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Systems Approach to Vaginal Delivery of Drugs II: *In Situ* Vaginal Absorption of Unbranched Aliphatic Alcohols

S. HWANG, E. OWADA, T. YOTSUYANAGI, L. SUHARDJA, N. F. H. HO, G. L. FLYNN, and W. I. HIGUCHI [x]

Abstract □ The absorption of unbranched aliphatic alcohols in the rabbit vagina was studied using a perfusion method, and the absorption rates were found to be first order with respect to the drug concentration in the vagina from methanol to octanol. A physical model involving an aqueous diffusion layer in series with a membrane consisting of aqueous pores and lipoidal pathways was used for analyzing the data. The physically based parameters in the model were determined. An effective diffusion layer thickness ("unstirred layer") of around 0.035 cm was found. The increase in the permeability coefficient for the lipoidal pathway per methylene group was around 2.5 for this homologous series.

Keyphrases □ Drug delivery, vaginal—*in situ* absorption of unbranched aliphatic alcohols, rabbits □ Absorption, vaginal—unbranched aliphatic alcohols, rabbits □ Alcohols, unbranched aliphatic—vaginal absorption, rabbits □ Permeability—unbranched aliphatic alcohols, vaginal absorption, rabbits

The objectives of this investigation were: (*a*) to develop suitable methodology in an appropriate animal system and to obtain firm, baseline data on vaginal absorption; (*b*) to delineate the general barrier properties of the vaginal mucosa; and (*c*) to develop quantitative, integrated models describing both the release of drugs from vaginal devices and subsequent drug absorption.

A method was described previously (1) for evaluating drug absorption in the vagina, using the rabbit doe as a prototype animal. A rib-cage-type cell, which provides a closed absorptive compartment in the vaginal tract, was designed and surgically implanted in the rabbit. Drug absorption was determined by perfusing the drug solution through this system and following the time changes in drug concentration in the system. The study showed that the method generally affords good precision and should provide a sound basis for meeting the objectives of this research.

The present study employed this general perfusion technique and was concerned with the permeability behavior of a homologous series of unbranched aliphatic alcohols in the rabbit vaginal membrane. These compounds were expected to exhibit a systematic increase in the permeability coefficient with increasing carbon number, and a systems analysis of the resulting data was expected to define the operational barrier characteristics of the rabbit vaginal mucosa.

The method of data analysis essentially follows that delineated in previous studies on the human buccal membrane (2, 3), the rat intestinal membrane (4–7), and the silicone rubber membrane (8, 9).

An improved technique employing two simultaneously permeating species with different radiolabels (tritium and carbon-14) is introduced. By using one species as a control, the precision of the method is substantially improved. In addition, a GLC procedure was developed to investigate solutes that are not conveniently available with a radiolabel. Finally, a new cell with a magnetic stirrer was developed to manipulate the hydrodynamics within the absorption cell compartment independently of the hydrodynamics induced by the perfusate flow itself.

EXPERIMENTAL

Animals—Mature female rabbits (7–9 months old, New Zealand White) were used. Their body weights normally ranged from 3.5 to 5.0 kg. They were maintained in a temperature-controlled animal room (25°) with free access to water and a regular diet.

Materials—The homologous series of alcohols included methanol (^{3}H-methyl)[1], 1-^{14}C-1-propanol[1], 1-^{14}C-1-butanol[1], 1-pentanol[2], 1-^{14}C-1-hexanol, 1-heptanol[2], and 1-^{14}C-1-octanol[3]. They were used without further purification. Approximately 1.5 μCi of ^{14}C-labeled compound and 5 μCi of ^{3}H-labeled compound were used for each experiment. Pentanol and heptanol were studied at a concentration of 2–3 m*M*.

Perfusion System—The perfusion system basically consisted of an outside solution reservoir and the rib-cage cell surgically implanted in the vaginal tract. The entire perfusion path was made of glass tubing and stainless steel material except the short portion [about 2.54 cm (1 in.) polyethylene tube] between the rib-cage cell and the fenestra rotunda. The vaginal membrane was in direct contact with the drug solution in the rib-cage cell.

Because preliminary studies showed that solute losses to the perfusion system could become serious, especially for the higher alcohols, special measures were taken to eliminate this problem. All surfaces including the reservoir were coated with a silicone solution[4] to prevent solute binding onto the parts of the system. The carbon-lined cylinder on the pump[5] was replaced by a stainless steel cylinder.

As previously described, the rib-cage provided an interior volume of 8.1 cm^3 and a geometrical surface area of 22.5 cm^2. It was inserted through the wall of the upper part of the vaginal tract after an appropriate incision.

Also, to minimize solute losses, all exposed Teflon surfaces in the rib-cage cell were covered with stainless steel sheeting. With all of the described measures, solute losses were reduced to a negligible level for all tested steroids and for all alcohols up to octanol.

Rib-Cage with Magnetic Stirring Bar—To assess the importance of the diffusion layer, a cell with a magnetic stirring bar (about 1 cm long) was designed to manipulate the hydrodynamics within the absorption cell compartment. The stirring bar was coated with gold by vacuum deposition. A hole was drilled perpendicular to the axis of the stirring bar, and the bar was mounted to rotate about the inlet center tube as the axis when a magnetic stirrer (300 rpm) was positioned appropriately (1–2 cm) above the rabbit abdomen.

Because of the unreliable performance of the stirring bar when the experiments were conducted more than 1 day after the rib-cage cell implantation, all stirring experiments were carried out on the same day of the surgery.

Absorption Studies—The absorption experiments were carried out in a manner described previously (1), except for a dual-solute transport modification. Experiments were scheduled on 5 successive days beginning 2 days after the surgical implantation of the rib-cage cell. On each day, two successive experiments were conducted with each rabbit. The rabbit was first anesthetized with pentobarbital sodium, 25 mg/kg, and the perfusion system was connected through the fenestra rotunda. The vaginal tract was then washed with normal saline solution for about 5 min at 35 ml/min and then for an additional 2 min with the buffer solution to be used in the experiment.

The buffer used was pH 6.0, 0.1 *M* phosphate buffer with isotonic sodium chloride. All absorption experiments were conducted with a perfusion flow rate of 35 ml/min at 37°.

To improve the precision of the results, a reference compound, usually methanol (^{3}H-methyl), was employed in all runs with ^{14}C-labeled compounds. An aliquot of the tritiated methanol was introduced simultaneously with the ^{14}C-labeled alcohol into the reservoir at time zero. Samples were removed periodically and analyzed for both activities with a liquid scintillation counter[6] employing a dioxane cocktail[7].

GLC Analysis of Pentanol and Heptanol—GLC measurements were made with a gas chromatograph[8] equipped with a hydrogen flame-ionization detector and an electronic integrator. A coiled stainless steel column (0.9 m × 2 mm i.d.) of 80–100-mesh Porapak Q[9] was used.

During analysis, the column, the injection port, and the detector block were maintained isothermally at 230, 260, and 300°, respectively. Nitrogen was used as the carrier gas at 25 ml/min. Under these conditions, butanol, pentanol, and heptanol had retention times of 0.9, 1.7, and 5.3 min, respectively. Butanol was used as an internal standard for the analysis of pentanol and heptanol.

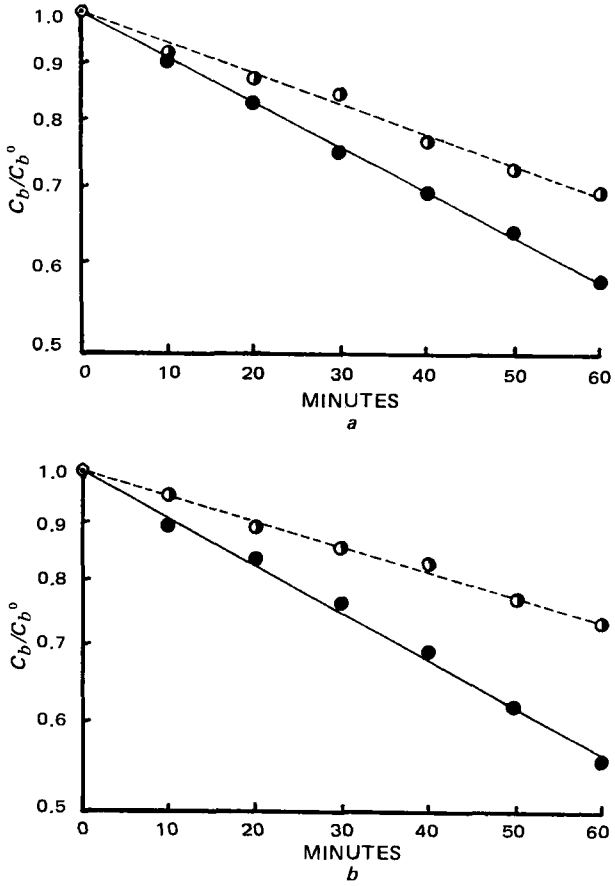

Figure 1—*Typical results for the vaginal absorption of the alcohols using the dual permeant technique. Key (for* a*):* ◑, *methanol; and* ●, *hexanol. Key (for* b*):* ◑, *methanol; and* ●, *octanol.*

RESULTS AND DISCUSSION

Absorption Experiments with Alcohols—The absorption data were treated as previously described (1) using:

$$\frac{dC_b}{dt} = -K_u C_b \qquad \text{(Eq. 1)}$$

$$K_u = P_{app}\left(\frac{A}{V}\right) \qquad \text{(Eq. 2)}$$

where C_b is the concentration of the drug in the bulk solution, K_u is the first-order rate constant, A is the geometrical surface area of the vaginal tract, V is the volume of the perfusion solution, and P_{app} is the apparent permeability coefficient of the membrane.

Without exception, the log (C_b/C_b^0) (where C_b^0 is the zero-time concentration) *versus* time plots of the data were linear with all of the alcohols as was found previously with butanol (Fig. 1). The P_{app} values were computed from the K_u values taken from the slopes of the plots using A = 22.5 cm^2 and V = 34 ml.

Tables I–IV summarize the results of all experiments with the ^{14}C-labeled alcohols. The data also show the value of having the reference solute, methanol, run simultaneously with the alcohol. Although the standard deviation of the absolute P_{app} varied from 14 to 28%, the standard deviation of the ratio, $R = P_{app}/P_{app}$ (methanol), was much less (5–8%).

[1] New England Nuclear Corp., Boston, Mass.
[2] Analytical standard, provided by PolyScience Corp., Niles, Ill.
[3] International Chemical and Nuclear Corp., Irvine, Calif.
[4] Siliclad, Clay Adams, Parsippany, N.J.
[5] FMI lab pump, model RRP 2G 150, Fluid Metering Inc., Oyster Bay, N.Y.
[6] Beckman LS 200.
[7] 2,5-Diphenyloxazole, 6 g; naphthalene, 100 g; and dioxane *qs*, 1000 ml.
[8] Model 5830A, Hewlett-Packard, Avondale, Pa.
[9] Alltech Associates, Inc., Arlington Heights, Ill.

Table I—Apparent Permeability Coefficients for 1-Propanol and Methanol in the Rabbit Vagina at pH 6 (37°)[a]

	$P_{app} \times 10^4$, cm/sec		Propanol/ Methanol
	Methanol	Propanol	
	1.32	1.52	1.15
	1.48	1.42	0.962
	1.74	2.05	1.17
	1.40	1.44	1.03
	1.06	1.18	1.12
	1.03	1.23	1.19
	1.21	1.36	1.13
Mean	1.32	1.46	1.11
SD	0.249	0.287	0.082

[a] Three rabbits were used.

Pentanol and heptanol were studied using GLC after all ^{14}C-labeled alcohol experiments were completed. Methanol was included in the schedule of every rabbit. However, simultaneous methanol–pentanol or methanol–heptanol two-solute runs were not carried out with the GLC procedure. The mean P_{app} values for each rabbit were used for the ratio calculation (Table V). Octanol was also run in these three rabbits so that there would be a common solute between the two groups. The good agreement between the octanol–methanol ratio in Table IV and that in Table V indicates that the results in Table V may be compared to the previous results (Tables I–IV).

Figure 2 is a plot of the mean ratio (R) as a function of the carbon number for the alcohols up to octanol. The data in Fig. 2 possess a strong resemblance to the alcohol absorption data obtained with the rat intestine (jejunum) previously reported (7). Both in the present experiments and in the rat intestine studies, the P_{app} showed little or no chain length effect at the low carbon numbers (≤3). Then, from butanol, the P_{app} began to increase rapidly up to octanol. At octanol, the ratio in the rat intestine studies ranged between 2.0 and 2.8, depending upon the hydrodynamics.

In the present study with the rabbit vagina, P_{app} (octanol)/P_{app} (methanol) approximately equaled 2.0. Beyond octanol, the P_{app} values plateaued in the rat intestine studies. The alcohol data beyond octanol for the present study with the rabbit vagina are not reported because of significant solute loss to the perfusion system. Experiments with decanol in the rabbit vagina indicated, however, that P_{app} may plateau around decanol. Therefore, the parallel behavior appears to be total for these two biological systems.

A physical model was reported (6) for the rat intestine data based upon a composite barrier comprised of an aqueous diffusion layer in series with a membrane having two parallel pathways for solute transport, a lipoidal pathway and an aqueous pore pathway. This model has been remarkably successful in treating the rat jejunum data. It is proposed that this same physical model may apply to alcohol absorption in the rabbit vagina.

Demonstration of Existence of Diffusion Layer by Additional Stirring in Rib-Cage Cell—Uptake experiments of ^{14}C-octanol–^{3}H-methanol with magnetic stirring (with 35-ml/min flow) were carried out on the same day after surgical implantation of the cell. Four runs—with or without stirring—were carried out with each of four rabbits (Table VI). The variation in the results was much greater than when the experiments were conducted 2 or more days after surgery (Tables I–IV). The effect of stirring was to increase the R(octanol) ratio by about 10%. A statistical analysis of the data showed this difference to be significant.

Table II—Apparent Permeability Coefficients for 1-Butanol and Methanol in the Rabbit Vagina at pH 6 (37°)[a]

	$P_{app} \times 10^4$, cm/sec		Butanol/ Methanol
	Methanol	Butanol	
	2.02	2.16	1.07
	2.03	2.13	1.05
	1.52	1.73	1.13
	1.34	1.62	1.21
	1.74	2.08	1.20
	1.44	1.65	1.14
	1.51	1.65	1.09
Mean	1.66	1.86	1.13
SD	0.279	0.250	0.062

[a] Four rabbits were used.

Table III—Apparent Permeability Coefficients for 1-Hexanol and Methanol in the Rabbit Vagina at pH 6 (37°)[a]

	$P_{app} \times 10^4$, cm/sec		Hexanol/ Methanol
	Methanol	Hexanol	
	2.64	3.71	1.41
	1.89	2.88	1.52
	1.83	2.65	1.45
	1.25	1.61	1.29
	1.53	2.55	1.67
	1.53	2.55	1.67
	1.33	2.08	1.56
Mean	1.71	2.53	1.48
SD	0.471	0.666	0.120

[a] Three rabbits were used.

Proposed Physical Model and Analysis of Alcohol Data—Figure 3 illustrates the proposed model in which there is an aqueous diffusion layer[10] on the lumen side in series with the membrane, consisting of parallel lipoidal and aqueous pore pathways for passive diffusion of the solutes. Immediately beyond the membrane, there is a perfect sink (serosal). The appropriate equation expressing P_{app} for this situation is (7):

$$P_{app} = \frac{1}{\frac{1}{P_{aq}} + \frac{1}{P_p + P_l}} \qquad \text{(Eq. 3)}$$

where P_{aq} is the permeability coefficient of the diffusion layer, P_p is the permeability coefficient of the pore pathway, and P_l is the permeability coefficient of the lipoidal pathway.

Following the concept of the incremental partition coefficient (2, 3):

$$P_l = P_l^0 \times 10^{\pi n} \qquad \text{(Eq. 4)}$$

where P_l^0 is the permeability coefficient of the lipoidal pathway for the hypothetical solute of zero carbon number, n is the carbon number, and π is the logarithm of the incremental constant.

Although the permeability coefficient for the aqueous pore, P_p, might be expected to be a function of the molecular size and/or aqueous diffusivity (7) for a given homologous series, it will be as-

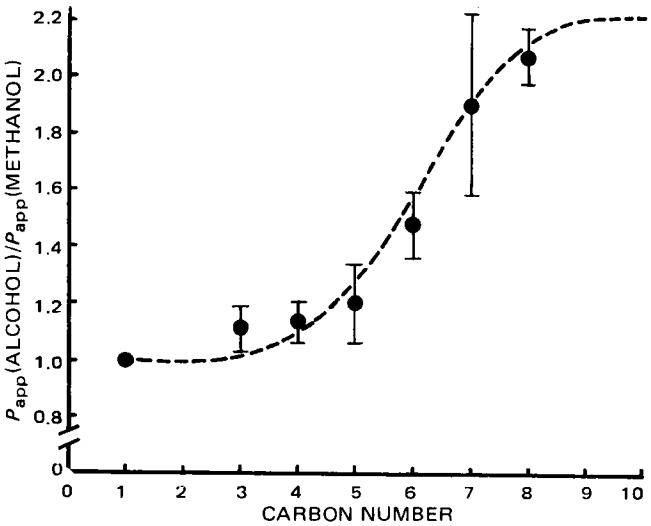

Figure 2—*Effect of carbon number on the normalized permeability coefficient,* $P_{app}(alcohol)/P_{app}(methanol)$, *at pH 6 (37°). Bar indicates mean ± SD.*

[10] The diffusion layer is an effective diffusion layer. In fact, both convective and molecular diffusive components should contribute to the transport (10).

Table IV—Apparent Permeability Coefficients for 1-Octanol and Methanol in the Rabbit Vagina at pH 6 (37°)[a]

	$P_{app} \times 10^4$, cm/sec		
	Methanol	Octanol	Octanol/ Methanol
	1.59	3.33	2.09
	1.64	3.48	2.12
	1.65	3.52	2.13
	1.38	2.92	2.12
	1.36	2.68	1.97
	1.23	2.39	1.94
	1.16	2.56	2.21
Mean	1.43	2.98	2.08
SD	0.199	0.462	0.095

[a] Three rabbits were used.

sumed to be a constant for the alcohols. The consequence of assuming P_p proportional to the aqueous diffusivity will be examined later.

The permeability coefficient of the aqueous diffusion layer, P_{aq}, will be assumed to be described by:

$$P_{aq}(n) = \frac{D_{aq}(n)}{h} \qquad \text{(Eq. 5)}$$

where $D_{aq}(n)$ is the aqueous diffusion coefficient for the alcohol of carbon number n, and h is diffusion layer thickness. The consequence of assuming P_{aq} to be proportional to the two-thirds power[11] instead of the first power of D_{aq} will be examined later. The Stokes–Einstein relationship, $D_{aq} \propto 1/(\text{molar volume})^{1/3}$ will be used to account for the n-dependence of D_{aq}.

With these considerations, Eq. 3 may be written:

$$P_{app} = \frac{1}{\left(\frac{MV}{91.5}\right)^{1/3} \frac{h}{D_{aq}(\text{butanol})} + \frac{1}{P_p + P_l^0 \times 10^{\pi n}}} \qquad \text{(Eq. 6)}$$

where MV is the molar volume of the alcohol in question (molecular weight divided by density), and 91.5 is the molar volume of butanol. The diffusivity for butanol, D_{aq}(butanol), was taken to be 1.42×10^{-5} cm²/sec as reported previously (11).

A best fit theoretical curve of $R[P_{app}/P_{app}(\text{methanol})]$ *versus* n was deduced using Eq. 6 and varying the parameters P_p, P_l^0, π, and h. A P_{app} value for methanol of $1.41 \pm 0.26 \times 10^{-4}$ cm/sec was used, based on experiments involving 13 rabbits. The best fit curve is shown in Fig. 2 and the following "best" parameter values were used: $P_p = 1.9 \times 10^{-4}$ cm/sec, $P_l^0 = 1.5 \times 10^{-6}$ cm/sec, $\pi = 0.40$, and $h = 0.035$ cm.

An analysis of the results given in Fig. 2 showed that the goodness of fit of the theoretical curve with the experimental data was rather

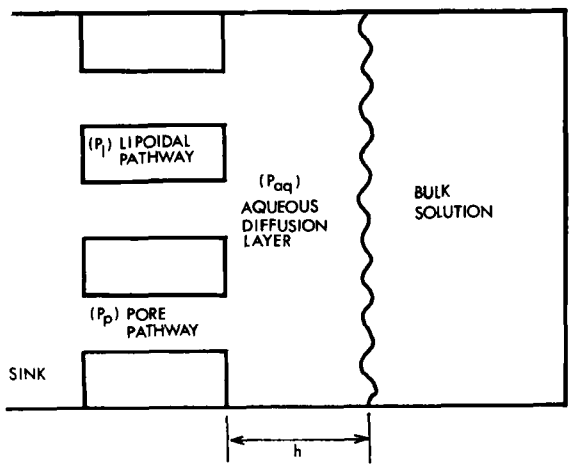

Figure 3—*Schematic model of the vaginal membrane as a transport barrier. Aqueous diffusion layer is in series with the membrane consisting of parallel lipoidal and aqueous pore pathways.*

[11] A D_{aq} two-thirds power dependence may be more appropriate if convection as well as molecular diffusion is taken into account.

Table V—Normalized Permeability Coefficients, P_{app} (Compound)/P_{app} (Methanol), for Pentanol, Heptanol, Octanol, and Hexanoic Acid

Compound	pH	P_{app}(Compound)/ P_{app}(Methanol)[a]
Hexanoic acid	3	2.29 ± 0.71
Octanol	6	2.15 ± 0.61
Heptanol	6	1.91 ± 0.32
Pentanol	6	1.20 ± 0.14

[a] Mean ± *SD* from three rabbits.

Table VI—Effect of Stirring on Octanol Absorption in the Rabbit Vagina

Rabbit	Experimental Order[a]	Ratio of P_{app} (Octanol/Methanol) NS	S
98	S–NS	1.98	2.43
	NS–S	1.90	1.92
99	NS–S	1.83	1.98
	S–NS	1.69	2.00
103	S–NS	2.33	2.74
	NS–S	2.73	2.90
104	NS–S	2.76	2.90
	S–NS	2.50	2.83
	Mean ± *SE*	2.22 ± 0.149	2.46 ± 0.155[b]

[a] NS = nonstirring condition; S = stirring condition. [b] Significantly different from NS, $p < 0.01$ (paired t-test).

sensitive to the P_p, P_l^0, and π values and somewhat insensitive to the choice of h. Interestingly, each of the four parameters dominated in different regions of the curve. Therefore, other combinations of P_p, π, and P_l^0 that are significantly different from this set do not yield good fitting curves.

That the h value of 0.035 cm is reasonably good was confirmed by the hexanoic acid data. Another experiment[12] showed that hexanoic acid absorption at pH 3 was nearly completely aqueous diffusion controlled, *i.e.*, nearly completely determined by the P_{aq} (or D_{aq}/h) term. This finding would correspond to an expected R value of around 2.6. The R value actually found for hexanoic acid in the present experiments (Table V) was 2.29 ± 0.71, in good agreement with $h = 0.035$ cm.

Further Examination of Proposed Model—Two variations in the method of data treatment were considered. First, to assess the possible influence of convective transport, a two-thirds power dependence of D_{aq} for P_{aq} (instead of Eq. 5) was investigated. In this case, the best curve based on Eq. 6 gave a somewhat smaller dip at the lower end of the curve in Fig. 2, but the best fitting value of π deduced for this situation was not significantly different from the one obtained from the original model.

The second modification assumed P_p to be proportional to D_{aq}. This modification made the dip at ethanol deeper and wider. However, the best π value was not significantly altered.

Both this latter analysis and that based upon Eq. 6 (Fig. 2) indicate that the behavior of the alcohols at the lower carbon numbers, *i.e.*, methanol, propanol, and butanol, is not in complete quantitative accord with the simple model (Fig. 3). Such a deviation from the model predications would suggest at least two possibilities. First, the effective aqueous pores may not be truly "aqueous" but somewhat semipolar in character and may have an associated modest π value. Second, an effective third parallel pathway with a modest π value for alcohol transport may exist.

Both of these modifications would tend to influence somewhat the interpretation of the transport data for the lower alcohols but would have relatively little influence upon that for the higher alcohols that are dominated by the principal lipoidal pathway and the aqueous diffusion layer.

In conclusion, the simple two-phase model works well in describing

[12] S. Hwang, E. Owada, L. Suhardja, N. F. H. Ho, G. L. Flynn, and W. I. Higuchi, to be published.

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