the alcohol absorption in the rabbit vagina. However, the possibility of more sophisticated models is not precluded.

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# Systems Approach to Vaginal Delivery of Drugs III: Simulation Studies Interfacing Steroid Release from Silicone Matrix and Vaginal Absorption in Rabbits


**N. F. H. HO [x], L. SUHARDJA, S. HWANG, E. OWADA, A. MOLOKHIA, G. L. FLYNN, W. I. HIGUCHI, and J. Y. PARK**



**Abstract** □ A composite physical model involving the simultaneous receding boundary release of drug from a drug suspension–silicone polymer matrix system, diffusion across the aqueous layer, and passive transport across the vaginal membrane consisting of parallel lipoidal and aqueous pore pathways is described. Simulation studies with progesterone and hydrocortisone illustrate matrix release-limiting, membrane absorption, and aqueous diffusion layer-limiting cases when the cylindrical silicone delivery device is interfaced with the vaginal membrane of the rabbit.



**Keyphrases** □ Drug delivery, vaginal—progesterone and hydrocortisone release from silicone matrix, vaginal absorption, rabbits □ Absorption, vaginal—progesterone and hydrocortisone from silicone matrix, rabbits □ Silicone matrix system—release of progesterone and hydrocortisone, vaginal absorption, rabbits □ Progesterone—release from silicone matrix, vaginal absorption, rabbits □ Hydrocortisone—release from silicone matrix, vaginal absorption, rabbits □ Steroids—progesterone and hydrocortisone, release from silicone matrix, vaginal absorption, rabbits


As part of continuing research on the systems approach to an understanding of the vaginal delivery of drugs from a quantitative mechanistic standpoint, results of studies on membrane permeability of the rabbit vagina (1, 2) and *in vitro* release from the silicone polymer[1] matrix (3–5) and the composite physical model and equations are interfaced and integrated in this report. A rigorous description is presented for the drug release–drug absorption process. Several combination mechanisms are predicted from the analyses of these model simulation studies with progesterone and hydrocortisone. The simulations serve as the basis for the experimental design and subsequent interpretation of ongoing *in situ* studies in which the steroid–silicone polymer matrix is interfaced with the rabbit vagina.

[1] Silastic, Dow Corning, Midland, Mich.

## THEORY

**Physical Model**—The model for the simultaneous release of a nonelectrolyte drug from a water-insoluble polymer matrix and transport across an aqueous diffusion layer and vaginal membrane is shown in Fig. 1. Following Roseman and Higuchi (3), it is assumed that: (*a*) the finely divided drug particles are uniformly dispersed in the matrix shaped as a cylinder, (*b*) the drug has a finite solubility in the matrix, (*c*) it diffuses through the matrix rather than the pores, and (*d*) there is no penetration of water into the matrix and no release of drug from the ends of the cylindrical matrix.

An aqueous diffusion layer surrounding the matrix is in series with the vaginal membrane, consisting of parallel lipoidal and aqueous pore pathways. Sink conditions on the serosal side prevail. Quasi-steady-state kinetics are assumed everywhere.

**Total Flux Expressions**—The fluxes of the drug in the matrix, aqueous diffusion layer, and vaginal membrane are:

$$J_{ma} = -\frac{2\pi h D_e (C_s - C_s')}{\ln a/a_0} \qquad \text{(Eq. 1)}$$

$$J_{aq} = 2\pi h a_0 \frac{D_{aq}}{h_{aq}} (C_a - C_b) \qquad \text{(Eq. 2)}$$

$$J_{me} = 2\pi h a_m \left[ \frac{\alpha D_0 C_0}{h_m} + \frac{(1-\alpha) D_p C_p}{h_m} \right] \qquad \text{(Eq. 3)}$$

where $h$ is the length of the cylinder; $D_e$ is the effective diffusion coefficient in the matrix; $a$, $a_0$, and $a_m$ are the radial dimensions of the receding boundary in the matrix, cylinder, and vaginal membrane

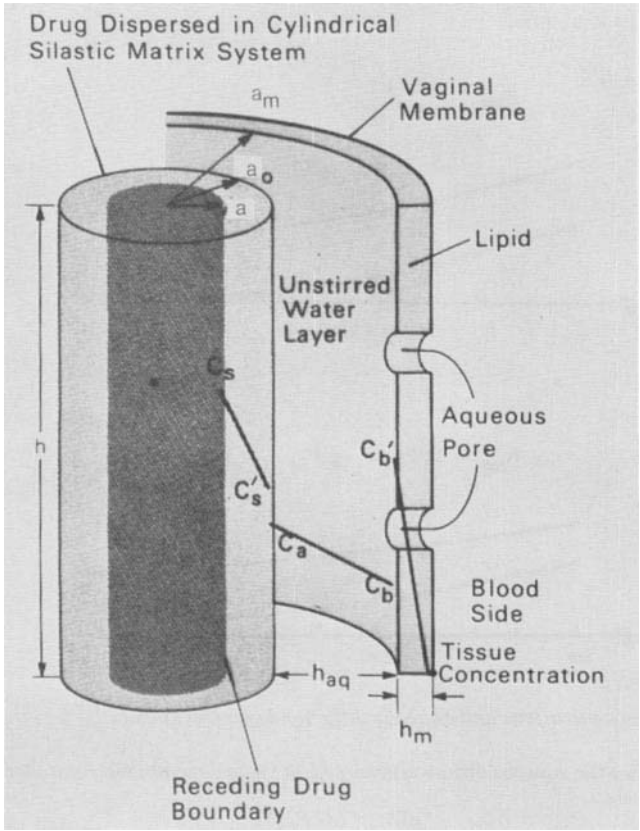



**Figure 1**—*Physical model of the simultaneous release of a contraceptive drug, which is uniformly dispersed in a water-insoluble silicone polymer matrix in cylindrical form, and the transport of the drug across the unstirred water layer and then the parallel lipoidal and aqueous pore pathways of the vaginal membrane. The shaded interior indicates the cylindrical region of drug in the polymer matrix, which diminishes uniformly as drug is released. (See text for details.)*

surface, respectively; $h_{aq}$ and $h_m$ are the thicknesses of the aqueous diffusion layer and the vaginal membrane, respectively; $D_{aq}$, $D_0$, and $D_p$ are the diffusion coefficients in the aqueous layer, lipoidal membrane, and aqueous pores, respectively; $\alpha$ is the volume fraction of lipid biophase in the membrane; $C_s$ and $C_s'$ are the solubility of the drug in the matrix and the concentration at the surface on the matrix side, respectively; $C_a$ and $C_b$ are the concentrations in the aqueous layer at the matrix surface and membrane surface, respectively; and $C_0$ and $C_p$ are the concentrations in the membrane at the interface of the lipid, pores, and aqueous layer.

The radial receding boundary, $a$, is a function of the amount of drug released and time. The effective diffusion coefficient in the matrix is also described by:

$$D_e = \frac{\epsilon D}{\tau} \qquad \text{(Eq. 4)}$$

where $D$ is the intrinsic diffusion coefficient, $\epsilon$ is the porosity, and $\tau$ is the tortuosity.

The partition coefficients of the drug for the polymer matrix–water, $K_s$, and lipoidal biophase–water, $K$, are defined as follows:

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

$$K = \frac{C_0}{C_b} = \frac{C_0}{C_p} \qquad \text{(Eq. 6)}$$

The continuity of flow across the various barriers is given by:

$$J_{ma} = J_{aq} = J_{me} \qquad \text{(Eq. 7)}$$

With Eqs. 1–3 and 5–7:

$$J_{ma} = \frac{2\pi h D_e C_s}{\frac{D_e K_s}{a_0}\left(\frac{1}{P_{aq}} + \frac{1}{P_m}\right) - \ln a/a_0} \qquad \text{(Eq. 8)}$$

The permeability coefficient of the aqueous diffusion layer is:

$$P_{aq} = \frac{D_{aq}}{h_{aq}} \qquad \text{(Eq. 9)}$$

A linear approximation of the aqueous diffusion layer thickness, $h_{aq}$, has been shown to be sufficient when the radial distance from the center of the cylinder to the vaginal membrane, $a_m$, is not too different from the radius of the cylinder, $a_0$; *i.e.*, $a_m/a_0 \leq 1.10$ (6). The permeability coefficient[2] of the membrane is the sum of the permeability coefficients of the lipoidal and aqueous pore pathways, *i.e.*:

$$P_m = \frac{\alpha D_0 K}{h_m} + \frac{(1-\alpha)D_p}{h_m} \qquad \text{(Eq. 10}a\text{)}$$

$$P_m = P_0 + P_p \qquad \text{(Eq. 10}b\text{)}$$

**Change in Receding Boundary in Matrix and Amount of Drug Released with Time**—The flux in the matrix is related to the rate of drug release from the matrix and to the rate of change in the receding boundary in the matrix. Accordingly:

$$J_{ma} = \frac{dQ}{dt} = -2\pi h A a \frac{da}{dt} \qquad A \gg C_s \qquad \text{(Eq. 11)}$$

where $Q$ is the amount of drug released, $h$ is the length of the cylinder, $a$ is the radial coordinate of the receding boundary, and $t$ is time. An important assumption made here is that $A$, the initial amount of drug per volume of cylinder, is much greater than $C_s$, the solubility of the drug in the matrix.

By combining Eqs. 8 and 11 and integrating between $a(0) = a_0$ and $a(t)$, the change in the receding boundary with time is:

$$\left[\frac{D_e K_s}{2a_0}\left(\frac{1}{P_{aq}} + \frac{1}{P_m}\right) + \frac{1}{4}\right](a_0^2 - a^2) + \frac{a^2}{2}\ln a/a_0 = \frac{D_e C_s}{A}t \qquad \text{(Eq. 12)}$$

Because of Eq. 11, the amount and fraction of drug released are:

$$Q = \pi h A(a_0^2 - a^2) \qquad \text{(Eq. 13}a\text{)}$$

$$\frac{Q}{\pi a_0^2 h A} = \left[1 - \left(\frac{a}{a_0}\right)^2\right] \qquad \text{(Eq. 13}b\text{)}$$

It follows that:

$$\frac{1}{2\pi h A}\left[\frac{D_e K_s}{a_0}\left(\frac{1}{P_{aq}} + \frac{1}{P_m}\right) + \frac{1}{2}\right]Q + \frac{1}{2}\left(a_0^2 - \frac{Q}{\pi h A}\right)\ln\sqrt{1 - \frac{Q}{\pi h a_0^2 A}} = \frac{D_e C_s}{A}t \qquad \text{(Eq. 14)}$$

or:

$$\left[\frac{D_e K_s}{a_0}\left(\frac{1}{P_{aq}} + \frac{1}{P_m}\right) + \frac{1}{2}\right]Q + (\pi h a_0^2 A - Q)\ln\left(1 - \frac{Q}{\pi h a_0^2 A}\right)^{1/2} = (2\pi h D_e C_s)t \qquad \text{(Eq. 15)}$$

**Simplified Expressions of Receding Boundary and Amount Released with Time**—It is useful to obtain more simplified forms of Eqs. 12 and 15 for the changes of the receding boundary in the matrix and the amount released with time, particularly at relatively early time periods.

Recognizing that $a/a_0 \leq 1.0$, one gets $\ln a/a_0 \approx (a/a_0) - 1$. Thus, Eq. 12 becomes:

$$\left[\frac{D_e K_s}{2a_0}\left(\frac{1}{P_{aq}} + \frac{1}{P_m}\right) + \frac{1}{4}\right](a_0^2 - a^2) - \frac{a^2}{2a_0}(a_0 - a) = \frac{D_e C_s}{A}t \qquad \text{(Eq. 16)}$$

It is recognized that when $(Q/\pi h a_0^2 A) \ll 1.0$, it follows that $1/2 \ln [1 - (Q/\pi h a_0^2 A)] \approx -(Q/2\pi h a_0^2 A)$.

With some rearrangement in the algebra, Eq. 15 reduces to a quadratic expression:

$$\frac{Q^2}{2\pi h a_0^2 A} + \frac{D_e K_s}{a_0}\left(\frac{1}{P_{aq}} + \frac{1}{P_m}\right)Q = (2\pi h D_e C_s)t \qquad \text{(Eq. 17)}$$

[2] The permeability coefficient of the pore can also be defined in a more descriptive manner, *i.e.*, $P_p = [(1-\alpha)D_{aq}F]/h_m$, where $D_{aq}$ is the bulk aqueous diffusion coefficient, and $F$ is the filtration factor (7).

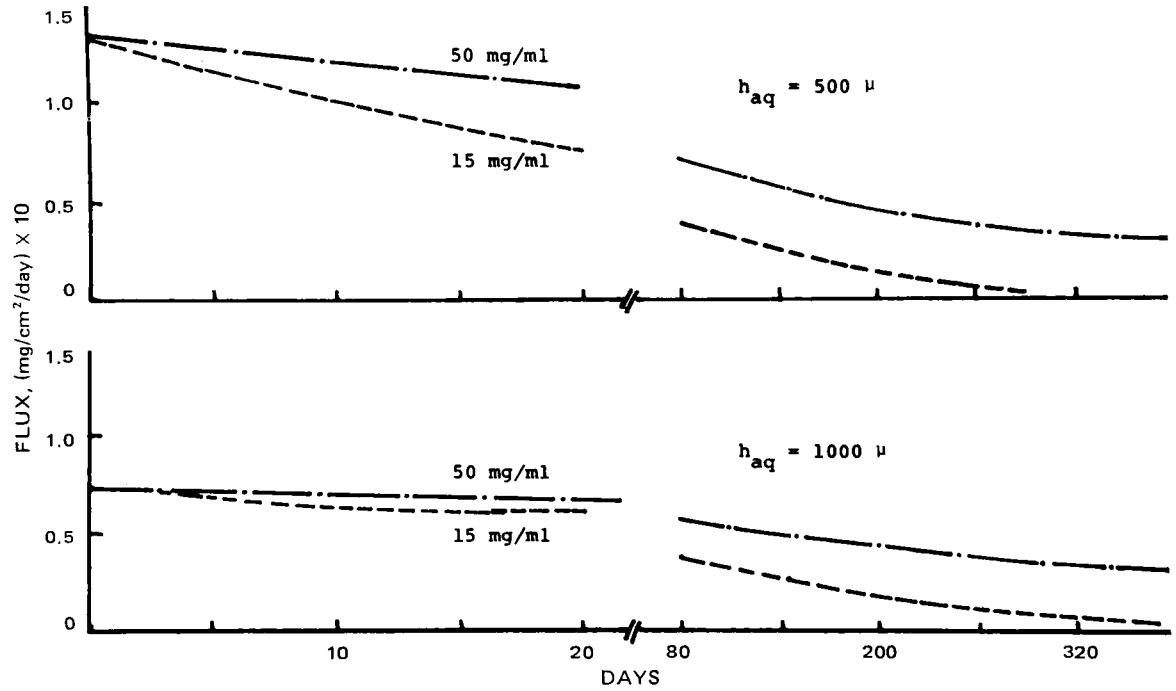



**Figure 2**—*Predicted flux of progesterone with time at various loading concentrations and aqueous diffusion layer thicknesses.*

After differentiating with respect to time, the rate of the amount of drug released from the matrix per unit area is:

$$\frac{1}{2\pi h a_0}\frac{dQ}{dt} = \frac{dQ'}{dt} = \frac{D_e C_s A}{\sqrt{\left[D_e K_s\left(\frac{1}{P_{aq}} + \frac{1}{P_m}\right)\right]^2 + 4D_e C_s A t}} \quad \text{(Eq. 18)}$$

For the aqueous diffusion layer and/or vaginal membrane-controlled case:

$$\frac{dQ'}{dt} = \frac{C_s P_{aq} P_m}{K_s(P_{aq} + P_m)} \quad \text{(Eq. 19)}$$

and for the matrix-controlled case:

$$\frac{dQ'}{dt} = \frac{1}{2}\sqrt{\frac{D_e C_s A}{t}} \quad \text{(Eq. 20)}$$

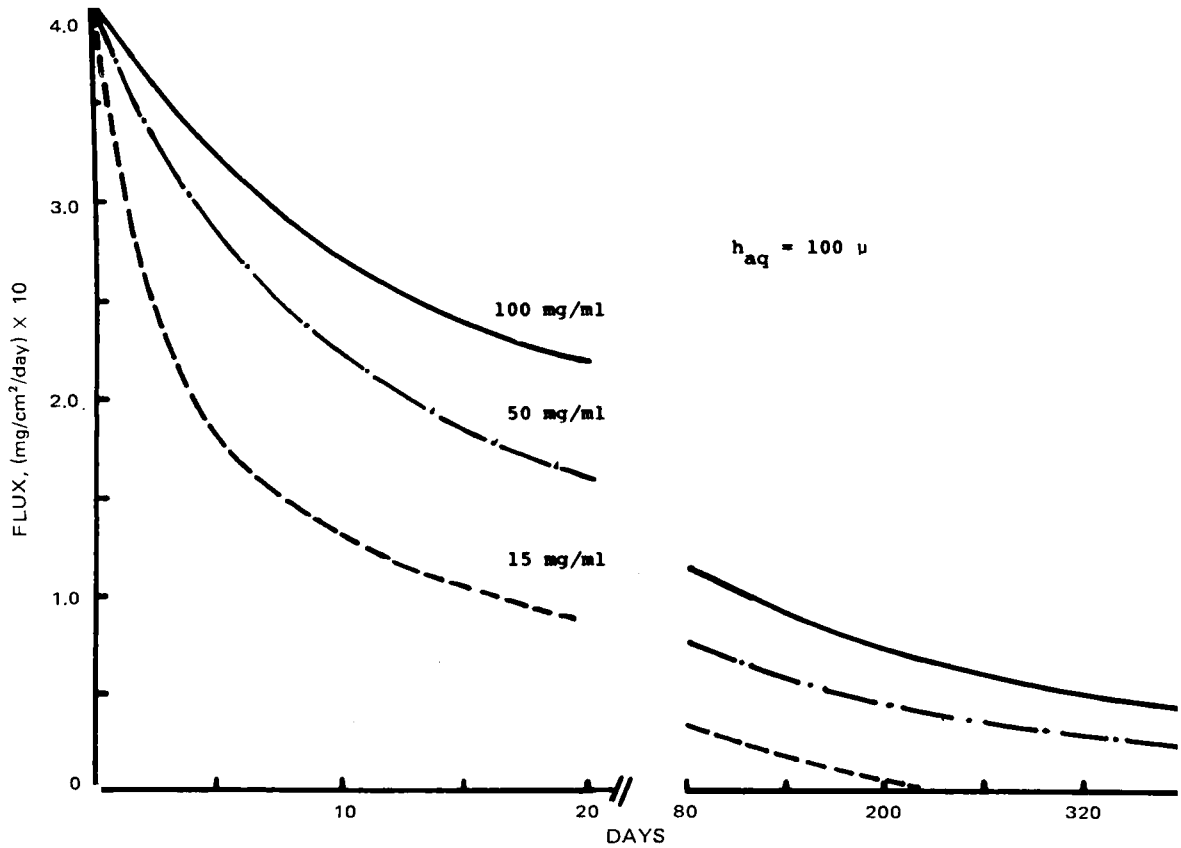



**Figure 3**—*Predicted flux of progesterone with time at various loading concentrations and 100-μm diffusion layer thickness.*

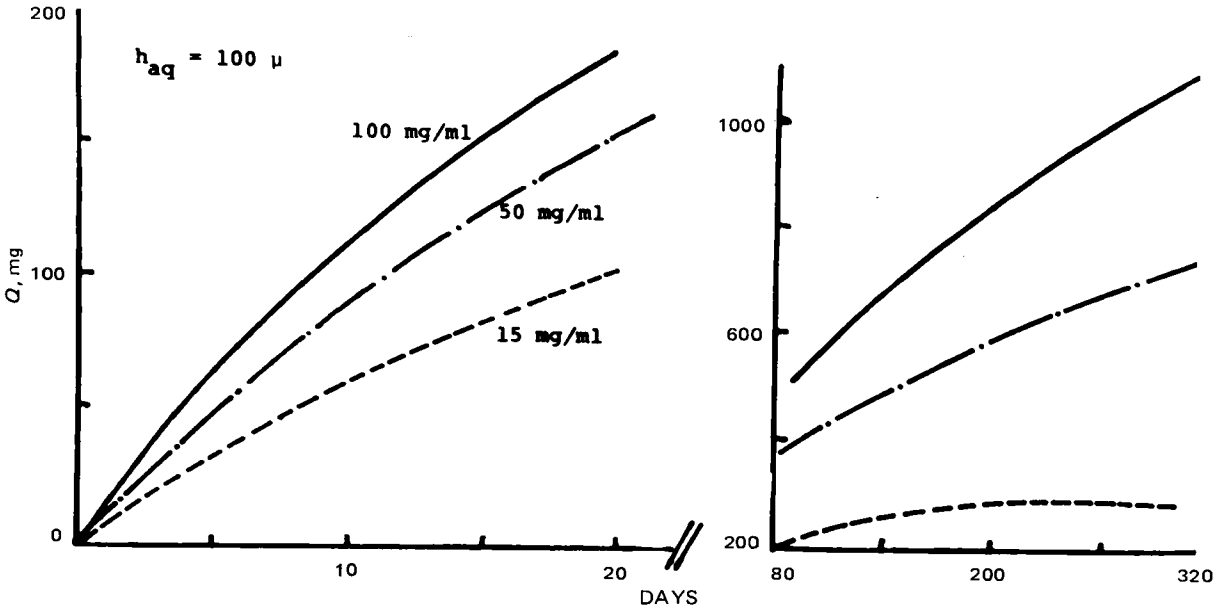



**Figure 4**—*Predicted total amount of progesterone released with time at various concentrations and 100-μm aqueous diffusion layer thickness.*

Taking Eqs. 18–20 together, one readily observes that the rate (or flux) changes from the non-matrix-controlled case to the matrix-controlled case with time as the resistance in the receding boundary increases.

## SIMULATION STUDIES

By using the preliminary results of the *in situ* vaginal absorption of the various steroids in the rabbit, the *in vitro* physicochemical characterization of the steroids with the silicone membrane, the *in vitro* release kinetic studies of steroids from the silicone matrix (3), and the theoretical physical model, the findings of these studies will now be integrated. Simulations of the simultaneous release of progesterone from a cylindrical poly(dimethyl siloxane) matrix and vaginal absorption will serve as the prototype in assessing the concurrent physicochemical roles of the membrane, aqueous diffusion, and receding boundary layers. Another steroid in these simulation studies is hydrocortisone. Table I gives the values of the physical parameters of progesterone and hydrocortisone and the silicone cylinder. The size of the cylinder is the same as the rib-cage cell used previously (1).

The predictions obtained here are being used in ongoing studies where the steroid release from a silicone matrix is interfaced with vaginal membrane absorption in the rabbit.

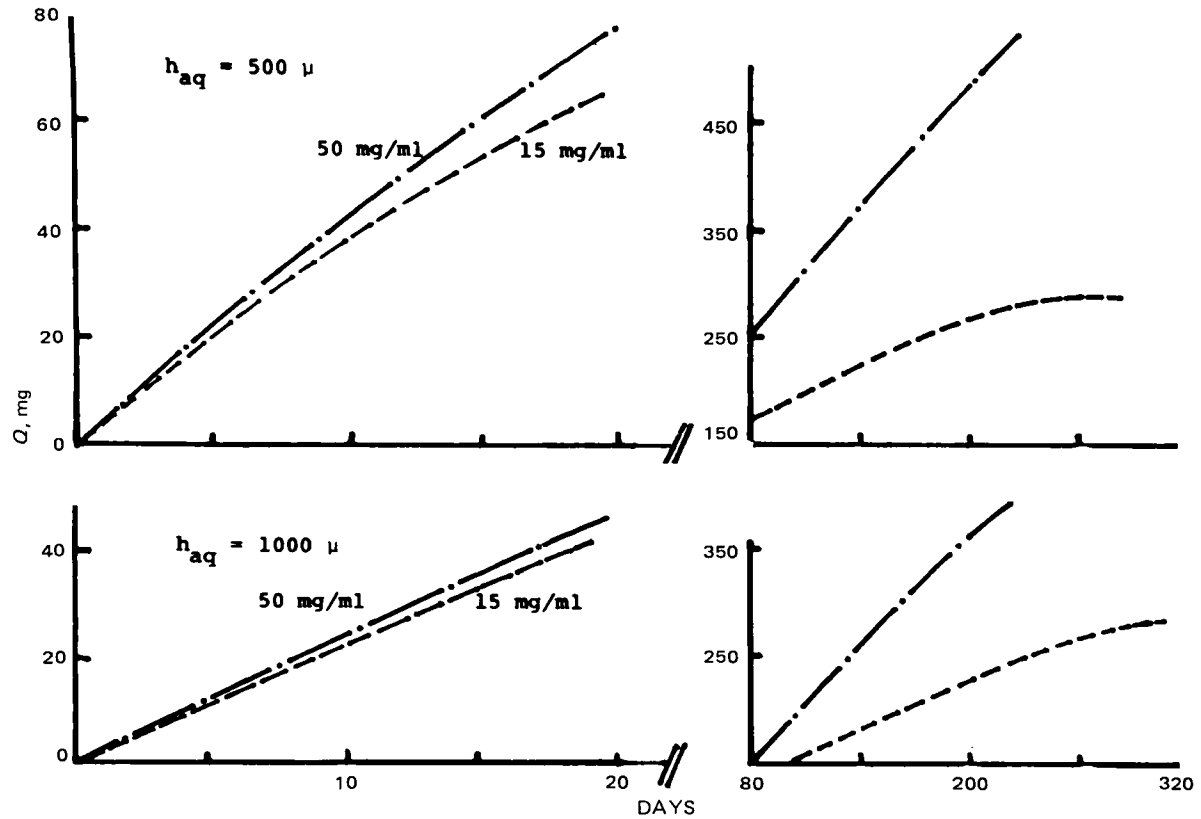



**Figure 5**—*Predicted total amount of progesterone released with time at various concentrations and aqueous diffusion layer thicknesses.*

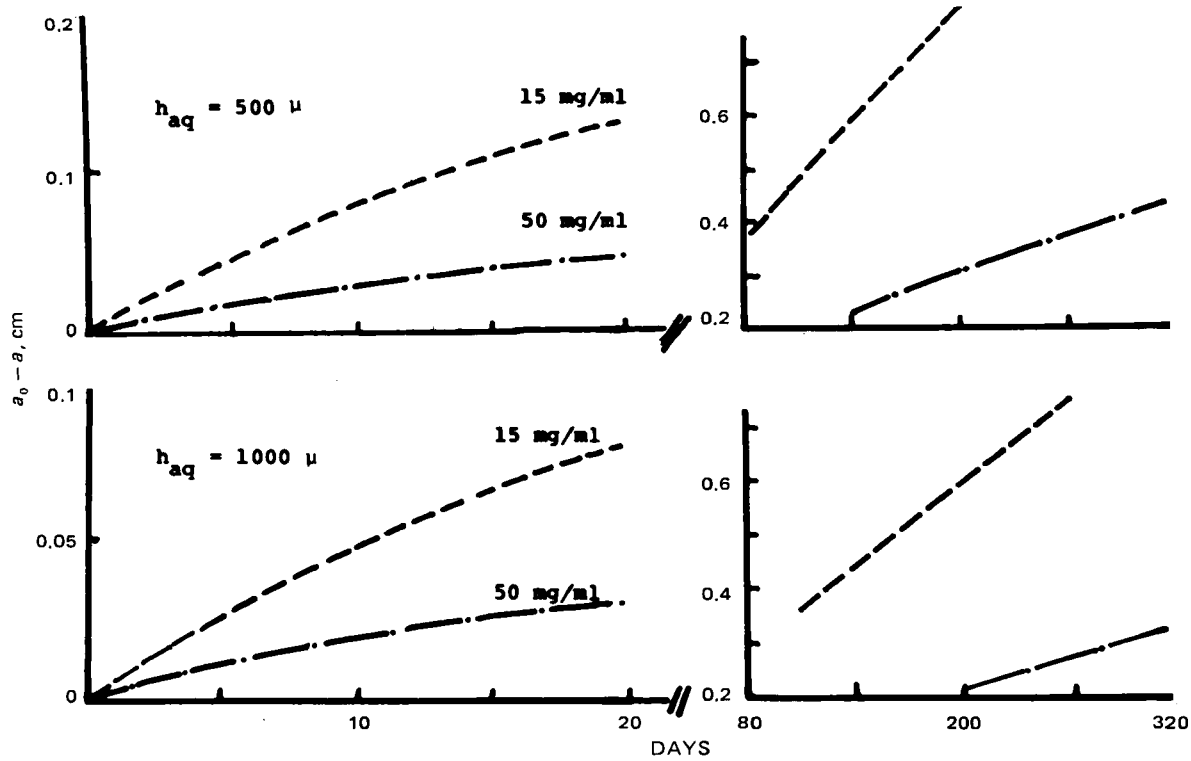



**Figure 6**—*Predicted change in receding boundary zone thickness with time at various concentrations of progesterone and diffusion layer thicknesses.*

**Simulation Studies with Progesterone**—The flux per unit area of the cylinder *versus* time profiles are shown in Figs. 2 and 3 for different aqueous diffusion layer thicknesses and initial concentrations of progesterone in the matrix. When the aqueous diffusion layer is 500–1000 μm thick (Fig. 2), the fluxes tend to be invariant with time for relatively long periods and then to decrease gradually with time. This time-independent characteristic is maintained longer when the aqueous layer between the cylinder and vaginal membrane is quite thick (1000 *versus* 500 μm) and the initial loading steroid concentration is also high (50 *versus* 15 mg/ml).

The mechanistic interpretation is that the rate in the first time period is determined by the aqueous diffusion layer barrier. The membrane resistance is a factor of 10 less than the diffusion layer resistance when the aqueous layer is 1000 μm thick and, similarly, a factor of 5 less when it is 500 μm thick. Also, the high loading concentrations tend to counterbalance the increasing resistance due to the receding boundary of drug in the cylindrical matrix with time by providing a sufficiently high effective concentration gradient in the matrix. At later times, the rate changes to the more matrix-controlled mechanism. It is significant that the rate in Fig. 2 remains fairly constant for about 6 months. Thus, one can expect the metering out of reasonably constant increments of drug in that period.

The early time profiles of Fig. 3 are in sharp contrast to those in Fig. 2. Here the aqueous diffusion layer thickness is 100 μm, which would be the likely situation when the progesterone–silicone cylinder is in snug fit with the membrane of the vaginal tract. The rate is essentially matrix controlled. Again, the effect of the loading concentration on the rate is observed. With the 100-mg/ml concentration, the early time periods are more influenced by the diffusion layer than they are at the lower concentrations. At low concentrations, the release of the

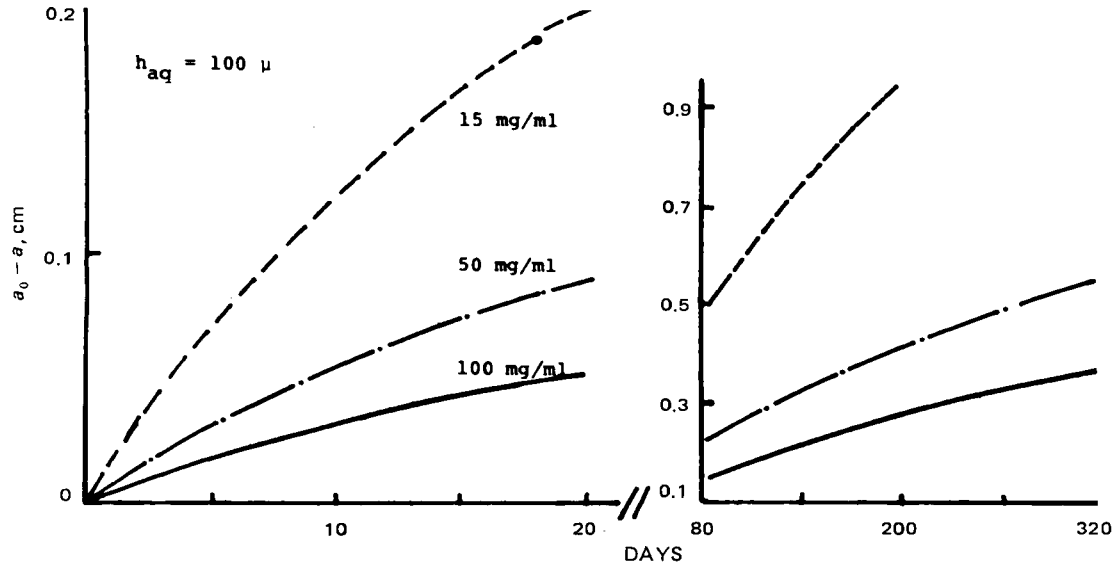



**Figure 7**—*Predicted change in receding boundary zone thickness with time at various loading concentrations of progesterone and 100-μm aqueous diffusion layer thickness.*

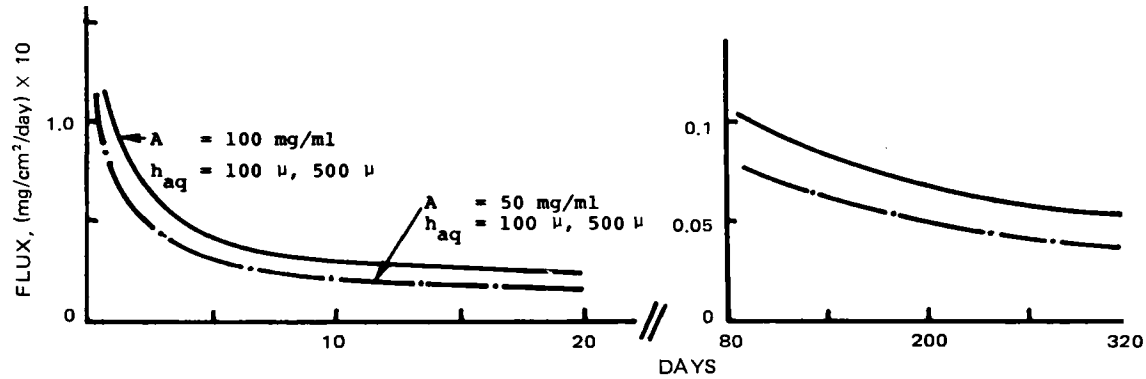



**Figure 8**—*Predicted fluxes of hydrocortisone with time at various loading concentrations and aqueous diffusion layer thicknesses.*

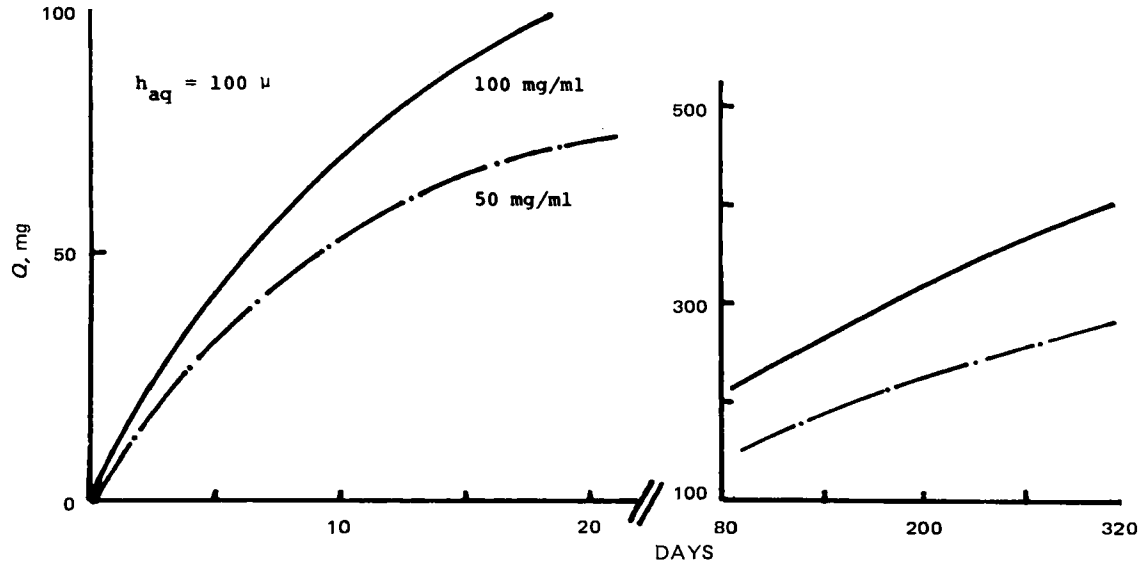



**Figure 9**—*Predicted total amount of hydrocortisone released with time at various loading concentrations and 100-μm aqueous diffusion layer thickness.*

steroid from the matrix is the predominantly rate-controlling factor once the cylinder is inserted into the vagina.

Figures 4 and 5 show the predicted total amounts of progesterone released from the cylinder (6 cm long and 2 cm diameter) as a function of time for various loading concentrations (15, 50, and 100 mg/ml) and aqueous diffusion layer thicknesses (100, 500, and 1000 μm). In the 500- and 1000-μm diffusion layer situations (Fig. 5), the initial slopes are unaffected by the loading concentrations since the transport kinetics are diffusion controlled. The initial rates are zero order as predicted in Eq. 19. Because the 15-mg/ml concentration cannot sustain the duration of the diffusion-controlled period as long as the 50-mg/ml concentration case, the slope monotonically decreases with

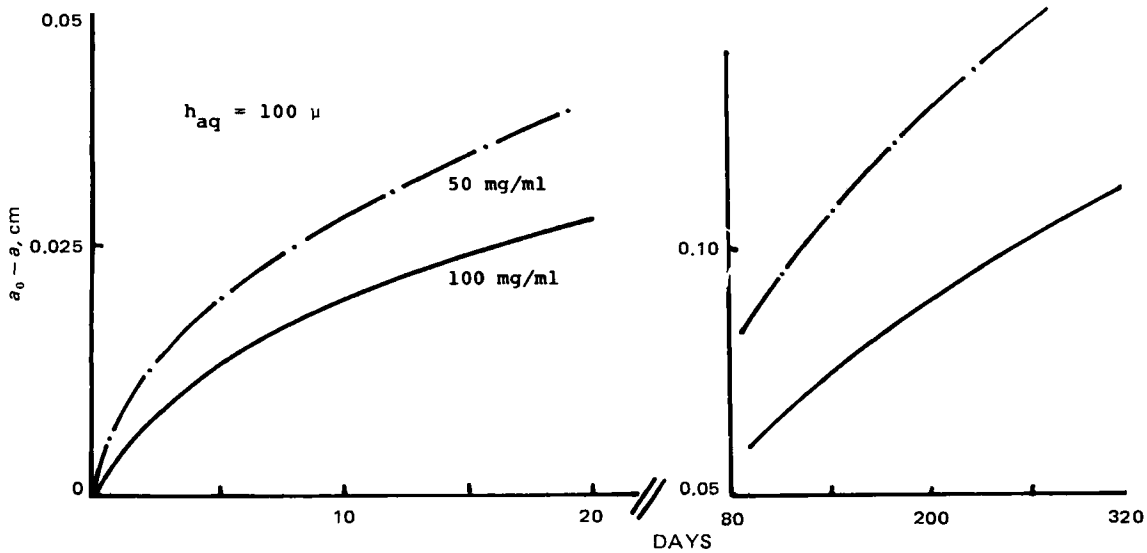
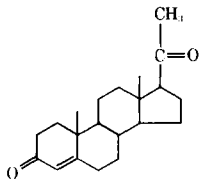
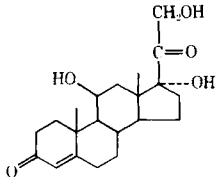



**Figure 10**—*Predicted change in the receding boundary zone thickness with time at various concentrations of hydrocortisone and 100-μm aqueous diffusion layer thickness.*

Table I—Values of Physical Parameters Used in the Simulation Studies Interfacing Steroid Release from Silicone Matrix with Vaginal Absorption in the Rabbit[a]

| Parameter | Progesterone[b] | Hydrocortisone |
|---|---|---|
| Structure |  |  |
| Solubility in matrix, $C_s$, mg/ml | 0.572 | 0.014 |
| Solubility in water, $C_{aq}$, mg/ml | 0.0114 | 0.28 |
| Diffusion coefficient in matrix, $D_e$, cm²/sec | $4.5 \times 10^{-7}$ | $4.5 \times 10^{-7}$ |
| Diffusion coefficient in water, $D_{aq}$, cm²/sec | $7 \times 10^{-6}$ | $7 \times 10^{-6}$ |
| Silicone–water partition coefficient, $K_s$ | 50.2 | 0.05[c] |
| Permeability coefficient[d] of rabbit vaginal membrane, $P_m$, cm/sec | $7 \times 10^{-4}$ | $5.8 \times 10^{-5}$ |
| $P_{aq}$ (when $h_{aq}$ = 100 μm) | $7 \times 10^{-4}$ | $7 \times 10^{-4}$ |
| $P_{aq}$ (when $h_{aq}$ = 1000 μm) | $0.7 \times 10^{-4}$ | $0.7 \times 10^{-4}$ |

[a] Other pertinent specifications were: silicone cylinder, 1.0-cm radius, 6.0-cm height; steroid concentrations, 15, 50, and 100 mg/ml; and aqueous diffusion layer, $10^{-2}$, $5 \times 10^{-2}$, and $10^{-1}$ cm. [b] Physical constants of progesterone in Silastic 382 such as $C_s$, $C_{aq}$, $D_e$, and $K_s$ were determined previously (3). [c] The $K_s$ value of hydrocortisone was determined with Silastic 382. [d] The $P_m$ values of progesterone and hydrocortisone were obtained from vaginal absorption studies (to be reported).

time until the total drug delivery capacity is depleted. The initial steroid concentration and size of the cylinder determine the drug capacity. The curves in Fig. 4 with the 100-μm diffusion layer are indicative of the situation where the transport mechanism is essentially matrix controlled at the onset. Other factors being constant, the total delivery capacity depends upon the loading concentration as expected; however, the total time taken to release the total amount of drug depends on both the concentration and transport mechanism.

The predicted changes in the receding boundary zone thickness with time at various progesterone concentrations and aqueous diffusion layer thicknesses are shown in Figs. 6 and 7. This zone of depleted drug would be translucent as compared to the opaque core of the drug–matrix suspension. According to Roseman and Higuchi (3), the measurement of this zone with time gives a rapid estimation of the amount of drug released with time. For a fixed diffusion layer thickness, the radial thickness of the zone increases more rapidly with time with the lower concentration. In general, the rate of change in zone thickness is rapid when the progesterone concentration is low and the diffusion layer is small.

**Simulation Studies with Hydrocortisone**—As can be seen in Fig. 8 by the rapid fall in the fluxes with time, the overall transport kinetics are mechanistically controlled by the release of hydrocortisone from the silicone cylinder at concentrations of 50 and 100 mg/ml and aqueous boundary layers of 100- and 500-μm thickness. From the 8th

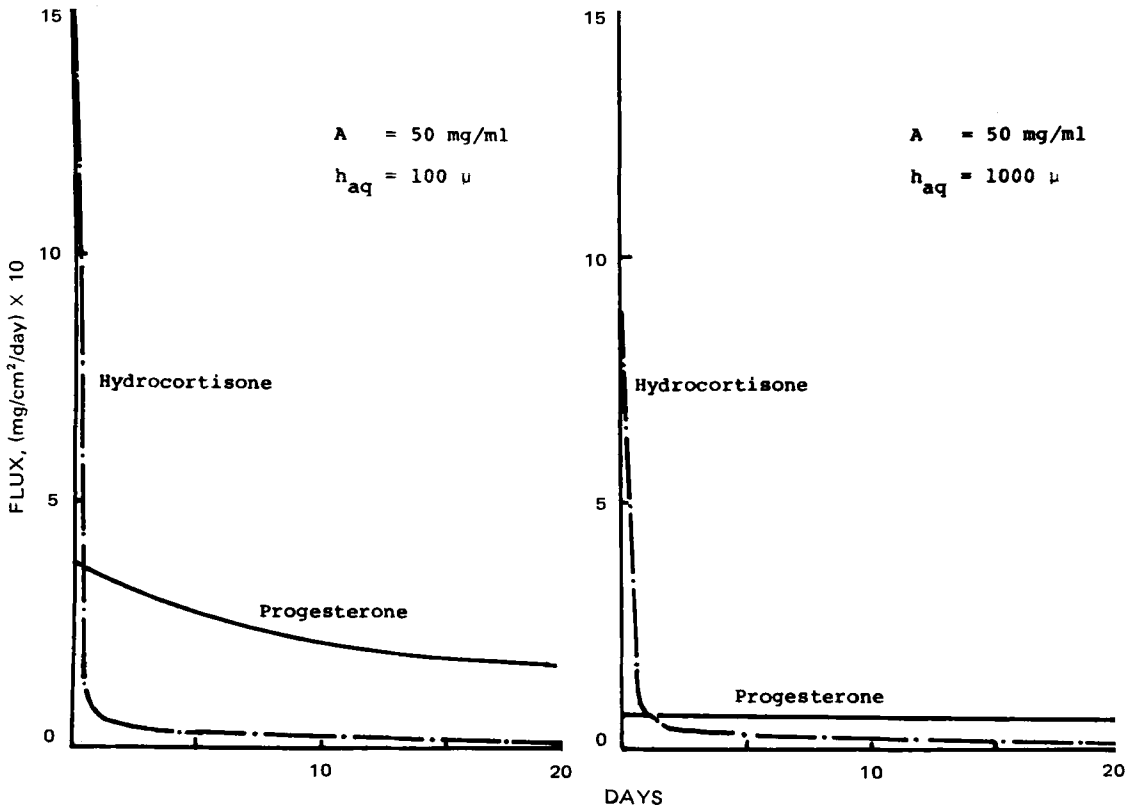



**Figure 11**—*Comparison of fluxes of progesterone and hydrocortisone with time.*

day, the fluxes decrease very slowly and, perhaps from a practical viewpoint, may be considered to be fairly constant between the 10th and 80th day.

For a given concentration of 50 or 100 mg/ml, the initial flux per unit area of the cylinder is $1.5 \times 10^{-1}$ for the 100-$\mu$m diffusion layer case and $1.15 \times 10^{-1}$ for the 500-$\mu$m layer case; however, the fluxes converge in 6 hr. The corresponding time changes in the total amount of drug released from the matrix and the receding boundary zone thickness are found in Figs. 9 and 1, respectively.

**Physical Significance between Progesterone and Hydrocortisone Simulation Studies**—A comparison between the progesterone and hydrocortisone simulation studies gives an interesting mechanistic insight into the transport processes involved. It is believed that these model simulations, which encompass the interactions among the drug delivery device, the vaginal membrane, and the aqueous diffusion layer between the device and membrane, are the first of their kind.

The flux per unit area of the cylinder *versus* time profiles in Fig. 11 typify the differences in the transport mechanisms of progesterone and hydrocortisone. The concentration is fixed at 50 mg/ml, but the diffusion layer thickness is varied from 100 to 1000 $\mu$m. The pertinent physically meaningful parameters of these steroids ($C_s$, $K_s$, $P_m$, and $P_{aq}$) are given in Table I.

Considering only the aqueous diffusion layer and the vaginal membrane, one finds that for progesterone the resistance[3] of the diffusion layer is equal to that of the membrane when the diffusion layer thickness ($h_{aq}$) is 100 $\mu$m and is 10-fold greater when $h_{aq}$ is 100 $\mu$m. Correspondingly, for the more polar hydrocortisone, the resistance of the diffusion layer is 12-fold less than that of the membrane when $h_{aq}$ is 100 $\mu$m and the resistances are about equal when $h_{aq}$ is 1000 $\mu$m. Thus, in general, the transport of progesterone across the aqueous and membrane layers tends to be more on the aqueous diffusion-controlled side and the transport of hydrocortisone is more membrane controlled.

When one now brings in the steroid–silicone device, the additional resistance in the matrix, which increases with the recession of the boundary with time and is in series with the aqueous layer and membrane resistances, must be considered. With the large matrix–aqueous partition coefficient, $K_s$, for progesterone, the change in the net flux with time is largely influenced by the aqueous diffusion layer in the first 20 days. In comparison with the small $K_s$ of 0.05 for hydrocortisone, the net flux changes quite rapidly with time from membrane control to matrix control.

In conclusion, the *in vivo* studies of progesterone-containing silicone vaginal devices in Rhesus monkeys (8) support the physical model simulations in this present paper. In particular, it was noted (8) that the amount of steroid released was independent of progesterone concentration in the silicone device at the high 10 and 30% dose levels (in other words, pseudo-zero-order release rates); these observations were compatible with the rate-controlling process being the diffusion of the steroid across the aqueous boundary layer and the vaginal membrane until the depleted layer in the matrix is large. In another *in vivo* situation involving the matrix release of medroxyprogesterone in the human female, Roseman and Higuchi (3) estimated the aqueous layer between the device and the vaginal membrane to be about 500 $\mu$m.

Studies are continuing in which the steroid–silicone matrix is interfaced *in situ* in the rabbit vagina to demonstrate the concept of the systems model approach to drug delivery in the vagina.

[3] The resistance is defined as the reciprocal of the permeability coefficient; hence, the resistances of the diffusion layer and membrane are $1/P_{aq}$ and $1/P_m$, respectively.

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# Systematic Identification of Drugs of Abuse II: TLC


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**Abstract** □ A limited number of spray reagents and solvent systems were selected or developed to separate and identify over 40 of the most commonly encountered drugs of abuse. A new reagent is reported, and new uses were developed for well-known reagents. A flowsheet for the systematic utilization of the spray reagents is given, and use of this sequence made it possible to identify systematically an unknown drug using only two to four TLC plates, providing that the drug was one of the compounds investigated. This TLC system also can be used to complement and confirm results obtained from spot tests.



**Keyphrases** □ Drugs of abuse—TLC identification, spray reagents and solvent systems selected and developed □ Abuse drugs—TLC identification, spray reagents and solvent systems selected and developed □ TLC—identification, drugs of abuse, spray reagents and solvent systems selected and developed


TLC is presently considered one of the most suited techniques for drug analysis. It is fast, requires minimal equipment, can be carried out using a minimal amount of sample, and provides highly reliable results (1).

TLC analysis with different solvent systems and different modes of detection presents a reinforced selectivity. The corroborative findings show that this technique, when properly performed, achieves effectual specificity. Thus, the multiple TLC identity test is considered equivalent in its relevancy, analytical power,