(25.55 kcal/mol) is rather high, the degradation of flurogestone acetate (in vaginal fluid) could be the result of a solvolytic process, which generally has an energy of activation in the range of 10–30 kcal/mol (6). The higher the value of $E_a$, the greater the thermal stability of the drug.

## CONCLUSIONS

The HPLC method developed is specific and allows a good separation of flurogestone acetate from its degradation products. The degradation is both acid- and base-catalyzed, but is much slower in the simulated vaginal fluid (pH 7.3). Thermodynamic studies indicate that the degradation in simulated vaginal fluid is very slow, as it requires a fairly high energy of activation (25.55 kcal/mol).

This assay should be suitable for determination of the release kinetics of flurogestone acetate from the vaginal sponges and its absorption rate through the vaginal wall. Since it is also a stability-indicating method, the metabolism of flurogestone acetate, if any, in the simulated vaginal fluid or vaginal mucosa could be detected (9).

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# Intravaginal Controlled Administration of Flurogestone Acetate II: Development of an *In Vitro* System for Studying the Intravaginal Release and Permeation of Flurogestone Acetate


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Received October 3, 1983, from the *Controlled Drug Delivery Research Center, College of Pharmacy, Rutgers–The State University of New Jersey, Piscataway, NJ 08854.* Accepted for publication November 30, 1983.



**Abstract** □ A relatively simple and easily constructed *in vitro* system was developed for studying the mechanism of release and intravaginal absorption of flurogestone acetate from vaginal sponges. The stability-indicating high-performance liquid chromatographic method developed earlier was used to provide a rapid, reproducible, and sensitive assay. The *in vitro* intravaginal release/permeation system developed was capable of determining the rate of flurogestone acetate release from vaginal sponges and, simultaneously, the rate of absorption through the vaginal wall. The design, calibration, and applicability of the system, and the release and absorption profiles of the drug from vaginal sponges in this system are discussed.



**Keyphrases** □ Drug release—flurogestone acetate, intravaginal, sheep □ Flurogestone acetate—intravaginal release and permeation measurement *in vitro* □ Intravaginal administration—flurogestone acetate, sheep


In 1975, the use of flurogestone acetate-releasing vaginal sponges (Fig. 1) to replace the conventional daily injection of progesterone for estrus synchronization in sheep was introduced (1). On intravaginal administration, the polyurethane sponges release the drug continuously for 15 d, this suppresses estrus and ovulation. Two to four days after removal of the sponges, the sheep reenter estrus and ovulate. During this period, artificial insemination can be performed at a predetermined schedule to promote a specific breeding program (2).

Knowledge of the pattern and rate of drug release is essential for an understanding of the action of flurogestone acetate-impregnated sponges in the vagina (3). Development of a suitable *in vitro* drug release/permeation system is essential to understand the mechanisms of drug release and permeation under *in vivo* conditions (4). Currently, the release profiles are determined by extracting the residual drug content in the vaginal sponges and then assaying it by GC (2) or by radioactivity count (5). However, these *in situ* experiments require the use of large numbers of animals over an extended period of time. Also, the lack of assay sensitivity can jeopardize the

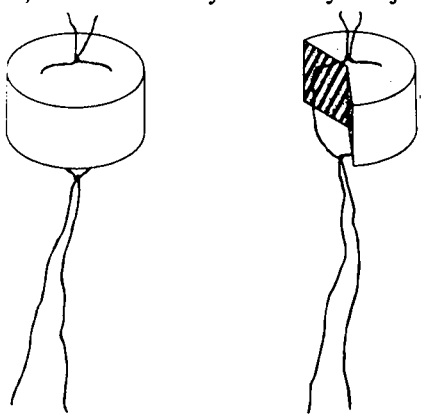

**Figure 1**—*Diagrammatic illustration of the flurogestone acetate-releasing vaginal sponges*[1].

[1] Synchro-Mate Pessary; G. D. Searle and Co., Chicago, Ill.




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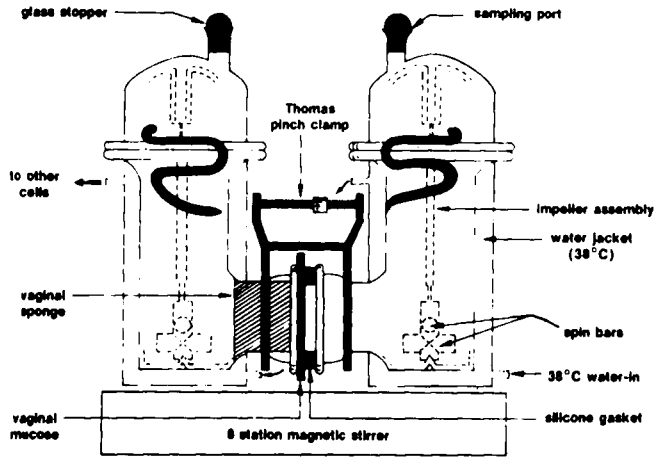


**Figure 2**—*Intravaginal release/permeation system designed to measure the* in vitro *release of flurogestone acetate from vaginal sponges and vaginal absorption profiles from various solutions of flurogestone acetate.*

accurate determination of the kinetics of the drug-release profile. One prime concern in making release/permeability measurements is determining the rates reliably and in as short a time as possible. The development of such a technique could also make possible the direct measurement of the drug-release flux (6).

With these considerations in mind, a relatively simple and easily constructed *in vitro* intravaginal drug release/permeation system was designed. In conjunction with the HPLC method (7), a reproducible technique for determining the drug release kinetics was developed. The release rates of flurogestone acetate from the vaginal sponges and the permeation rates of the drug through the vaginal mucosa were investigated.

## EXPERIMENTAL SECTION

**Materials**—All chemicals and reagents were analytical grade unless otherwise indicated. Flurogestone acetate[2], testosterone[3], anhydrous dibasic sodium phosphate[4], anhydrous citric acid[4], polyethylene glycol 400 (laboratory grade)[4], and glass-distilled methanol[5] were used as received. Freshly prepared deionized water[6] was used throughout the study.

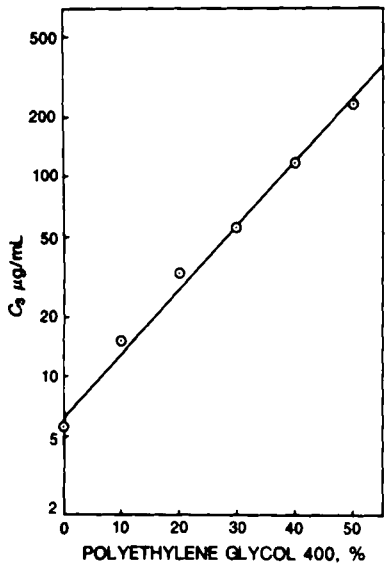


**Figure 3**—*Exponential relationship between solution solubility ($C_s$) and the volume fraction (% v/v) of the polyethylene glycol 400 in the simulated vaginal fluid at 38°C.*

[2] Searle Laboratories, Skokie, Ill.
[3] Sigma Chemical Co., St. Louis, Mo.
[4] Fisher Scientific, Fair Lawn, N.J.

**Table I—Composition of Elution Media [a] Containing Various Volume Fractions of Polyethylene Glycol 400 in Simulated Vaginal Fluid**

| Polyethylene Glycol 400 Conc., % v/v | 0.02 M Citric Acid, mL | 0.04 M $Na_2HPO_4$, mL | Polyethylene Glycol 400 Volume, mL |
|---|---|---|---|
| 0 | 95 | 405 | 0 |
| 10 | 100 | 400 | 100 |
| 20 | 135 | 365 | 200 |
| 30 | 170 | 330 | 300 |
| 40 | 200 | 300 | 400 |
| 50 | 235 | 265 | 500 |

[a] The final volume was made up to 1000 mL with distilled water; pH = 7.3.

**Drug Release/Permeation System**—The system[7] developed for studying the pattern of drug release/permeation is shown schematically in Fig. 2. Each of the donor and receptor cells holds up to 1 L of elution medium which is thermostated at 38°C (the vaginal temperature of the sheep) by a circulating water bath[8]. The impeller assembly can be rotated at a constant speed (30–400 rpm) by a six-station heavy-duty magnetic stirrer (42 × 44 × 12 cm). All six diffusion cells (three pairs) are operated simultaneously at the same speed by a single control.

**High-Performance Liquid Chromatography**—A chromatograph equipped with a reciprocating-piston pump[9], injector[10], UV detector (at 254 nm)[11], and a strip-chart recorder[12] (1–10 mV) was employed in conjunction with a 5-µm (3.9 mm × 15 cm) $C_{18}$ column[13] for separation. The operating conditions of the HPLC method (7) were slightly modified. A less-polar mobile phase of the methanol–water (65:35) was used. The column and solvent were maintained at ambient temperature. At a solvent flow rate of 1 mL/min, the retention times for flurogestone acetate and testosterone (internal standard) were reduced to ~4 and ~8 min, respectively, to facilitate the assay procedure.

**Drug Delivery Device**—The vaginal sponges, each containing 40 mg of flurogestone acetate, were commercially available[14]. Each polyurethane sponge was loaded (with hypodermic syringes) with 2 mL of solution containing 20 mg/mL of the drug in acetone–absolute ethanol (1:4). The sponges

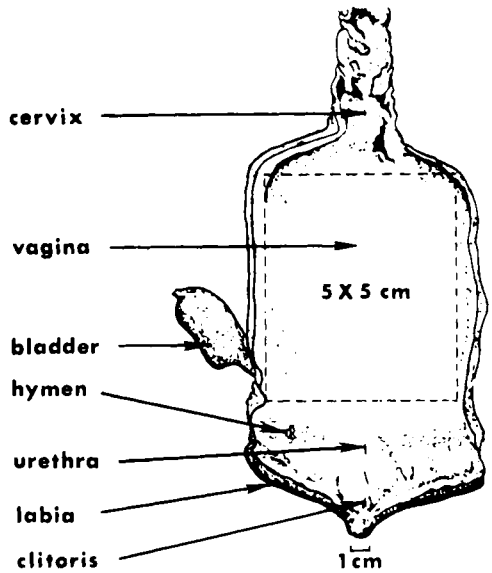


**Figure 4**—*Sheep vagina that has been cut open vertically. A piece of mucosa (5 × 5 cm), separated from the wall, is sandwiched between diffusion cells for permeation studies.*

[5] Burdick & Jackson Laboratories, Muskegon, Mich.
[6] Nanopure; Sybron/Barnstead, Boston, Mass.
[7] Bellco Glass, Vineland, N.J.
[8] Water Bath Model 80; Fisher Scientific Co., Springfield, N.J.
[9] Model 6000 A; Waters Associates, Milford, Mass.
[10] Model U6K; Waters Associates.
[11] Model 440; Waters Associates.
[12] Omniscribe Recorder; Houston Instruments, Austin, Tex.
[13] 5-µm Spherical $C_{18}$; Waters Associates.
[14] Chronogest vaginal sponges (40 mg of flurogestone acetate) (800 Grade); Intervet, France.

**Table II—Operating Conditions and the Experimentally Obtained Hydrodynamic Parameters**

| Polyethylene Glycol 400, % v/v | Rotation Speed, rpm | Kinematic Viscosity, $cm^2/s$ | $D \times 10^6$, $cm^2/s$ | $k \times 10^4$, cm/s | $Sh_r$[a] | $\delta_D \times 10^4$, cm[b] |
|---|---|---|---|---|---|---|
| 0 | 60 | 0.007 | 4.47 | 22.2 | 995 | 20.1 |
| | 165 | 0.007 | 4.47 | 31.8 | 1421 | 14.1 |
| | 295 | 0.007 | 4.47 | 52.5 | 2347 | 8.5 |
| 20 | 60 | 0.016 | 1.96 | 6.18 | 631 | 31.7 |
| | 165 | 0.016 | 1.96 | 15.6 | 1595 | 12.6 |
| | 295 | 0.016 | 1.96 | 26.5 | 2706 | 7.4 |
| 40 | 60 | 0.045 | 0.695 | 1.02 | 294 | 68.0 |
| | 165 | 0.045 | 0.695 | 2.31 | 664 | 30.1 |
| | 295 | 0.045 | 0.695 | 4.95 | 1425 | 14.0 |

[a] Sherwood number (see text). [b] Calculated from Eq. 2.

were then placed, thread up (Fig. 1), on polyethylene over a wire grid and allowed to dry overnight (8).

**Elution Medium**—The elution medium was prepared by mixing a given volume of polyethylene glycol 400 with a concentrated solution of simulated vaginal fluid and then diluted to 1 L with distilled water (Table I). The concentrated simulated vaginal fluid was prepared by mixing various quantities of 0.04 M $Na_2HPO_4$ and 0.02 M citric acid. After the addition of polyethylene glycol 400, the water was added. The pH of the elution medium was 7.3 ± 0.5 (the vaginal pH of sheep).

**Determination of Drug Solubility**—The solubility of flurogestone acetate at the study temperatures was determined by vigorously mixing an excess of drug particles in 10 mL of elution medium containing various volume fractions of polyethylene glycol 400. At equilibrium (24 h), samples were rapidly filtered through preheated syringes equipped with a filter holder. The clear filtrate was then assayed by HPLC. An exponential relationship between the solubility of the drug and the volume fraction of polyethylene glycol 400 was found (Fig. 3), as expected (9), from the following:

$$\log C_s = \log C_{SVF} + e \cdot f \qquad \text{(Eq. 1)}$$

where, $C_s$ and $C_{SVF}$ denote the solubilities of flurogestone acetate in the polyethylene glycol 400–simulated vaginal fluid and in pure simulated vaginal fluid, respectively; $e$ is the slope of the log solubility *versus* volume fraction profile; and $f$ is the volume fraction of polyethylene glycol 400 (v/v) added. The solubility of the drug ($C_{SVF}$ = 5.4 μg/mL) was enhanced remarkably by the addition of polyethylene glycol 400; the perfect sink condition was thus maintained.

**Calibration of the System**—*Time to Reach 38°C*—The donor and receptor compartments were maintained at 38°C, and then 600 or 1000 mL of simulated vaginal fluid (at room temperature) was poured into each compartment

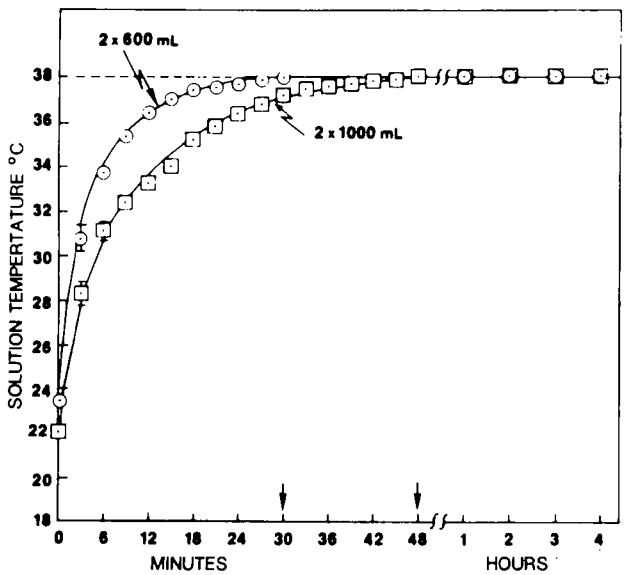


**Figure 5**—*Time required for the solution temperature in the donor and receptor compartments to reach the equilibrium temperature of 38°C (vaginal temperature of the sheep) from room temperature (n = 3); stirring speed 360 rpm.*

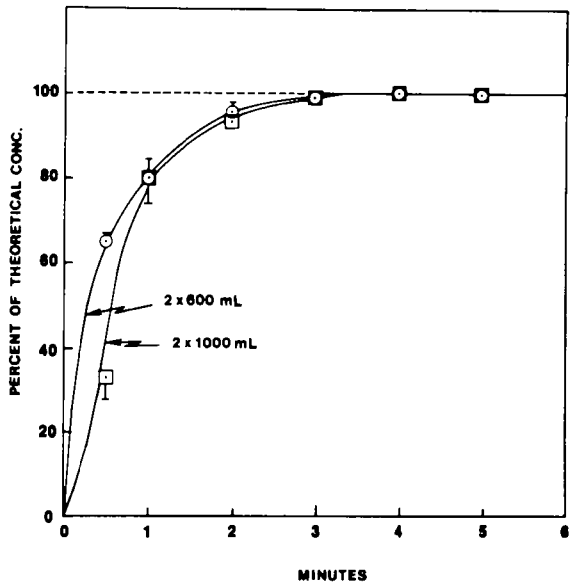


**Figure 6**—*Time required for the solution in the receptor compartment to reach a theoretical concentration after addition of a known concentration of flurogestone acetate stock solution to the donor solution (n = 3).*

while the stirrer rotated at 330 rpm. Temperature of the elution medium in the receptor compartment was measured[15] every 3 min until the equilibrium temperature of 38°C was reached.

*Hydrodynamics of Mixing*—After the simulated vaginal fluid solution in each compartment reached 38°C, known concentrations of flurogestone acetate (0.5–1.0 mL) was added to the donor solution, while the stirrer rotated at 330 rpm. Samples were removed from the receptor solution every 30–60 s until the theoretical concentration was reached. Samples were then assayed for the drug by HPLC.

*Drug Release Study*—A vaginal sponge containing 40 mg of flurogestone acetate was inserted into the flange opening of the donor compartment and an impermeable barrier was sandwiched between the two compartments (Fig. 2). The magnetic stirrer was turned on and adjusted to 330 rpm. Then, 1000 mL of the elution medium containing various volume fractions of polyethylene glycol 400 (preheated to 38°C) was poured into each of the compartments. At scheduled intervals, a 2-mL aliquot of elution medium was withdrawn, but not replaced, from each compartment and assayed for the drug by HPLC.

*Drug Permeation Study*—The sheep's vagina[16] was cut open vertically (10, 11) and the mucosa was separated from the wall (Fig. 4). The vaginal mucosa was sandwiched between the donor and receptor compartments and clamped. Six hundred milliliters of saturated or unsaturated flurogestone acetate solution (40% polyethylene glycol 400 in simulated vaginal fluid) and 600 mL of drug-free solution (20% polyethylene glycol 400 in simulated vaginal fluid) were added to the donor and receptor compartments, respectively. Samples were removed from the receptor compartment at scheduled intervals for the duration of the experiment. Aliquots were assayed for the drug by HPLC.

**Analytical Procedure**—The HPLC assay procedure developed earlier (7) was utilized here. A fixed quantity of testosterone was added to each sample as an internal standard to ensure the injection-to-injection reproducibility required. Aliquots were injected into the HPLC column, and the peak height ratios of flurogestone acetate to testosterone were determined and compared with the standard curve for the calculation of flurogestone acetate concentrations.

## RESULTS AND DISCUSSION

After assembly, the entire *in vitro* intravaginal release/permeation system (Fig. 2) is totally enclosed so that solvent loss is minimized during a long-term experiment. When a sponge is inserted into the flange opening, the drug-release profile from the sponge can be studied. When the vaginal mucosa is present, permeation can be evaluated. When both are present, release and permeation can be investigated simultaneously.

The impeller assembly of the intravaginal release/permeation system provides excellent stirring (up to 400 rpm), which significantly reduces the thickness of the hydrodynamic diffusion layer on the surface of sponge and

[15] Thermalert Model TH-6D; Baily Instruments, Saddle Brook, N.J.
[16] Dealeman Meats; Warren Township, N.J.

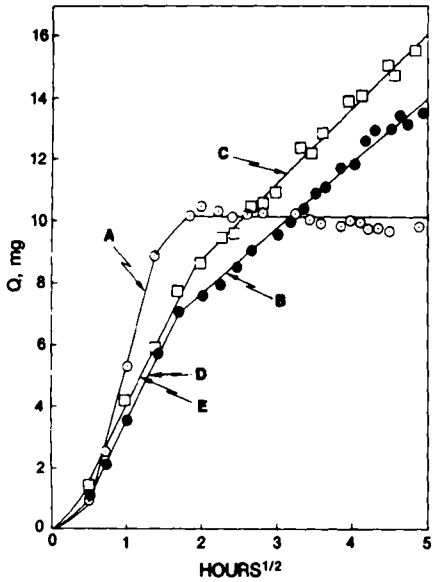


**Figure 7**—*Linear relationship between the cumulative amount of flurogestone acetate (Q) released from the vaginal sponge (containing 40 mg of the drug) into 1000 mL of elution medium (at nonsink conditions) and the square root of time ($t^{1/2}$). Note the change in the slopes at ~3 h. Key: (A) 0% polyethylene glycol 400, 8.64 mg/h$^{1/2}$; (B) 20% polyethylene glycol 400, 2.14 mg/h$^{1/2}$; (C) 30% polyethylene glycol 400, 2.40 mg/h$^{1/2}$; (D) 4.95 mg/h$^{1/2}$; (E) 4.89 mg/h$^{1/2}$.*

mucosa (Table II). The thickness of the hydrodynamic diffusion layer ($\delta_D$) is related to the Sherwood number ($Sh$) (12) by the following:

$$\delta_D = \gamma\epsilon/Sh_r = D/k \qquad \text{(Eq. 2)}$$

where $\gamma$ is the radius of the sponge, $\epsilon$ is the porosity of the sponge, $Sh_r$ is the Sherwood number around the radian of the sponge, $D$ is the diffusion coefficient, and $k$ is the mass transfer coefficient. When the Sherwood number is >200, the thickness of the diffusion layer is very small (12); therefore, the effect of solution hydrodynamics on the release of drug from the sponge is negligibly small. This is consistent with the experimental results (Table II).

It is critically important that the magnitude of $\delta_D$ be held constant (and as small as possible) so the real mechanisms of drug release and permeation can be obtained and a meaningful comparison between experimental observations can be made. A rotation speed of 330 rpm was used, which maintains a constant thickness of hydrodynamic diffusion layer of $<14 \times 10^{-4}$ cm on the immediate surface of the sponge, and also provides a homogenous drug concentration in the elution medium. Additionally, a drug-stable and water-miscible polymer, *i.e.* polyethylene glycol, was added to the simulated vaginal fluid (elution medium) to enhance the solubility of the drug and to simulate the biological sink. Under these conditions, the cell sensitivity is fairly high, so that hourly measurements of drug release/permeation flux is feasible. The drug release/permeation profile is followed closely by directly assaying the drug concentration in the elution medium. Although the construction of this system is relatively simple, the rate of drug release/permeation can be determined reliably in a short period of time.

The results indicate that it requires 30 and 48 min, respectively, for the elution media (2 × 600 mL and 2 × 1000 mL) to reach the equilibrium temperature of 38°C from room temperature (22°C) (Fig. 5). Therefore, the solutions were always preheated to 38°C before each experiment. For both volumes of solutions (*i.e.*, 2 × 600 mL and 2 × 1000 mL), it took only 3 min

**Table III—Effect of Polyethylene Glycol 400 Concentration on Rate of Drug Release from Vaginal Sponges** [a]

| Polyethylene Glycol 400, % v/v | Kinematic Viscosity, cm$^2$/s | $Q/t^{1/2}$, mg/h$^{1/2}$ [b] | |
|---|---|---|---|
| | | Initial | Steady State |
| 0 | 0.007 | 8.64 | — |
| 20 | 0.018 | 4.95 | 2.14 |
| 30 | 0.028 | 4.89 | 2.40 |
| 40 | 0.044 | 2.67 | 2.67 |
| 50 | 0.072 | 2.55 | 2.55 |

[a] Each contains 40 mg of flurogestone acetate. [b] Calculated from Figs. 7 and 8.

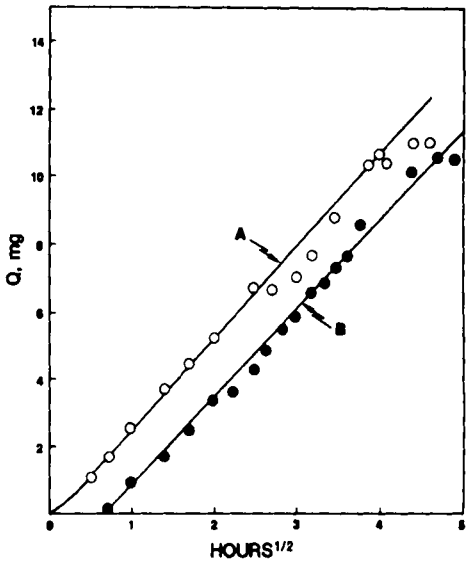


**Figure 8**—*Linear relationship between the cumulative amount of flurogestone acetate (Q) released from the vaginal sponge (containing 40 mg of the drug) into 1000 mL of elution medium (at sink condition) and square root of time ($t^{1/2}$). Note that there is no change in slope. Key: (A) 50% polyethylene glycol 400, 2.55 mg/h$^{1/2}$; (B) 40% polyethylene glycol 400, 2.67 mg/h$^{1/2}$.*

to reach the theoretical concentration when a rotation speed of 330 rpm was applied (Fig. 6), indicating very rapid mixing even in large volumes.

The release profiles of flurogestone acetate from vaginal sponges into simulated vaginal fluid containing various volume fractions of polyethylene glycol 400 were evaluated. The quantity of drug released was initially high and then decreased. This pattern of a nonlinear drug-release profile was also observed earlier in both *in vitro* (13-17) and *in vivo* (18, 19) studies of matrix-type drug dispersing devices.

Theoretically, when the matrix diffusion is the rate-controlling factor for the drug-release process, the release of drug from an insoluble, inert, polymeric matrix (like the polyurethane sponge in this study) is best described by the following (16):

$$Q = \left[\frac{D\epsilon}{\tau}(2A - \epsilon C_s)C_s t\right]^{1/2} \qquad \text{(Eq. 3)}$$

where $Q$ is the cumulative amount of drug released, $D$ is the diffusivity, $\epsilon$ is

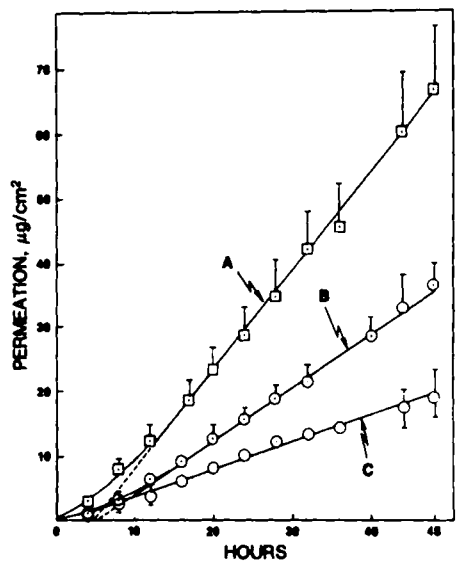


**Figure 9**—*Linear relationship between the cumulative amount of flurogestone acetate permeating the vaginal mucosa into 600 mL of elution medium and time (t). Note that a zero-order absorption pattern was obtained. The donor solution contained 40% polyethylene glycol 400; the receptor solution contained 20% polyethylene glycol 400. Bars represent* SE. *Key: (A) $C_D^s$ = 116.2 µg/mL (36.48 µg/cm$^2$/d); (B) $^1/_2C_D^s$ = 66.3 µg/mL (20.68 µg/cm$^2$/d); (C) $^1/_4C_D^s$ = 30.96 µg/mL (9.98 µg/cm$^2$/d).*

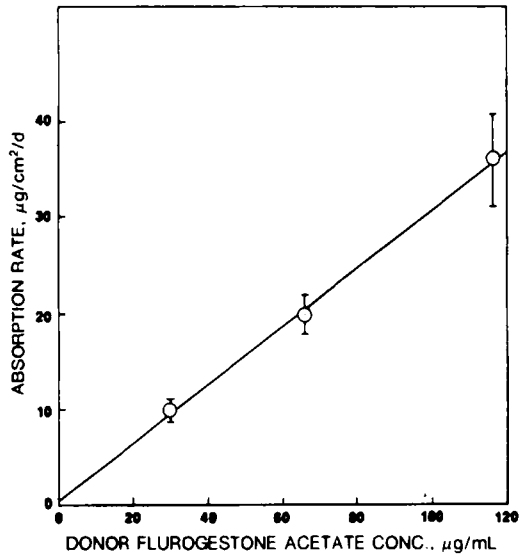


**Figure 10**—*Linear dependence of the steady-state intravaginal rate of absorption across an isolated vaginal mucosa on the concentration of flurogestone acetate in the donor solution (mucosa side). A $P_v$ value of 0.311 cm/d is obtained from the slope.*

the porosity, and $\tau$ is the tortuosity in the sponge matrix; $A$ is the initial loading dose of drug in the sponge; $C_s$ is the solubility of the drug in the elution medium; and $t$ is time. The theoretical model described in Eq. 3 indicates that the cumulative amount of drug released should be a linear function of the square root of time ($t^{1/2}$). Experimentally, this $Q$ *versus* $t^{1/2}$ linearity was achieved (Figs. 7 and 8). There was, however, a break in the slope of the $Q$ *versus* $t^{1/2}$ line when the elution medium was at non-sink conditions (0–30% polyethylene glycol 400–simulated vaginal fluid) (Fig. 7). On the other hand, perfect $Q$ *versus* $t^{1/2}$ linearity was achieved when the elution medium was at sink conditions (40–50% polyethylene glycol 400–simulated vaginal fluid) (Fig. 8).

The results clearly indicate that the release of drug from the vaginal sponge can be divided into two steps: the initial release, which is controlled by the dissolution process of solid drug from the surface of the vaginal sponge, and the steady-state release (which prevails after complete dissolution of the surface drug), in which the drug dispersed inside the sponge matrix is released by the matrix diffusion-controlled mechanism. This is illustrated by comparing the $Q/t^{1/2}$ values generated in various combinations of polyethylene glycol 400 and simulated vaginal fluid (Table III). It has been reported that the initial release rates are remarkably affected by the solution hydrodynamics on the surface of the sponge, depending on both the fluid viscosity and the impeller rotation speed (12). As viscosity of the solution increases (from 0 to 50% polyethylene glycol 400), the initial rate of drug release decreases. On the other hand, the effect of solution hydrodynamics on the steady-state release rates is rather negligible and, therefore, the rates become fairly independent of polyethylene glycol 400 concentration. As polyethylene glycol 400 concentration goes beyond 30%, the steady-state rate of release stays at essentially the same level ($2.54 \pm 0.14$ mg/h$^{1/2}$).

The permeation profiles of flurogestone acetate from the 40% polyethylene glycol 400–simulated vaginal fluid solution (which contains various drug concentrations) through the vaginal mucosa were investigated (Fig. 9). The cumulative amount of drug absorbed ($Q$) was a linear function of time. As the concentration of flurogestone acetate in the donor compartment decreases (from a 100% to a 25% saturated solution), the rate of drug permeation, $(Q/t)_v$, through the vaginal mucosa was observed to decrease proportionally (Fig. 10). The steady-state permeation rate, $(Q/t)_v$, across the vaginal mucosal barrier is defined by:

$$(Q/t)_v = P_v \cdot \Delta C_v \qquad \text{(Eq. 4)}$$

where $P_v$ and $\Delta C_v$ are the permeability coefficient and the concentration gradient across the vaginal barrier, respectively. From the slope of the regression line of $(Q/t)_v$ *versus* $\Delta C_v$, a permeability coefficient of 0.311 cm/d was determined for the intravaginal permeation of flurogestone acetate through the vaginal mucosa of sheep.

## CONCLUSIONS

A relatively simple drug release/permeation system was designed for the measurement of *in vitro* drug release and permeation profiles. The system developed is capable of maintaining sink conditions by the use of water-miscible polyethylene glycol 400, which tends to simulate the biological sink. By doing so, it is expected to achieve a better *in vitro–in vivo* correlation. The effect of the diffusion boundary layer on the release and permeation of the drug is minimized by maintaining a thin, but constant, thickness of the hydrodynamic diffusion layer on the surface of the sponge and vaginal mucosa. This was accomplished by constant stirring and maintaining a fixed temperature throughout the experiments. The release of flurogestone acetate from the vaginal sponge followed a surface dissolution-matrix diffusion-type consecutive release. The initial rate was apparently influenced by both the fluid viscosity and impeller rotation speed. The steady-state release, which is described by a linear $Q$ *versus* $t^{1/2}$ profile, was then established. The intravaginal absorption rate of the drug from the solution was observed to be constant and was proportional to the flurogestone acetate concentration in the donor solution. An intravaginal permeability coefficient of 0.311 cm/d was determined. It is surprising to note that the release rate of flurogestone acetate from the sponge is much faster than the rate of absorption (compare Fig. 8 with Fig. 9). An ideal device should deliver the drug at a rate equal to the rate of absorption. This could be achieved by making the device release the drug in zero-order fashion. Since the dose of flurogestone acetate required for estrus synchronization in sheep is only 0.3–0.4 mg/d, a slower release rate than that of the present sponge would be desired. It is apparent that an intravaginal drug delivery system which releases the drug at a slower, but constant, rate should be developed.

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