordingly. To test this model, the relationship between T_g and D_p was examined. This is shown in Table 3. The T_g of

TABLE 3

Glass Transition Temperatures and Diffusion Coefficients of Progesterone Through $(MeRSiO)_x$ Membranes at 37°C

$(MeRSiO)_x$		Tg (°C)	D_p (X 10^7) (cm^2/s)
R =	Me	-123	9.03
	Et	-135	3.23
	Pr	-120	3.35
	Hex	-108	3.09
	Oct	- 92	2.43

$(MeEtSiO)_x$ is lower than that of $(Me_2SiO)_x$, yet $(MeEtSiO)_x$ had a lower D_p than $(Me_2SiO)_x$, indicating a poor fit for the $(MeEtSiO)_x$ in this system. To shed more light on this problem, the compressibility of $(MeRSiO)_x$ was examined. It was found that the compressibility of $(MeRSiO)_x$ decreased with an increase in the size of R group. A plot of D_p vs. compressibility gave reasonably good correlation as shown in Figure 4. Since the compressibility of polymer is related to the free volume, the free volume model might be applicable in this case. More work is planned in this area.

D. Effect of Temperature

The rate of permeation of progesterone through the $(MeRSiO)_x$ was found to increase with temperature. A plot of $(dQ/dt)_\infty \cdot \ell$ vs. 1/T gave a straight line from which the activation energy was determined. Results are shown in Table 4. As the size of R group was increased, the activation

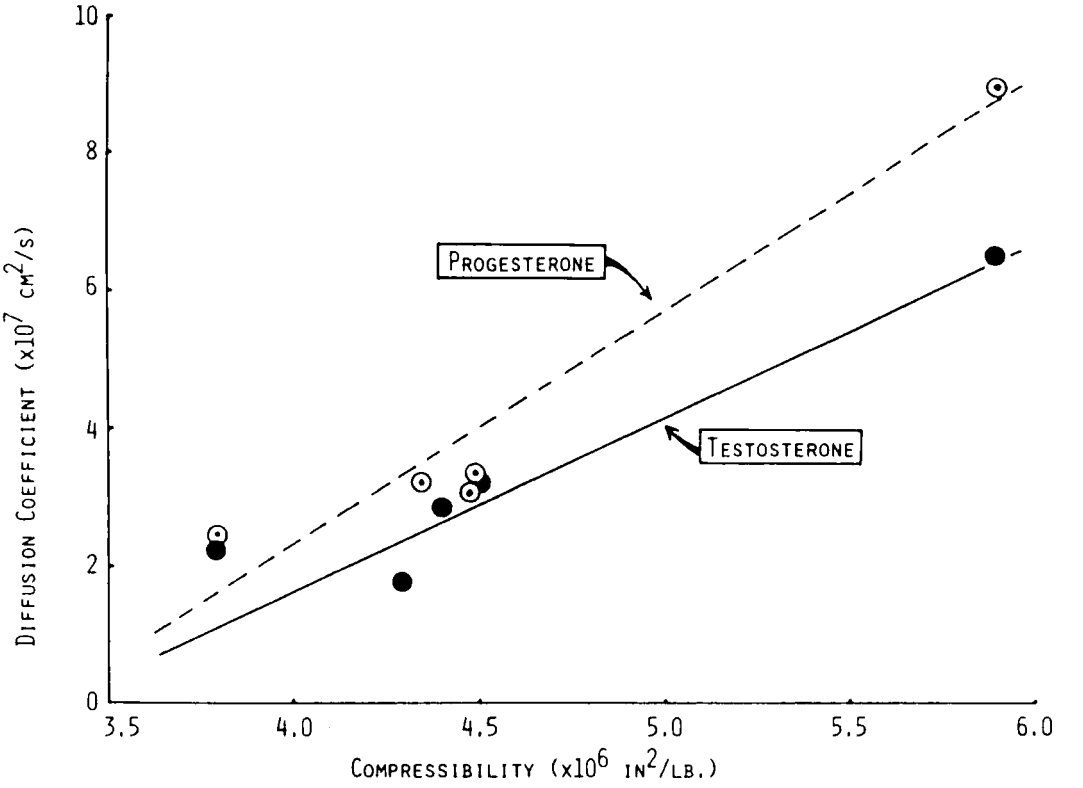

FIGURE 4

Diffusion coefficients vs. polymer compressibility.

energies increased as expected, except for polymethylethylsiloxane. The activation energies of permeation for progesterone through $(MeRSiO)_x$ membranes were found to be about 13-15 kcal/mole.

E. Future Work

The crosslink densities of the elastomeric membranes employed in this work have not yet been determined. Since the rate of permeation was expected to decrease with an increase

TABLE 4

Activation Energy for Progesterone Transport through $(MeRSiO)_x$

$(MeRSiO)_x$	Activation Energy (Kcal/mol)
R = Me	13.4
Et	12.5
Pr	14.7
Hex	15.6
Oct	15.8

in the crosslink density, the effect of crosslink density on $(dQ/dt)_\infty \cdot \ell$ will be studied quantitatively. The three key parameters, $(dQ/dt)_\infty \cdot \ell$, D_p and C_p will be generated using the same crosslink densities and the effect of the size of R group on the permeability will be analyzed based on both the free volume model and the molecular model[30].

CONCLUSIONS

The effect of alkyl substituent (R) in $(MeRSiO)_x$ polymers on the rate of permeation of progesterone and testosterone was investigated. It was found that polydimethylsiloxane membrane gave the highest rate of permeation for both progesterone and testosterone. As the size of the alkyl substituent was increased from methyl to ethyl, the rate of permeation decreased significantly, followed by a gradual increase in the rate of permeation as the size of the alkyl group was further

increased from ethyl to octyl. This was explained in terms of diffusivity and solubility. That is, as the size of the alkyl group was increased from methyl to octyl, the diffusivities decreased, whereas the solubilities increased. As a result, the permeabilities of progesterone decreased initially but increased gradually thereafter, going from $(Me_2SiO)_x$ to $(MeOctSiO)_x$.

An attempt was made to interpret the dependence of D_p on the size of R group in terms of the free volume model. A plot of D_p vs. polymer compressibility gave good correlation indicating that the free volume model might be applicable in this system.

Permeabilities of testosterone were found to be one order of magnitude lower than those of progesterone. This was attributed to the lower solubilities of testosterone in $(MeRSiO)_x$ polymers when compared to those for progesterone. The effect of alkyl group on the permeabilities of testosterone follows the same pattern as that observed with progesterone.

The activation energies of permeation for progesterone through $(MeRSiO)_x$ membranes were found to be in the range of 13-15 kcal/mol.

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