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Release of Medroxyprogesterone Acetate from a Silicone Polymer

T. J. ROSEMAN* and W. I. HIGUCHI†

Abstract □ The *in vitro* release of medroxyprogesterone acetate from a silicone rubber matrix was studied. A nonlinear dependence of release rate upon medroxyprogesterone acetate concentration within the matrix was found. Based upon a model system, equations were derived to explain this behavior and to include other parameters which may influence the release rate. Since the model, in part, is dependent upon a receding medroxyprogesterone acetate layer within the matrix, a photograph depicting depletion zones as a function of time is presented. In contrast to the T. Higuchi model for drug release, this model includes the boundary diffusion layer. Comparison of the two models suggested that when the boundary layer was considered, a better fit of experimental data to theory was found. The applicability of the model to an *in vivo* system is discussed. This study has suggested that the partition coefficient, diffusion coefficients, medroxyprogesterone acetate concentration within the polymer, and agitation conditions play important roles in the release process.

Keyphrases □ Medroxyprogesterone acetate release rate, *in vitro*—physicochemical factors □ Silicone rubber matrix—medroxyprogesterone acetate release □ Matrix boundary diffusion layer model—equations derived □ Partition coefficient—silicone, medroxyprogesterone acetate □ Vapor phase chromatography—determination

The use of a rubber material as a delivery system for various chemicals has been a subject of considerable interest. The B. F. Goodrich Co. (1) has recently incorporated toxic substances into a rubber matrix and observed effective antifouling activity for prolonged periods. Some therapeutic implications of silicone rubber as a drug delivery system have been described previously (2).

The advantage of silicone rubber as a dosage form for medroxyprogesterone acetate has been discussed by Mishell *et al.* (3). It was shown that medroxyprogesterone acetate was readily absorbed from a vaginal device in sufficient quantity to inhibit ovulation. This drug delivery system promises to be a unique approach in the field of contraception.

Although other investigators (4, 5) have studied the diffusion of drugs across silicone membranes, an *in vitro* study on the release of a drug embedded in a silicone matrix has not been presented. Therefore, the present study was designed to investigate the physicochemical factors involved in the release of medroxyprogesterone acetate from a silicone matrix system. The interdependence of various parameters can be described by mathematical relationships based upon a physical model which is an extension of concepts set forth by Higuchi (6).

EXPERIMENTAL

Medroxyprogesterone acetate[1]–silicone[2] cylinders, 4 cm. by 0.5 cm., were prepared by levigating the required amount of drug into the elastomer and polymerizing with catalyst. The mixture was then forced into prewashed vinyl tubing and allowed to cure. After the cylinders were removed from the tubing and weighed, 24 were mounted between two circular disks and secured in a 3-l. jacketed beaker. Figure 1 is a schematic diagram of the *in vitro* dissolution apparatus. Distilled water from eight 5-gal. carboys was pumped at a rate of about 60 l./day through a 37° water bath, which preheated the water, into the beaker. The effluent was discarded into a drain. This constant flow of water approximates a "perfect sink" condition, *i.e.*, there is no significant concentration build-up in the dissolution media. The same water bath provided 37° water which was continuously circulated through the walls of the beaker,

[1] The Upjohn Co.'s trademark for medroxyprogesterone acetate is Provera.
[2] Silastic Elastomer, Dow Corning Corp., Midland, Mich.

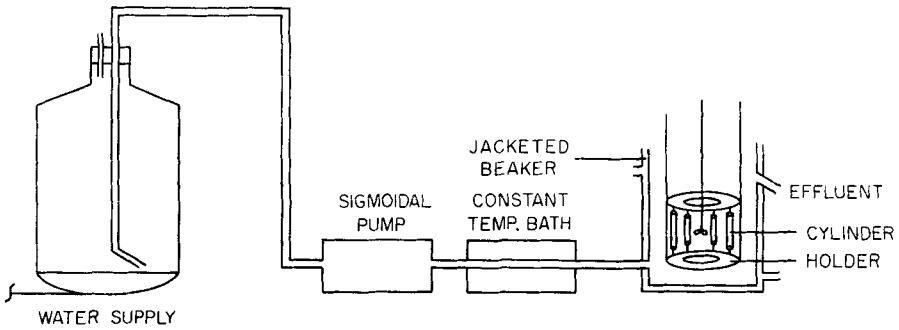

Figure 1—*Dissolution apparatus for silicone cylinders.*

thereby maintaining a constant temperature during dissolution. The solution was agitated by an impeller which was driven by a Servodyne drive system.[3] The impeller was situated in the center of the beaker and extended to the bottom of the cylinders. Its location was fixed for all experiments.

In order to quantitate the initial release rates, the effluent was collected, extracted, and assayed for its medroxyprogesterone acetate content by a modified USP procedure (7). The long time release data (1 week or greater) was obtained by withdrawing the cylinders and determining the residual medroxyprogesterone acetate content by vapor phase chromatography. The difference between the initial and final values gave the amount lost at any given time.

The zones of depletion were measured microscopically with a calibrated reticule. Cross-sectional slices of the cylinder were used for the measurement.

The partition coefficient of medroxyprogesterone acetate was determined by equilibrating flat sheets (about 7 × 2 × 0.05 cm.) of the silicone material in a solution of tritium-labeled medroxyprogesterone acetate at 37°. Sheets were removed at 1-day and 4-day intervals to ensure that equilibrium had resulted. They were then extracted with methylene chloride and the solvent evaporated to dryness. After the addition of 15 ml. of Diotol counting solvent, the samples were counted in a liquid scintillation spectrometer.[4] The partition coefficient was calculated by dividing the counts per volume in the equilibrated solution by counts per volume in the silicone sheet.

THEORETICAL CONSIDERATIONS

The mechanisms of drug release from various matrix systems have previously been discussed (6). It was assumed that the rate-limiting step was the diffusion of drug from the matrix (matrix controlled). Under certain conditions, it is conceivable that the rate of diffusion from the surface of the matrix to the surrounding bulk solution will make a significant contribution to the total diffusional process. Therefore, the mathematics for this system (matrix-boundary diffusion layer model) is presented for two geometric cases. The assumptions in the derivations are: (*a*) A pseudo-steady state exists; (*b*) $A >> C_s$, the concentration of drug in the matrix is much greater than its solubility in the matrix; (*c*) the diffusion coefficients are constant; (*d*) diffusion is the rate-controlling step, rather than dissolution; (*e*) the diffusional process occurs through the matrix phase rather than through pores or channels within the matrix.

Planar Case—Figure 2 is a hypothetical diagram of the matrix-boundary diffusion layer model. The rate of diffusion across a plane of unit area is given by Fick's law,

$$G = -D\frac{dC}{dx} \qquad \text{(Eq. 1)}$$

where G is the rate of diffusion across the plane, dC/dx is the concentration gradient, and D is the diffusion coefficient. The amount depleted from the matrix per unit time per unit area becomes

$$\frac{dQ}{dt} = -G = \frac{D_e}{l}(C_s - C_s') \qquad \text{(Eq. 2)}$$

where C_s and D_e are the solubility and effective diffusion coefficient, respectively, in the matrix phase, C_s' is the concentration in the matrix at $x = 0$, and l is the diffusional distance (zone of depletion). The effective diffusion coefficient is given by

$$D_e = \frac{D_s\epsilon}{\tau} \qquad \text{(Eq. 3)}$$

where ϵ is the volume fraction of the matrix, τ is the tortuosity of the matrix, and D_s is the diffusion coefficient in the matrix phase. It follows that the rate of diffusion across the diffusion boundary layer (h_a) is given by

$$\frac{dQ}{dt} = \frac{D_a}{h_a}[C_a' - C_B(t)] \qquad \text{(Eq. 4)}$$

where D_a is the diffusion coefficient in the aqueous phase, C_a' the concentration in water at $x = 0$, and C_B the concentration at $x = h_a$. Equating Eqs. 2 and 4, under steady-state conditions, utilizing the relationship

$$K = \frac{C_a}{C_s} = \frac{C_a'}{C_s'} \qquad \text{(Eq. 5)}$$

where C_a is the solubility in the aqueous phase, and K is the partition coefficient, and solving for C_s', the rate becomes

$$\frac{dQ}{dt} = \frac{D_e}{l}\left[C_s - \frac{C_sD_eh_a + D_alC_B(t)}{KD_al + D_eh_a}\right] \qquad \text{(Eq. 6)}$$

For the condition $A >> C_s$, where A is the concentration of drug in

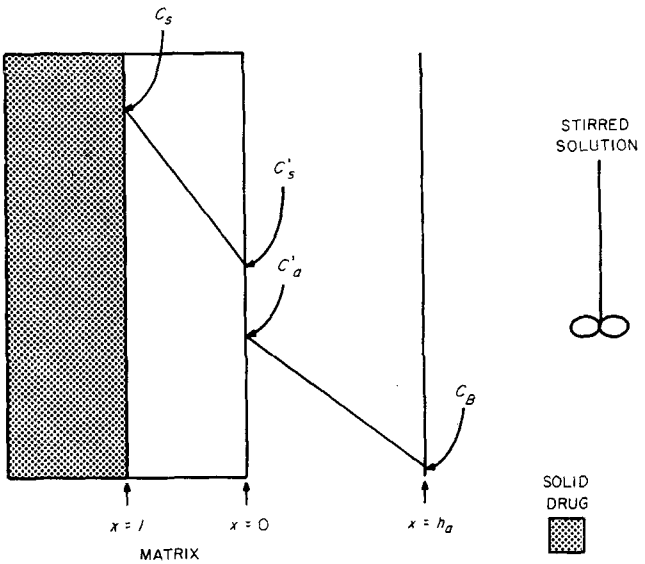

Figure 2—*Hypothetical diagram for the matrix-boundary diffusion layer model.*

[3] Cole Parmer, Chicago, Ill.
[4] Packard Tri-Carb, Packard Instrument Co.

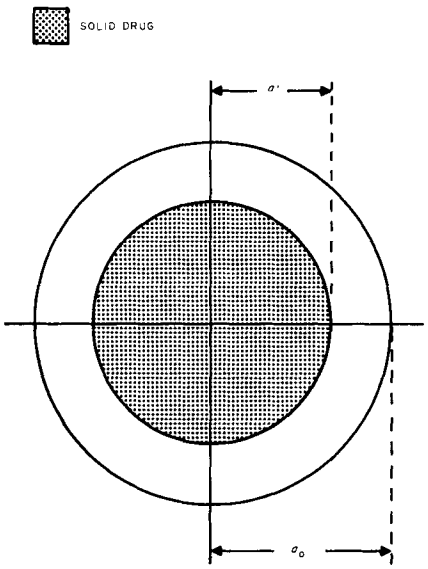

Figure 3—*Schematic diagram of a cross-sectional view of a cylinder where* $l = a_0 - a'$.

the matrix, the rate of release per unit area is

$$\frac{dQ}{dt} = A\frac{dl}{dt} \qquad \text{(Eq. 7)}$$

Equating Eqs. 5 and 6 and simplifying give

$$\left(Kl + \frac{D_e}{D_a}h_a\right)\int_0^l Adl = D_eC_sK\int_0^t dt + D_e\int_0^t C_B(t)dt \qquad \text{(Eq. 8)}$$

Integrating and setting $C_B = 0$ ("perfect sink" condition) the above reduces to

$$l^2 + \frac{2D_eh_al}{KD_a} = \frac{2D_eC_st}{A} \qquad \text{(Eq. 9)}$$

Since

$$Q = Al \qquad \text{(Eq. 10)}$$

Eqs. 9 and 10 define the Q *versus* t plots. When $l^2 >> 2D_eh_al/KD_a$, Eq. 9 reduces to the matrix-controlled process,

$$l^2 = \frac{2D_eC_st}{A} \qquad \text{(Eq. 11)}$$

It follows that

$$Q = (2AD_eC_st)^{1/2} \qquad \text{(Eq. 12)}$$

Equations 11 and 12 have been derived previously (6).

Cylindrical Case—The equations describing the release of a drug from a cylindrical matrix can be derived using the basic relationships that exist in the planar system. The amount (Q') depleted per unit time is

$$\frac{dQ'}{dt} = -2\pi hD_e a\frac{dC}{da} \qquad \text{(Eq. 13)}$$

where h is the height of the cylinder and a is the radius of the area under consideration. All other symbols have been defined previously. Since, according to Fig. 3, $C = C_s$ at $a = a'$ and $C = C_s'$ at $a = a_0$, integration of Eq. 13 yields

$$\frac{dQ'}{dt} = \frac{-2\pi hD_e(C_s' - C_s)}{\ln\dfrac{a'}{a_0}} \qquad \text{(Eq. 14)}$$

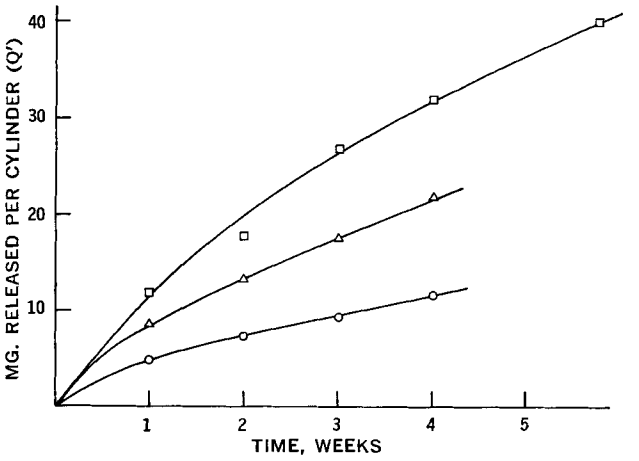

Figure 4—*Total amount of medroxyprogesterone acetate released from silicone cylinders as a function of time for three concentrations. Key:* ○ = 3.0%; △ = 12.0%; □ = 24.0%.

Assuming $C_B = 0$, the rate of diffusion from the surface is given by

$$\frac{dQ'}{dt} = \frac{2\pi ha_0D_a}{h_a}C_a' \qquad \text{(Eq. 15)}$$

After equating Eqs. 14 and 15, substituting Eq. 5, solving for C_s', and rearranging, the rate becomes

$$\frac{dQ'}{dt} = \frac{2\pi ha_0KD_a}{h_a}\left(\frac{D_eC_sh_a}{-KD_aa_0\ln\dfrac{a'}{a_0} + D_eh_a}\right) \qquad \text{(Eq. 16)}$$

For $A >> C_s$

$$\frac{dQ'}{dt} = -2\pi hAa'\frac{da'}{dt} \qquad \text{(Eq. 17)}$$

Equating Eqs. 16 and 17:

$$\int_{a_0}^{a'}\left(KD_aa_0\ln\frac{a'}{a_0} - D_eh_a\right)a'da' = \frac{KD_eC_sD_aa_0}{A}\int_0^t dt \qquad \text{(Eq. 18)}$$

Integration and substitution yield

$$\frac{a'^2}{2}\ln\frac{a'}{a_0} + \frac{1}{4}(a_0^2 - a'^2) + \frac{D_eh_a}{2KD_aa_0}(a_0^2 - a'^2) = \frac{C_sD_et}{A} \qquad \text{(Eq. 19)}$$

For the matrix-controlled system, this reduces to

$$\frac{a'^2}{2}\ln\frac{a'}{a_0} + \frac{1}{4}(a_0^2 - a'^2) = \frac{C_sD_et}{A} \qquad \text{(Eq. 20)}$$

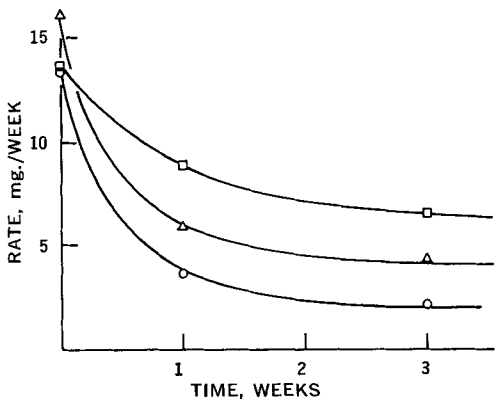

Figure 5—*Rate as a function of time for three medroxyprogesterone acetate concentrations in silicone cylinders. Key:* ○ = 3.0%; △ = 12.0%; □ = 24.0%.

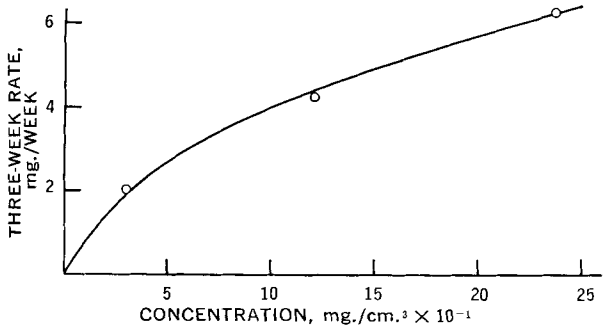

Figure 6—*Three-week release rate from silicone cylinders* versus *medroxyprogesterone acetate concentration.*

Since

$$Q' = \pi h A (a_0^2 - a'^2) \qquad \text{(Eq. 21)}$$

Eqs. 19 or 20 and 21 define the Q' *versus* t plots.

RESULTS AND DISCUSSION

Figures 4 and 5 show the amount of medroxyprogesterone acetate released (Q') and the rate of release respectively as a function of time for the silicone cylinders at three medroxyprogesterone acetate concentrations. It is interesting to note that the initial rates (Fig. 5) are relatively constant while at later times there is a nonlinear dependence of rate upon concentration. Figure 6 shows this dependence at 3 weeks. As the medroxyprogesterone acetate diffuses from the matrix, rather well-defined zones of depletion develop. An example of the zones at various times is illustrated in Fig. 7 for a transparent silicone material. Initially, the transparent material is rendered opaque by the presence of medroxyprogesterone acetate. As the medroxyprogesterone acetate diffuses from the matrix, clear zones result. The longer release times show the larger zones. The unique advantage of this system is that the zones can be measured directly. These then can be compared to theoretical values. The value of Q' can be evaluated from Eq. 21 as long as $A >> C_s$.

Although Eq. 20 was not reported by Higuchi (6), its derivation follows from the other geometric cases which were presented for the release from a homogeneous matrix. Equation 19 represents an extension of Eq. 20 which includes the aqueous boundary diffusion layer. To compare the theories, the following values were assigned:

C_a — The solubility of medroxyprogesterone acetate in water at 37° is 3.25×10^{-3} mg./ml.

D_a — The diffusion coefficient in water was determined from the Sutherland-Einstein equation (8). The calculated value was 6.54×10^{-6} cm.²/sec.

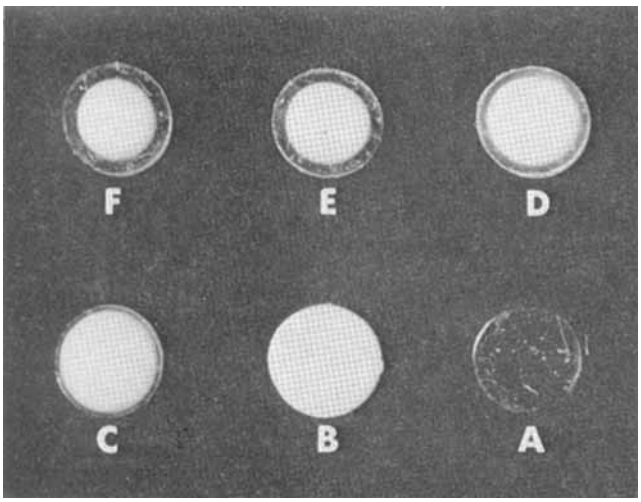

Figure 7—*Cross-sectional views of silicone (transparent) cylinders. Key:* A = *placebo;* B = *drug-filled initial;* C = *1 week;* D = *2 weeks;* E = *3 weeks;* F = *4 weeks.*

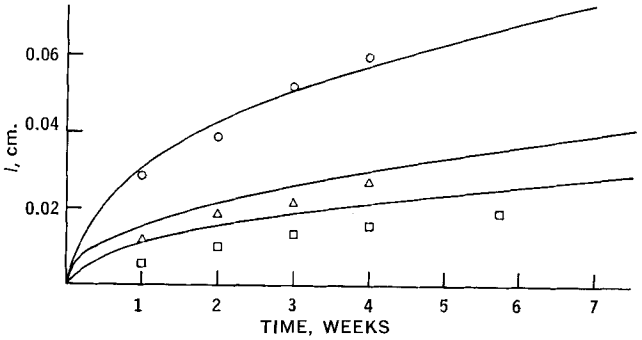

Figure 8—*Thickness of depletion zone as a function of time for medroxyprogesterone acetate-silicone cylinders. Curves drawn are based upon theoretical calculations for the matrix-controlled model. The symbols represent experimental data. Key:* ○ = *3.0%;* △ = *12.0%;* □ = *24.0%.*

h_a — The thickness of the diffusion layer, calculated from the expression $h_a = D_a C_a / G_i$ where G_i is the initial rate, was 66.8×10^{-4} cm.

K — The value of K was determined to be 0.033 ± 0.003.

The values of ϵ, volume fraction of the polymer, and τ, tortuosity, have not been given since these are incorporated into an effective diffusion coefficient. Due to the presence of vacuoles, drug, and filler, the value of ϵ will be less than one. The tortuosity factor accounts for indirect pathways that may result from presence of filler within the matrix.

Since $l = a_0 - a'$, Eqs. 19 and 20 were compared considering l as the variable. The continuous lines in Fig. 8 show l as a function of time as calculated from Eq. 20, for the matrix-controlled case, at three different medroxyprogesterone acetate concentrations. The value of D_e was chosen to be 2.0×10^{-7} cm.²/sec. to fit the data for $A = 30$ mg./cm.³ The symbols represent the experimental points. A similar plot is given in Fig. 9, the l values being calculated from Eq. 19, for the matrix-boundary diffusion layer model. In this case D_e was chosen to be 2.6×10^{-7} cm.²/sec. to fit the data for $A = 30$ mg./cm.³ Comparison of Figs. 8 and 9 indicates that the matrix-boundary diffusion layer model gives a better fit of theory with data. If Eq. 19 represents the correct model, then an increase in h_a should increase the time to reach a given l distance. Since h_a is dependent on hydrodynamic flow, a decrease in stirring rate should result in a higher h_a value. The effect of stirring for $A = 30$ mg./cm.³ is illustrated in Fig. 10. The corresponding h_a value, calculated from initial rate data for the 70 r.p.m. experiment, is 146×10^{-4} cm. Inserting this value back into Eq. 19 and recalculating l as a function of time resulted in good agreement of theory with experimentally measured l values. Further support of the matrix-boundary diffusion

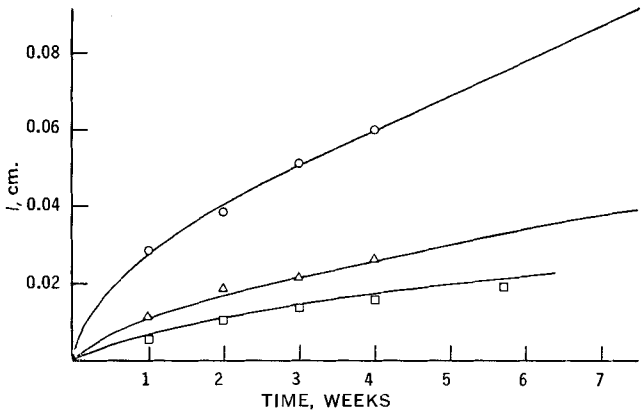

Figure 9—*Thickness of depletion zone as a function of time for medroxyprogesterone acetate-silicone cylinders. Curves drawn are based upon theoretical calculations for the matrix-boundary diffusion model. The symbols represent experimental data. Key:* ○ = *3.0%;* △ = *12.0%;* □ = *24.0%.*

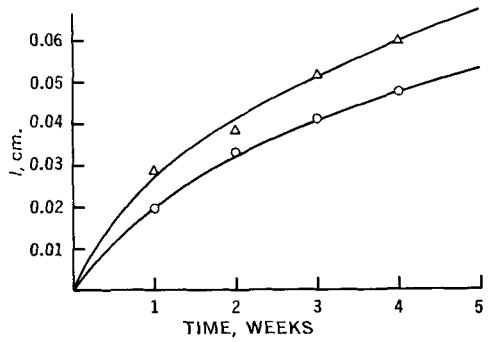

Figure 10—*Thickness of depletion zone as a function of time for 3.0% medroxyprogesterone acetate-silicone cylinders. Key: △ = 700 r.p.m.; ○ = 70 r.p.m.*

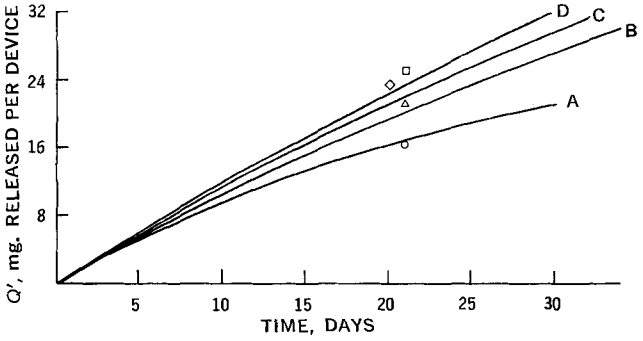

Figure 11—*Release profiles for medroxyprogesterone acetate-silicone devices. Curves are theoretical while symbols are* in vivo *data. Key: ○ = 10 mg./cm.³–A; △ = 20 mg./cm.³–B; □ = 40 mg./cm.³–C; ◇ = 80 mg./cm.³–D.*

layer model stems from an examination of initial rate data. For a purely matrix-controlled system, initial steady-state rates would be dependent upon $(A)^{1/2}$.[5] Figure 5 shows that this is clearly not the case. The initial rates are relatively constant.

Although it appears that Eq. 19 is operating, it would be of interest to determine the limits of its applicability. Setting $\alpha = D_e C_s h_a / D_a C_a$ for the planar case Eq. 9 (recalling that $K = C_a/C_s$), it can be shown that when $\alpha \ll l$, variation in stirring rates would not affect the release rates, since the release of the drug would be matrix controlled. For drugs with high values for α, *i.e.*, $\alpha \cong l$, the effects of agitation would be significant, and therefore the matrix-boundary diffusion layer model would apply. It can be seen that the values of C_s, D_e, C_a, and D_a determine which model is operating. An analogous situation exists in the area of the kinetics of dyeing (9). It would be expected that compounds of similar molecular size and weight would exhibit relatively constant D_e/D_a values. Since the C_s/C_a (K) ratios are more sensitive to molecular structure, they can vary quite markedly (10). This would suggest that the partition coefficient can substantially influence the drug release mechanism. It follows then that compounds which have relatively small K values would follow the matrix-boundary diffusion layer model, while those with large values would be solely matrix controlled. Future studies will be designed to explore the relationship of K to the release mechanism.

Analyses of *in vivo* data from medroxyprogesterone acetate-silicone vaginal devices suggest that the amount released per time per unit area is considerably less than the *in vitro* system. If it is assumed that the contributing factor[6] to these results is a larger aqueous diffusion layer, then the *in vivo* data can be compared to theory by utilizing Eq. 19. Based upon the data, h_a can be estimated at 580×10^{-4} cm. This value can now be inserted back into Eq. 19 and utilizing Eq. 21, a theoretical plot of Q' *versus* t can be obtained, Fig. 11. All other parameters have been previously defined. The plot is made for four concentrations: 10 mg./cm.³, 20 mg./cm.³, 40 mg./cm.³, and 80 mg./cm.³. The symbols in Fig. 11 represent the *in vivo* data, determined by residual analyses of the device for its drug content. Considering the assumptions which were made, the agreement of theory with data is acceptable. It is interesting to note that the curves are initially similar while at 21 days the lower concentration gives a substantially lower dose of drug. It is apparent that the effect of concentration is relatively minor until the zones of depletion are sufficiently large.

CONCLUSIONS

A model system was presented for the release of a water-insoluble steroid, medroxyprogesterone acetate, embedded in a solid silicone rubber. The experimental findings were not totally consistent with concepts already set forth for matrix systems. Therefore, a model was developed which considered the boundary diffusion layer. In this instance, equations were consistent with the experimental results. The amount of drug present within the matrix (A), the diffusion coefficients in the solid and aqueous phases, and the partition coefficient (K), were included. The dependence of the amount released (Q') upon A was in agreement with the values calculated from theory. It was suggested that the partition coefficient strongly influenced the release mechanism.

The applicability of the model to an *in vivo* system was also evaluated. Based on the assumption that the slower release observed *in vivo* was due to a larger boundary diffusion layer, plots were made for the theoretical *in vivo* release at four drug levels within the matrix. Except for the thickness of the diffusion layer, all parameters were the same as the *in vitro* system. The amount of medroxyprogesterone acetate lost after 3 weeks from vaginal devices was qualitatively in agreement with the theoretical values.

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[5] This can be derived from Eq. 12. It can also be shown that up to 50% release the plane surface is a good approximation for the cylindrical surface.

[6] Other factors such as the formation of an interfacial layer or lack of "perfect sink" conditions could also be important.