Release of Steroids from a Silicone Polymer

T. J. ROSEMAN

Abstract □ The *in vitro* release of four progesterone-type steroids from a silicone polymer was studied. The amount of drug released from this matrix system was found to be dependent upon the molecular structure of the steroid. Progesterone, for example, was released approximately eight times faster than 17α-hydroxyprogesterone under identical experimental conditions. Since the diffusion coefficients of the steroids were of the same magnitude, the diversity in release patterns was mainly attributed to the differences in the polymer solubilities of the steroid. Data are presented showing that the partition coefficient (polymer/water) and polymer solubility of the drug are sensitive functions of the structure of the steroids and account for the experimental findings. Application of equations previously derived for the matrix-boundary diffusion layer model resulted in good agreement with the experimental findings for the four steroids. As predicted, the Q' (amount released) *versus* $t^{1/2}$ (time$^{1/2}$) plots were not linear in the early time periods. The presence of filler particles within the polymer caused: (*a*) determined diffusion coefficients to decrease by an average value of 25%, (*b*) an increase in experimentally determined partition coefficients, and (*c*) a slight reduction in the amount released *versus* time plot for medroxyprogesterone acetate.

Keyphrases □ Silicone polymer—release of steroids, matrix-boundary diffusion layer model equations, effect of filler □ Steroids—factors affecting release from silicone polymer, effects of steroid structure □ Progesterone-type steroids—*in vitro* release from silicone polymer □ Drug delivery systems—release of progesterone-type steroids from silicone polymer, equations

The usefulness of a silicone polymer as a drug delivery system for medroxyprogesterone acetate[1] was previously described (1, 2). Implantation of the polymer into the body with the subsequent release of drug was shown to be an effective method of inhibiting ovulation. An in-depth study (3) was presented which described the *in vitro* release of medroxyprogesterone acetate from the polymer. The dependence of the release rate upon concentration of drug within the polymer and external stirring conditions was demonstrated. Based upon a physical model, equations were derived to explain these results and also to include other parameters such as the polymer/water partition coefficient and diffusion coefficients (aqueous and polymer) which can influence the release rate. Although it has been shown that different steroids diffuse at substantially different rates across silicone membranes (4), a quantitative study on the release of steroids embedded in a silicone matrix has not been presented. Therefore, this study was designed to demonstrate the applicability of the previous model to other steroids. Specific consideration is given to the contribution of the polymer/water partition coefficient, drug solubility in the polymer, and diffusion coefficients to the release process. The effect of filler particles (within the polymer) on the determined diffusion coefficient, partition coefficients, and drug release process is also discussed.

[1] Provera, The Upjohn Co.

EXPERIMENTAL

Determination of Amount of Drug Released—Annual cylinders (6.4 × 0.65 cm.) were prepared by levigating the required amount of drug[2] into the silicone polymer[3] and polymerizing with catalyst. The mixture was then placed into the appropriately sized molds and allowed to cure. Four rings were then mounted with stainless steel pins in the *in vitro* dissolution apparatus described previously (3). The effluent was collected at various time intervals and extracted with chloroform. The chloroform was evaporated to dryness under vacuum, and 10 ml. of isonicotinic acid hydrazide reagent, prepared according to the USP procedure (5) for medroxyprogesterone acetate, was added. After 1 hr., the absorbance was read at 380 nm. using a spectrophotometer[4]. The amount of drug present was determined from a calibration curve prepared with known amounts of drug.

Determination of Partition Coefficients—Tritium-labeled progesterone-7-^{3}H and 17α-hydroxyprogesterone-1,2-^{3}H were obtained commercially[5] and diluted with cold steroid to yield a specific activity of ~167 μc./mg. Medroxyprogesterone acetate had a specific activity of ~75 μc./mg.[6]. Saturated solutions of the steroid were prepared by equilibrating excess drug in water at 37°. The excess drug was then removed by filtering through a 0.22-μ millipore filter[7].

The partition coefficients of progesterone, 17α-hydroxyprogesterone, and medroxyprogesterone acetate were determined by equilibrating four flat sheets (about 7 × 2 × 0.05 cm.) of the silicone material in the filtered saturated solution (140 ml.) of labeled steroid at 37°. The sheets were removed after 1 day. This time was adequate to ensure that equilibrium had resulted. They were then extracted with methylene chloride and the solvent evaporated to dryness under nitrogen. After the addition of 15 ml. of a scintillation counting solvent[8], the samples were counted in a liquid scintillation spectrometer[9]. The partition coefficient (K) was calculated by: (*a*) dividing the counts per unit volume in the silicone sheet by the counts per unit volume in the equilibrated solution or (*b*) using the following expression:

$$K = \frac{V_1(C_i - C_e)}{V_2 C_e} \qquad \text{(Eq. 1)}$$

where:

V_1 = volume of solution
V_2 = volume of silicone sheets
C_i = initial concentration (or counts/ml.) of solution
C_e = equilibrium concentration (or counts/ml.) of solution

The partition coefficient of 6α-methyl-11β-hydroxyprogesterone was determined with unlabeled drug. In this case, C_i and C_e were determined chemically by the USP procedure described earlier, and Method (*b*) was used to determine K. In general, the two methods of calculation gave comparable results. However, since Method (*b*) is subject to errors associated with small differences of numbers, Method (*a*) is preferred. Average values of multiple experiments are reported.

Determination of Diffusion Coefficients—The diffusion coefficients of progesterone, 17α-hydroxyprogesterone, and medroxyprogesterone acetate were determined at 37° using a previously designed

[2] The steroids were obtained from The Upjohn Co. and were 97.2–100% pure.
[3] Silastic elastomer, Dow Corning Corp., Midland, Mich.
[4] Cary 11, Applied Physics Corp., Monrovia, Calif.
[5] New England Nuclear Corp., Boston, Mass.
[6] Courtesy of Dr. R. C. Thomas, Physical and Analytical Chemistry Unit, The Upjohn Co.
[7] Millipore Filter Corp., Bedford, Mass.
[8] 1000 ml. BNA Toluene (Allied Chemical), 42 ml. Liquoflor (New England Nuclear), and 100 ml. Biosolv (Beckman).
[9] Packard Tri Carb, Packard Instrument Co.

diffusion cell (6) with no screen and a 60-r.p.m. stirring motor. A silicone membrane (fillerless[10] or filled), having an exposed area of 10 cm.^{2} and a known thickness of approximately 0.051 cm., was placed in the center of the cell. At zero time, a saturated solution containing excess solid drug was placed in the donor reservoir while the receptor side contained distilled water. At various times, samples were withdrawn from the receptor side by completely flushing out its contents with water at 37°. Fresh water was immediately added. The amount of progesterone diffused across the membrane was determined by the previously stated assay method for the steroids. The diffusion coefficient (D_s) was calculated by the lag time method (7), *i.e.*, $D_s = X^2/6L$, where X is the thickness of the membrane and L is the lag time. The lag time was determined by the extrapolation of the steady-state portion of the curve to the x-axis. The diffusion coefficients of 17α-hydroxyprogesterone and medroxyprogesterone acetate were determined in a similar manner, except labeled steroid was used. The specific activities of the two steroids were ~200 and ~75 μc./mg., respectively. After samples were withdrawn, they were extracted with methylene chloride and evaporated to dryness under vacuum at 45°. After the addition of 15 ml. of counting solution, the samples were counted in the liquid scintillation spectrometer. The lag time was calculated from a plot of counts per minute *versus* time. In all runs, the concentration on the receptor side was <10% of saturation.

The membranes were prepared by polymerizing the fillerless or filled silicone material between two Plexiglas plates separated by 0.051-cm. spacers. Circular membranes of the desired diameter were then formed by applying pressure to a metal punch which rested on the membrane.

Determination of Water and Polymer Solubilities—The water solubilities (C_a) of the various steroids were determined by end-over-end rotation of 20-ml. ampuls containing an excess amount of material in 15 ml. of water at 37°. At equilibrium (24 hr. was determined to be adequate), samples were withdrawn and rapidly filtered through preheated syringes equipped with a millipore filter holder containing a 0.22-μ millipore filter. Ten milliliters of sample was extracted with chloroform and assayed. Runs were carried out in quadruplicate and averaged.

The solubility (C_s) of the various steroids in the polymer was calculated from the following relationship:

$$C_s = KC_a \qquad \text{(Eq. 2)}$$

where C_a is the water solubility.

THEORETICAL

The general model (matrix-boundary diffusion layer) describing the release of drug embedded in a matrix was presented previously for the case where diffusion occurs through the matrix phase (3). The assumptions in the derivation and derived equations were given in total. It was shown that under certain conditions the matrix-boundary diffusion layer model reduced to a matrix-controlled process which was presented earlier by Higuchi (8). The final equations are summarized here, and a comparison of the two geometrical cases of interest is presented.

Planar Case—

$$Q = Al \qquad \text{(Eq. 3)}$$

$$l^2 + \frac{2D_eh_aKl}{D_a} = \frac{2D_eC_st}{A} \qquad \text{(Eq. 4)}$$

where:

Q = amount released per unit area (mg./cm.^{2})
A = concentration of drug in matrix (mg./cm.^{3})
l = diffusional distance in polymer or zone of depletion (cm.)
D_a = diffusion coefficient in aqueous phase (cm.^{2}/sec.)
h_a = boundary diffusion layer (cm.)
K = partition coefficient (C_s/C_a)[11]
C_a = aqueous solubility (mg./cm.^{3})
C_s = solubility in matrix phase (mg./cm.^{3})
t = time (sec.)

[10] Gift from Dow Corning Corp., Midland, Mich.

[11] Note that K has been redefined to be C_s/C_a in contrast to the previous work (3) where $K = C_a/C_s$. Therefore, in Eqs. 4 and 7, K now appears in the numerator.

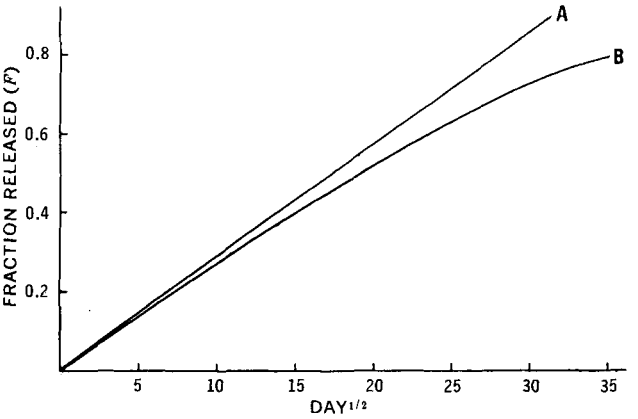

Figure 1—*Fraction of drug released as a function of the square root of time for the planar case (Curve A) and the cylindrical case (Curve B).*

and $D_e = D_s\epsilon/\tau$ where D_e is the effective diffusion coefficient in the matrix phase, and ϵ and τ are the volume fraction and tortuosity in the matrix phase, respectively.

Equations 3 and 4 define the Q *versus* t plots for the matrix-boundary diffusion layer model. When $l \gg 2D_eh_aK/D_a$, Eqs. 3 and 4 reduce to the matrix-controlled case, *i.e.*:

$$Q = (2AD_eC_st)^{1/2} \qquad \text{(Eq. 5)}$$

Cylindrical Case—

$$Q' = \pi hA(a_0^2 - a'^2) \qquad \text{(Eq. 6)}$$

$$\frac{a'^2}{2}\ln\frac{a'}{a_0} + {}^1/_4(a_0^2 - a'^2) + \frac{D_eh_aK}{2D_aa_0}(a_0^2 - a'^2) = \frac{C_sD_et}{A} \qquad \text{(Eq. 7)}$$

where:

Q' = amount released (mg.)
h = height of cylinder (cm.)
a_0 = radius of cylinder (cm.)
a' = distance from center of cylinder to receding drug boundary (cm.)

All other parameters were defined previously[12]. Equations 6 and 7 define the Q' *versus* t plots.

For the matrix-controlled case, Eq. 7 reduces to:

$$\frac{a'^2}{2}\ln\frac{a'}{a_0} + {}^1/_4(a_0^2 - a'^2) = \frac{C_sD_et}{A} \qquad \text{(Eq. 8)}$$

In this instance, Eqs. 6 and 8 define the Q' *versus* t plots.

Cylindrical *versus* Planar Geometry—When $A \gg C_s$, the fraction of drug released (F) from a cylinder is:

$$F = \frac{a_0^2 - a'^2}{a_0^2} \qquad \text{(Eq. 9)}$$

Division of Eq. 8 by a_0^2 and appropriate substitution of Eq. 9 yield:

$$\left[{}^1/_4F + \frac{1 - F}{4}\ln(1 - F)\right]^{1/2} = kt^{1/2} \qquad \text{(Eq. 10)}$$

where:

$$k = \left(\frac{C_sD_e}{A}\right)^{1/2}a_0 \qquad \text{(Eq. 11)}$$

The following equation results for the planar case, assuming an area of $2\pi a_0h$ and a volume of πa_0^2h:

$$F = 2\sqrt{2}\,kt^{1/2} \qquad \text{(Eq. 12)}$$

Figure 1 shows a plot of F *versus* $t^{1/2}$ for both equations where k was arbitrarily set equal to 1 (day$^{-1/2}$). It is apparent that the cylin-

[12] Note that $l = a_0 - a'$.

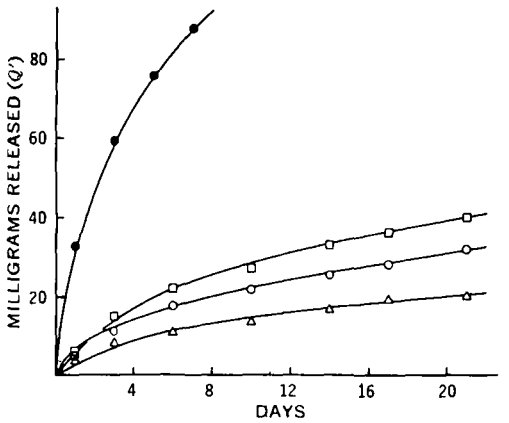

Figure 2—*Amount of steroid released from silicone cylinders as a function of time. Key: ●, progesterone; □, medroxyprogesterone acetate; ○, 6α-methyl-11β-hydroxyprogesterone; and △, 17α-hydroxyprogesterone.*

der is a good approximation (*i.e.*, a 10% or less deviation is noted) for the plane up to 50% drug release[13]. Due to the constancy of area, the planar case represents a simpler model. However, the cylindrical case is important because it is currently the most widely used form for implantation within the body. It follows, then, that when less than 50% of drug is released, a nonlinear region (parabolic displacement to longer times) in the beginning of a Q *versus* $t^{1/2}$ plot indicates that the matrix-boundary diffusion model is operative for either planar or cylindrical geometry.

RESULTS AND DISCUSSION

Drug-Release Mechanism—Figure 2 shows the amount of steroid released from the polymer as a function of time for four progesterone-type steroids. Although the general shapes of the curves are similar, substantial differences in the amounts released at any given time are noted. Progesterone, for instance, was released approximately eight times faster than 17α-hydroxyprogesterone under identical experimental conditions. The specific order of release was: progesterone > medroxyprogesterone acetate > 6α-methyl-11β-hydroxyprogesterone > 17α-hydroxyprogesterone.

Figure 3 shows the amount released (Q') *versus* $t^{1/2}$ plots. In all cases, the graphs do not show a linear relationship during early times. The exact duration of nonlinearity was dependent upon the particular steroid. Because progesterone was released rapidly, the nonlinear region is not as apparent as with the other three steroids. The release of medroxyprogesterone acetate was described previously by Eqs. 6 and 7 (3). Depending upon the magnitude of the various constants, these equations do predict the presence of a nonlinear region. Hence, it is reasonable to assume that the matrix-boundary diffusion layer model represented by these equations is applicable to the other steroids studied.

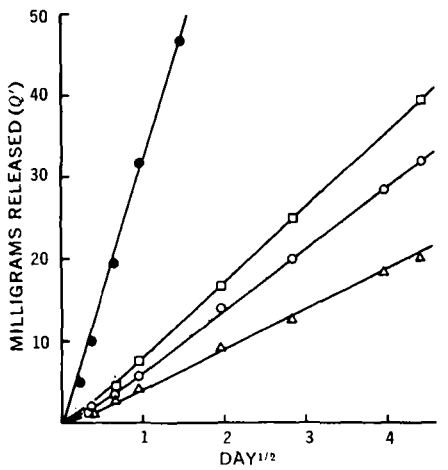

Figure 3—*Amount of steroid released from silicone cylinders as a function of the square root of time. Key: ●, progesterone; □, medroxyprogesterone acetate; ○, 6α-methyl-11β-hydroxyprogesterone; and △, 17α-hydroxyprogesterone.*

[13] A similar relationship was shown for the plane and sphere (8).

Table I—Solubilities (Milligrams per Milliliter) of the Steroids in Water, in Filled and Fillerless Polymer, and the Respective Partition Coefficients

Steroid	Filled Polymer		Fillerless Polymer		
	C_{sf}	K_f[a]	C_a	C_s	K[b]
Progesterone	0.572	50.2	0.0114	0.513	45.0
6α-Methyl-17-acetoxyprogesterone[c]	0.0985	30.3	0.00325	0.0874	26.9
6α-Methyl-11β-hydroxyprogesterone	0.0531	3.20	0.0166	—[d]	—[d]
17α-Hydroxyprogesterone	0.0178	2.18	0.0081	0.0072	0.89

[a] $K_f = C_{sf}/C_a$; K_f is the partition coefficient, and C_{sf} is the solubility of drug determined in filled polymer. [b] $K = C_s/C_a$. [c] Medroxyprogesterone acetate. [d] Chemical assay was not sensitive enough to determine K.

For the given drug–polymer system, the following parameters can be readily controlled: A, h, a_0, and h_a[14]. The values of C_s, C_a, D_e, and D_a are inherent properties of the drug. Therefore, by determining or estimating these latter parameters and reinserting the appropriate values into Eqs. 6 and 7, theoretical plots of amount released (Q') *versus* time (t) can be generated and compared to the experimental data. The values of C_s, C_a, and K for the different steroids are listed in Table I. Values for D_a were calculated from the equation of Sutherland–Einstein (9) and ranged from 6.5 to 7.1 × 10^{-6} cm.^{2}/sec. depending upon the steroid. Using the following numbers for the other constants in Eqs. 6 and 7, A = 15.2 mg./cm.^{3}, h = 18.1 cm., a_0 = 0.325 cm., and h_a = 66.8 × 10^{-4} cm.[15].

Figure 4 shows the experimental and theoretically determined Q' *versus* t plots. The theoretical plot was generated by a computer using D_e as the variable. The excellent agreement of the experimental data with the predicted curves supports the use of the matrix-boundary diffusion layer model. It is noteworthy that the early time data points are in good agreement with the theoretical curves. If the release of drug was solely matrix controlled during early times, then the Q' *versus* $t^{1/2}$ plots in Fig. 3 would be linear and poor agreement of data with theory would be noted in Fig. 4. This, however, is not the case.

Diffusion Coefficients—The values of D_e estimated by computer fit of the equations to the data are listed in Table II. Although the esti-

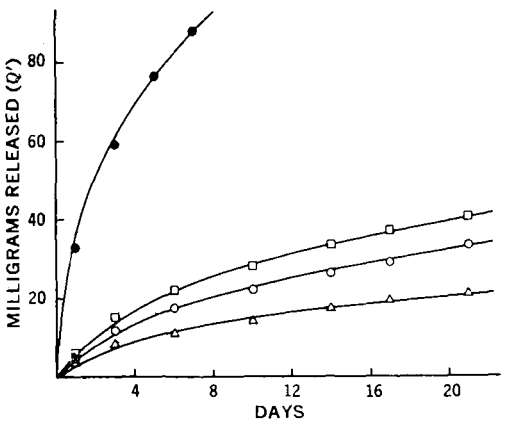

Figure 4—*Amount of steroid released from silicone cylinders as a function of time. Symbols represent experimental points while curves are drawn based upon theoretical calculations for the matrix-boundary diffusion layer model. Key: ●, progesterone; □, medroxyprogesterone acetate; ○, 6α-methyl-11β-hydroxyprogesterone; and △, 17α-hydroxyprogesterone.*

[14] h_a could not be controlled *in vivo*.
[15] See *Reference 3*.

Table II—Estimated and Determined Diffusion Coefficients of the Steroids in the Polymer Phase

Steroid	Diffusion Coefficient, cm.²/sec. × 10⁷ Estimated (D_e)[a]	Determined Filled (D_{sf})[b]	Determined Fillerless (D_s)[c]
Progesterone	16.5 (15.9–17.0)	4.50	5.78
6α-Methyl-17-acetoxyprogesterone[d]	3.71(3.43–3.99)	3.36	4.17
6α-Methyl-11β-hydroxyprogesterone	2.84[e](2.57–3.12)	—	—
17α-Hydroxyprogesterone	8.51(8.06–8.96)	3.88	5.65

[a] D_e estimated based upon Eqs. 6 and 7 to fit the experimental points. Values in parentheses are 95% confidence limits for the estimates. [b] D_{sf} is an apparent diffusion coefficient determined by the lag time method using a filled polymeric membrane. [c] D_s is the true diffusion coefficient determined by the lag time method using a fillerless polymeric membrane. [d] Medroxyprogesterone acetate. [e] This estimate is based upon C_s and K_f values for filled polymer. Hence, it would be expected that this estimate is low. It could be as high as 5×10^{-7} cm.²/sec.

mate for progesterone is somewhat high, these figures fall within the same magnitude. They are, however, subject to wide variations when small experimental error is present. For instance, a 15% experimental error in the data would result in a 40% error in the estimate. Therefore, the diffusion coefficients were independently determined to compare them with the estimated values. Table II shows that D_s for progesterone, medroxyprogesterone acetate, and 17α-hydroxyprogesterone all fall within a narrow range, *i.e.*, 4.17–5.78 × 10^{-7} cm.²/sec. In general, these agree fairly well with the estimated effective diffusion coefficients. Although the effective diffusion coefficient estimate (D_e) can be influenced by a tortuosity or volume fraction term ($D_e = D_s\epsilon/\tau$) due to the presence of filler particles within polymer, it will subsequently be shown that their effect was relatively small. Hence, for this polymer system, D_e can be compared to D_s.

The small fluctuations of the diffusion coefficients in the polymer phase for the steroids is consistent with the hole formation concept in diffusional processes. The rate of diffusion of a molecule through the polymer is dependent upon the formation of a hole of sufficient size to accommodate the diffusing species. Therefore, it would be expected that molecules of similar molecular size, such as steroids, would have similar diffusion coefficients. Comparison of these diffusion coefficients with those reported for smaller molecules in polyethylene (10) shows that the diffusion coefficients in the silicone polymer are order(s) of magnitude greater. These relatively high diffusion coefficients may be attributed to the ease of hole formation for the diffusing species due to the high internal chain mobility within the silicone polymer (11).

Partition Coefficients and Solubility—In contrast to the diffusion coefficients, the partition coefficients are sensitive functions of molecular structure. Although the partition coefficient is one contributing factor to the nonlinearity of the *Q' versus* $t^{1/2}$ plots at early times (*i.e.*, when $l \simeq 2D_e h_a K/D_a$), it in itself does not explain the diversities in the release of the steroids from the polymer. Since inspection of Eq. 4 shows that K and C_s occur independently of each other, it is fruitful to examine the linear region of the *Q' versus* $t^{1/2}$ plots. In this region, the release of drug is matrix controlled, (*i.e.*, $l \gg D_e h_a K/D_a$), resulting in mathematical expressions that give a direct dependence of the amount released on the solubility of the drug in the polymer (C_s). Figure 5 shows a plot of the slopes of the *Q' versus* $t^{1/2}$ plots *versus* the square root of the solubility of the drug in the polymer, assuming equal D_e values[16]. This graph clearly demonstrates that the amount of steroid released increases linearly with the square root of its solubility under the conditions described in this study. As a check on this plot, the calculated D_e from the least-squares slope of the line was 5.11×10^{-7} cm.²/sec., which is consistent with the values listed in Table II.

The C_s values listed in Table I show that progesterone has the highest solubility while the 6α-methyl-17-acetate, 6α-methyl-11β-hydroxy, and the 17α-hydroxy derivatives are lower in the order indicated. Based upon structure comparisons of these compounds, it appears that the presence of a hydroxyl group reduces the steroid

[16] Based upon the previous discussion on diffusion coefficients, this is a good assumption.

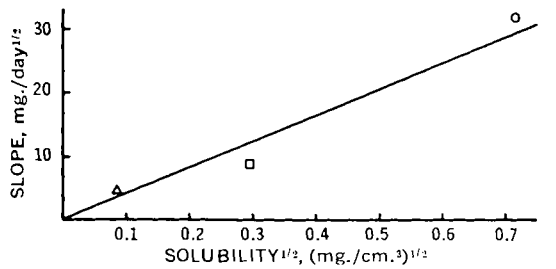

Figure 5—*Slope of Q' versus* $t^{1/2}$ *plots versus the square root of the solubility of the steroid in the silicone polymer. Key:* ○, *progesterone;* □, *medroxyprogesterone acetate; and* △, *17α-hydroxyprogesterone.*

solubility in the polymer quite markedly; for example, progesterone is 71 times more soluble than 17α-hydroxyprogesterone. The presence of the 17-acetate group has a similar but lesser effect. It is apparent that the presence of different functional groups on the parent steroid molecule can substantially influence C_s and, therefore, alter the release of drug from the polymer. Based upon the results of this study, *Q' versus t* plots or release rates of structurally similar steroids could be estimated once the C_s and K values are known.

Effect of Filler—It is common knowledge that siliceous earth fillers are incorporated into silicone polymers in concentrations as high as 20–25% to afford varying degrees of mechanical strength to the polymer. The presence of filler particles within the polymer is known to affect diffusion coefficients determined by the lag time technique (12). The adsorption of drug onto filler results in a positive displacement of lag times and, hence, diffusion coefficients are low. A similar effect was noted for the diffusion of sarin through petrolatum barriers containing silica gel fillers (13). Displacement of lag times in the presence of filler was adequately explained by deriving equations that depended upon Langmuir adsorption. The severe displacement of lag times in studies on the diffusion of ethyl *p*-aminobenzoate through silicone membranes containing high surface area fumed silica fillers was also shown to follow Langmuir adsorption during the nonsteady-state period (14). Partition coefficients, on the other hand, can be overestimated due to adsorption of drug onto the filler material during equilibration (12). In view of these studies, the effect of filler on the determined diffusion coefficients, partition coefficients, and drug transport was assessed.

Table I shows that the presence of filler material increases the determined values of the partition coefficients. Its effect on progesterone and medroxyprogesterone acetate was small, resulting in an increase of ~12%. A rather large increase (~150%), however, was noted for 17α-hydroxyprogesterone. Although comparable amounts of drug may have been adsorbed, the solubility (polymer) of the first two steroids was high enough to minimize the magnitude of the adsorption effect. For 17α-hydroxyprogesterone, the solubil-

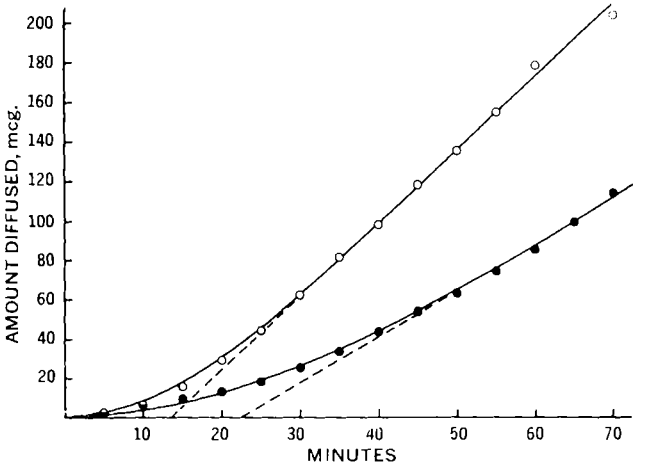

Figure 6—*Amount of progesterone diffused across a silicone membrane as a function of time. Dashed lines are the extrapolation of the steady-state portion of the curve to the* x-*axis, yielding the lag time. Key:* ○, *fillerless membrane* (X = *0.0516 cm.*); *and* ●, *filled membrane* (X = *0.0597 cm.*).

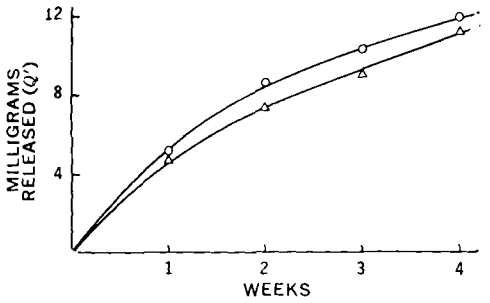

Figure 7—*Amount of medroxyprogesterone acetate released from 3% silicone cylinders (4 × 0.5 cm.) as a function of time. Key:* ○, *fillerless polymer; and* △, *filled polymer.*

ity was substantially less, resulting in a more pronounced adsorption effect.

Table II shows that filler decreased determined diffusion coefficients by an average value of 25%. In this instance, adsorption of drug onto filler particles caused a lengthening of the nonsteady-state period (lag time) and, hence, a reduction in determined diffusion coefficients. The adsorption effect in these studies, although consistent with previous work, was considerably less than that reported for ethyl *p*-aminobenzoate using a different polymer system (12). Although a different class of drug molecules was used, the contributing factor apparently was the difference in the filler types present in the polymer. It would be expected that a high surface area fumed silica as used in the ethyl *p*-aminobenzoate study (12) would cause a more dramatic effect on both partition and diffusion coefficients. In fact, Finger *et al.* (13) showed a direct dependence of lag time on the maximum adsorptive capacity of silica gel fillers in an ointment system.

Figure 6 shows the results of a typical membrane diffusion experiment for progesterone across fillerless and filled membranes. Examination of the steady-state portion of the curve, corrected for variations in the membrane thickness, shows that the rate of diffusion across a fillerless membrane is 1.1 times faster than the filled polymer. Since adsorption onto filler would not affect the steady-state rate, because all adsorption sites would be saturated, this result is attributed to a volume fraction (ϵ) and possibly a tortuosity effect (τ). The volume fraction of the matrix phase was calculated to be 0.88; hence, the tortuosity factor would be approximately 1. This is consistent with a previous estimate of 1.1 for τ (14). Further support for the relatively small effect of filler on the steady-state transport of drug is demonstrated in Fig. 7. This plot shows that the amount released at a given time is marginally affected by the presence of filler within this polymer.

SUMMARY

The release of progesterone-type steroids from a silicone was found to be matrix-boundary diffusion layer controlled during early times, while at later times the release process was matrix controlled; *i.e.*, Q' *versus* $t^{1/2}$ plots were linear. The differences in the amount of drug released from the matrix were dependent upon the molecular structure of the steroid. Progesterone, for instance, was released approximately eight times faster than 17α-hydroxyprogesterone. Since determined diffusion coefficients in the polymer phase were of the same magnitude, the diversity in release profiles was attributed to differences in the polymer solubilities of the steroids. Data are presented showing that the partition coefficient (polymer/water) and polymer solubility of the drug are sensitive functions of the structure of the steroids and account for the experimental findings. The presence of filler particles within the polymer caused: (*a*) determined diffusion coefficients to decrease by an average value of 25%, (*b*) an increase in experimentally determined partition coefficients, and (*c*) a slight reduction in the amount released *versus* time plot for medroxyprogesterone acetate.

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