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INTRAVAGINAL CONTROLLED ADMINISTRATION OF FLUROGESTONE ACETATE: (III) DEVELOPMENT OF RATE-CONTROL VAGINAL DEVICES+

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ABSTRACT

A Rate-Control vaginal device was developed which overcomes the low bioavailability and unpredictable Q - $t^{\frac{1}{2}}$ type release and absorption rate profiles of flurogestone acetate delivered by the currently marketed Syncro-Mate pessary.

The in vitro release and vaginal absorption profiles from the Rate-Control vaginal device were run simultaneously, a linear Q - t relationship was obtained with a significant improvement in bioavailability. A mathematical model was developed to correlate the in vitro drug release and the vaginal absorption profiles of flurogestone acetate from the vaginal devices.

The design, development and the simultaneous release and absorption profiles of flurogestone acetate from this new vaginal device were outlined and discussed.

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INTRODUCTION

Flurogestone acetate (FGA), a synthetic progestin, has been administered to sheep in the form of drug-impregnated vaginal sponge formulation, called Syncro-Mate pessary (G. D. Searle & Co.) or Chrono-gest pessary (Intervet s.a.), for prolonged estrus synchronization (1).

These cylinder-shaped polyurethane sponges (42 mm (d) x 30 mm (h)) were impregnated with 10-40 mg of FGA (2). The intravaginal release of FGA from these polyurethane sponges in the sheep (in-situ) was evaluated (3); and, the results indicated that an average of 16% of the drug in the sponge was released per day (estimated from the log-time relationship). For example, for a sponge containing 10 mg of drug, less than 0.5 mg of the drug would remain in the sponge at the end of 15-day treatment (normal application period), which is considered to be subeffective dose (3).

By studying the clearance of tritium-labelled FGA in 6 sheep, in which the sponges were left in the vagina for a period of up to 20 days, it was observed that only 12 to 24% of the dose have actually been absorbed from the vaginal tract, of which 98% were recovered in the urine and feces. The fact that only 18% of the applied dose (on the average) were actually absorbed during the 20-day application and the remaining 82% were essentially wasted, a great discrepancy existed between the dose absorbed and dose released.

Based on the results outlined above, Robinson recommended that redesign of the vaginal pessary should be investigated to prevent the initial release of excessively high and wasteful doses and to obtain a more satisfactory and uniform rate of release (4).

The *in vitro* release profiles of FGA from Syncro-Mate pessary were evaluated earlier in this laboratory and reported to follow a Q vs. $t^{\frac{1}{2}}$ relationship (5).

In the present study, the simultaneous release and absorption of FGA from the Syncro-Mate pessary were evaluated to determine their respective

rate profiles. A new Rate-Control vaginal device, which is expected to release FGA at a constant zero-order fashion, was also designed to eliminate the aforementioned pitfalls of Syncro-Mate pessary. A simple mathematical model was derived to correlate the *in vitro* release and vaginal absorption of FGA from the Rate-Control vaginal device. The results are discussed and analyzed in this report.

THEORETICAL ANALYSIS

Physical Model - A theoretical model for the *in vitro* simultaneous release and vaginal absorption of drug from a Rate-Control drug-releasing delivery device, which is in close contact with the vaginal mucosa, is shown in Figure 1. The important features of this theoretical model are: the simultaneous inward movement of the two receding interfaces of the drug dispersion zone/drug depletion zone in the device as drug is released with time, and the concentration gradients across the rate-limiting polymer coating membrane, the aqueous diffusion layer, the vaginal wall (composed of lipid continuum with interdispersed "pores" or aqueous shunt pathways), and the hydrodynamic boundary layer. The *in vitro* release and vaginal absorption of drug from this device are dependent upon a series of sequential steps: for vaginal absorption, the steps involve the dissolution of finely-divided, well-dispersed drug particles into the surrounding polymer matrix; drug diffusion through the polymer matrix to the matrix/membrane interface; partitioning of drug molecules from the matrix to the polymer coating membrane, permeation of drug molecules across the polymeric membrane, partitioning of drug molecules from the polymeric membrane to the aqueous diffusion layer, diffusion of drug molecules across the aqueous diffusion layer, uptake and penetration through the vaginal mucosa, partitioning and diffusion through the hydrodynamic boundary layer; Finally, distribution of drug into the receptor solution compartment.

For drug release, the steps involve the partitioning and diffusion through the polymer matrix, polymeric membrane and hydrodynamic boundary layer; and the distribution into the donor solution compartment.

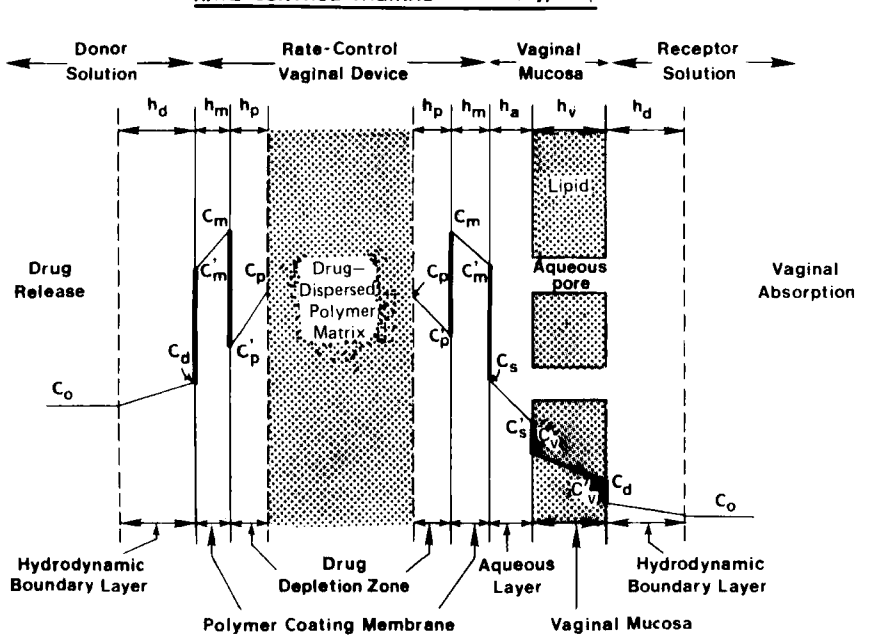

Figure 1: A theoretical model for the in vitro release and vaginal absorption of flurogestone acetate from a Rate-Control vaginal device (Type II, contains a medicated silicone device laminated with a polymeric membrane).

The following assumptions were made in establishing of this physical model:

(1) The drug in the matrix is finely divided and uniformly dispersed such that the dissolution in the polymer matrix is not the rate-determining step.

(2) A sharp boundary exists at the interface between the drug dispersion zone and the drug depletion zone within the device which recedes into the core of the device as time passes.

(3) The drug has a finite solubility in the polymer matrix, C_p, and that the drug loading dose per unit volume, A, including the undissolved and dissolved drug, is much greater than C_p.

(4) The drug reaches the matrix surface by diffusion through the matrix continuum; and end diffusion is negligible.

Under these assumptions, a series of concentration gradients for the drug will be established beginning at the receding interface of the drug dispersed zone/drug depletion zone and terminating at the outer reach of the hydrodynamic boundary layers, and in the elution medium the drug molecules are homogeneously distributed as soon as they are released. These gradients are depicted in Fig. 1, as a series of discontinuous gradients from the drug-dispersing polymer matrix to the elution medium.

The flux across a unit area of the drug depletion zone (J_p):

$$J_p = \frac{D_p}{h_p} (C_p - C_p') \qquad \text{Eq. 1}$$

Where, D_p is the diffusivity of a drug in the drug depletion zone with a thickness of h_p; C_p and C_p' are the solubility of drug in the polymer matrix and the concentration of drug at the polymer matrix/polymer coating membrane interface.

The flux across a unit area of the polymer coating membrane (J_m):

$$J_m = \frac{D_m}{h_m} (C_m - C_m') \qquad \text{Eq. 2}$$

Where, D_m is the diffusivity of a drug in a polymer coating membrane with a thickness of h_m; C_m and C_m' are the concentrations of drug at the polymer membrane/polymer matrix and membrane/solution interfaces, respectively.

The flux across a unit area of the aqueous diffusion layer (J_{aq}):

$$J_{aq} = \frac{D_{aq}}{h_{aq}} (C_s - C_s') \qquad \text{Eq. 3}$$

Where, D_{aq} is the diffusivity of a drug in the aqueous diffusion layer with a thickness of h_{aq}; C_s and C_s' are the concentrations of drug at the aqueous layer/polymeric membrane and aqueous layer/vaginal mucosa interfaces, respectively.

The flux across a unit area of the vaginal wall (J_v):

$$J_v = \frac{D_v}{h_v} (C_v - C_v') \qquad \text{Eq. 4}$$

Where, D_v is the diffusivity of a drug in the vaginal mucosa with a thickness of h_v; C_v and C_v' are the drug concentrations at the vaginal mucosa/aqueous layer and vaginal mucosa/hydrodynamic boundary layer interfaces, respectively.

The flux across a unit area of the hydrodynamic boundary layer (J_d):

$$J_d = \frac{D_d}{h_d}(C_d - C_d') = \frac{D_d}{h_d}(C_d) \qquad \text{since } C_d' \simeq 0 \qquad \text{Eq. 5}$$

Where, D_d is the diffusivity of a drug in the hydrodynamic boundary layer with a thickness of h_d; C_d and C_d' are the drug concentrations at the hydrodynamic layer/polymeric membrane and hydrodynamic layer/bulk solution interfaces, respectively.

The partition coefficient for the interfacial partitioning between the polymer coating membrane and polymer matrix (K_m):

$$K_m = \frac{C_m}{C_p'} = \frac{S_m}{C_p} \qquad \text{Eq. 6}$$

The partition coefficient for the interfacial partitioning between the aqueous diffusion layer and polymer coating membrane (K_s):

$$K_s = \frac{C_s}{C_m'} = \frac{S_{aq}}{S_m} \qquad \text{Eq. 7}$$

The partition coefficient for the interfacial partitioning between the vaginal mucosa and aqueous layer (K_v):

$$K_v = \frac{C_v}{C_s'} = \frac{S_v}{S_{aq}} \qquad \text{Eq. 8}$$

The partition coefficient for the interfacial partitioning between the hydrodynamic boundary layer and vaginal mucosa (K_d):

$$K_d = \frac{C_d}{C_v'} = \frac{S_d}{S_v} \qquad \text{Eq. 9}$$

Where, S_m, S_{aq}, S_v and S_d are the solubilities of a drug in the polymer coating membrane, aqueous layer, vagina and hydrodynamic boundary layer, respectively. (Other terms are as defined earlier.)

Since the fluxes across the series of barriers will reach a quasi-steady state:

$$J_p = J_m = J_{aq} = J_v = J_d = J \qquad \text{Eq. 10}$$

Incorporating Eq. (9) for C_d ($=K_dC_v'$) in Eq. (5) yields:

$$J_d = \left(\frac{D_dK_d}{h_d}\right) C_v' \qquad \text{Eq. 11a}$$

$$C_v' = \frac{J_dh_d}{D_dK_d} \qquad \text{Eq. 11b}$$

Inserting Eq. (11b) for C_v' in Eq. (4) and rearranging give:

$$J_v = \left(\frac{D_v}{h_v}\right)\left(C_v - \frac{J_dh_d}{D_dK_d}\right) \qquad \text{Eq. 12a}$$

Expanding Eq. (12a) yields:

$$J_v = \frac{D_vC_v}{h_v} - \frac{D_vJ_dh_d}{D_dK_dh_v} \qquad \text{Eq. 12b}$$

or

$$J_v + \frac{D_vJ_dh_d}{D_dK_dh_v} = \frac{D_vC_v}{h_v} \qquad \text{Eq. 12c}$$

Since $J_v = J_d = J$ (Eq. 10), hence

$$J\left(1 + \frac{D_vh_d}{D_dK_dh_v}\right) = \frac{D_vC_v}{h_v} \qquad \text{Eq. 12d}$$

Multiplying both sides of Eq. (12d) by (h_v/D_v) gives:

$$J\left(\frac{h_v}{D_v} + \frac{h_d}{D_dK_d}\right) = C_v \qquad \text{Eq. 12e}$$

Substituting Eq. (12e) for C_v in Eq. (8) and solving for C_s' ($=C_v/K_v$) yields:

$$C_s' = \frac{J}{K_v}\left(\frac{h_v}{D_v} + \frac{h_d}{D_dK_d}\right) \qquad \text{Eq. 13}$$

Substituting Eq. (13) for C_s' in Eq. (3) results in:

$$J_{aq} = \frac{D_{aq}}{h_{aq}}\left[C_s - \frac{J}{K_v}\left(\frac{h_v}{D_v} + \frac{h_d}{D_dK_d}\right)\right] \qquad \text{Eq. 14a}$$

Expanding Eq. (14a) gives:

$$J_{aq} = \left[\frac{D_{aq}C_s}{h_{aq}} - \frac{J\,D_{aq}}{h_{aq}K_v}\left(\frac{h_v}{D_v} + \frac{h_d}{D_dK_d}\right)\right] \qquad \text{Eq. 14b}$$

or

$$J_{aq} + \frac{J\,D_{aq}}{h_{aq}K_v}\left(\frac{h_v}{D_v} + \frac{h_d}{D_dK_d}\right) = \frac{D_{aq}C_s}{h_{aq}} \qquad \text{Eq. 14c}$$

Since $J_{aq} = J$ (Eq. 10), so

$$J\left[1 + \frac{D_{aq}}{h_{aq}K_v}\left(\frac{h_v}{D_v} + \frac{h_d}{D_dK_d}\right)\right] = \frac{D_{aq}D_s}{h_{aq}} \qquad \text{Eq. 14d}$$

Multiplying both sides of Eq. (14d) by (h_{aq}/D_{aq}) yields:

$$J\left[\frac{h_{aq}}{D_{aq}} + \frac{1}{K_v}\left(\frac{h_v}{D_v} + \frac{h_d}{D_dK_d}\right)\right] = C_s \qquad \text{Eq. 14e}$$

Substituting Eq. (14e) for C_s in Eq. (7) and solving for C_m' $(=C_s/K_s)$ give:

$$C_m' = \frac{J}{K_s}\left[\frac{h_{aq}}{D_{aq}} + \frac{1}{K_v}\left(\frac{h_v}{D_v} + \frac{h_d}{D_dK_d}\right)\right] \qquad \text{Eq. 15}$$

Subustituting Eq. (15) for C_m' in Eq. (2) yields:

$$J_m = \frac{D_m}{h_m}\left\{C_m - \frac{J}{K_s}\left[\frac{h_{aq}}{D_{aq}} + \frac{1}{K_v}\left(\frac{h_v}{D_v} + \frac{h_d}{D_dK_d}\right)\right]\right\} \qquad \text{Eq. 16a}$$

Expanding Eq. (16a) produces:

$$J_m = \frac{D_mC_m}{h_m} - \frac{J\,D_m}{h_mK_s}\left[\frac{h_{aq}}{D_{aq}} + \frac{1}{K_v}\left(\frac{h_v}{D_v} + \frac{h_d}{D_dK_d}\right)\right] \qquad \text{Eq. 16b}$$

$$J_m + \frac{J\,D_m}{h_mK_s}\left[\frac{h_{aq}}{D_{aq}} + \frac{1}{K_v}\left(\frac{h_v}{D_v} + \frac{h_d}{D_dK_d}\right)\right] = \frac{D_mC_m}{h_m} \qquad \text{Eq. 16c}$$

Since $J_m = J$ (Eq. 10), so

$$J\left\{1 + \frac{D_m}{h_mK_s}\left[\frac{h_{aq}}{D_{aq}} + \frac{1}{K_v}\left(\frac{h_v}{D_v} + \frac{h_d}{D_dK_d}\right)\right]\right\} = \frac{D_mC_m}{h_m} \qquad \text{Eq. 16d}$$

Multiplying both sides of Eq. (16d) by (h_m/D_m) yields:

$$J\left\{\frac{h_m}{D_m} + \frac{1}{K_s}\left[\frac{h_{aq}}{D_{aq}} + \frac{1}{K_v}\left(\frac{h_v}{D_v} + \frac{h_d}{D_dK_d}\right)\right]\right\} = C_m \qquad \text{Eq. 16e}$$

Substituting Eq. (16e) for C_m in Eq. (6) and solving C_p' $(=C_m/K_m)$ give:

$$C_p' = \frac{J}{K_m}\left\{\frac{h_m}{D_m} + \frac{1}{K_s}\left[\frac{h_{aq}}{D_{aq}} + \frac{1}{K_v}\left(\frac{h_v}{D_v} + \frac{h_d}{D_dK_d}\right)\right]\right\} \qquad \text{Eq. 17}$$

Incorporating Eq. (17) for C_p' in Eq. (1) results:

$$J_p = \frac{D_p}{h_p}\left[C_p - \frac{J}{K_m}\left\{\frac{h_m}{D_m} + \frac{1}{K_s}\left[\frac{h_{aq}}{D_{aq}} + \frac{1}{K_v}\left(\frac{h_v}{D_v} + \frac{h_d}{D_dK_d}\right)\right]\right\}\right] \qquad \text{Eq. 18a}$$

Expanding Eq. (18a) gives:

$$J_p = \frac{D_p C_p}{h_p} - \frac{J D_p}{h_p K_m}\left\{\frac{h_m}{D_m} + \frac{1}{K_s}\left[\frac{h_{aq}}{D_{aq}} + \frac{1}{K_v}\left(\frac{h_v}{D_v} + \frac{h_d}{D_d K_d}\right)\right]\right\} \quad \text{Eq. 18b}$$

or

$$J_p + \frac{J D_p}{h_p K_m}\left\{\frac{h_m}{D_m} + \frac{1}{K_s}\left[\frac{h_{aq}}{D_{aq}} + \frac{1}{K_v}\left(\frac{h_v}{D_v} + \frac{h_d}{D_d K_d}\right)\right]\right\} = \frac{D_p C_p}{h_p} \quad \text{Eq. 18c}$$

Since $J_p = J$ (Eq. 10), so,

$$J_p\left[1 + \frac{D_p}{h_p K_m}\left\{\frac{h_m}{D_m} + \frac{1}{K_s}\left[\frac{h_{aq}}{D_{aq}} + \frac{1}{K_v}\left(\frac{h_v}{D_v} + \frac{h_d}{D_d K_d}\right)\right]\right\}\right] = \frac{D_p C_p}{h_p} \quad \text{Eq. 18d}$$

Multiplying both sides of Eq. (18d) by h_p yields:

$$J_p\left[h_p + \frac{D_p}{K_m}\left\{\frac{h_m}{D_m} + \frac{1}{K_s}\left[\frac{h_{aq}}{D_{aq}} + \frac{1}{K_v}\left(\frac{h_v}{D_v} + \frac{h_d}{D_d K_d}\right)\right]\right\}\right] = D_p C_p \quad \text{Eq. 18e}$$

or,

$$J_p = \frac{D_p C_p}{[h_p + Y_1]} \quad \text{Eq. 18f}$$

Where,

$$Y_1 = \frac{D_p}{K_m}\left\{\frac{h_m}{D_m} + \frac{1}{K_s}\left[\frac{h_{aq}}{D_{aq}} + \frac{1}{K_v}\left(\frac{h_v}{D_v} + \frac{h_d}{D_d K_d}\right)\right]\right\} \quad \text{Eq. 19}$$

The flux (J_p) across the drug depletion zone is related to the rate of change in the thickness (h_p) of the drug depletion zone in the polymer matrix:

$$J_p = \frac{dQ}{dt} = A\left(\frac{dh_p}{dt}\right); \quad \text{if } A \gg C_p \quad \text{Eq. 20}$$

Where, Q is the cumulative amount of drug released; t is the time, A is the initial drug loading dose in a unit volume of the polymer matrix and C_p is the drug solubility in the polymer.

Letting Eq. (18f) equal Eq. (20) and rearranging yield:

$$dh_p\,(h_p + Y_1) = \left(\frac{D_p C_p}{A}\right)dt \quad \text{Eq. 21a}$$

Expanding Eq. (21a) gives:

$$h_p dh_p + Y_1 dh_p = \left(\frac{D_p C_p}{A}\right)dt \quad \text{Eq. 21b}$$

Integrating each part of Eq. (21b) between the boundary conditions of $h_p = 0$ at $t = 0$ and $h_p = h_p$ at $t = t$, the change in the thickness of the drug depletion zone with time is given by:

$$\frac{h_p^2}{2} + Y_1 h_p = \left(\frac{D_p C_p}{A}\right)t \qquad \text{Eq. 22}$$

Integrating Eq. (20) to give the cumulative amount of drug released:

$$Q = Ah_p \qquad \text{Eq. 23}$$

Incorporating Eq. (23) for h_p (=Q/A) in Eq. (22):

$$\frac{Q^2}{2A^2} + Y_1 \frac{Q}{A} = \frac{D_p C_p t}{A} \qquad \text{Eq. 24}$$

Multiplying both sides of Eq. (24) by "A" and rearranging yield:

$$\frac{1}{2A} Q^2 + Y_1 Q - (D_p C_p t) = 0 \qquad \text{Eq. 25}$$

Solving the above quadratic equation gives:

$$Q = \frac{-Y_1 + [Y_1^2 + 4\ (1/2A)\ (D_p C_p t)]^{\frac{1}{2}}}{2(1/2A)} \qquad \text{Eq. 26}$$

Simplifying Eq. (26) yields:

$$Q = A\left[-Y_1 + \left(Y_1^2 + \frac{2D_p C_p t}{A}\right)^{\frac{1}{2}}\right] \qquad \text{Eq. 27}$$

Differentiating Eq. (27) with time produces:

$$\frac{dQ}{dt} = \frac{A}{2}\left(Y_1^2 + \frac{2D_p C_p t}{A}\right)^{-\frac{1}{2}} \left(\frac{2D_p C_p}{A}\right) \qquad \text{Eq. 28a}$$

Rearranging Eq. (28a):

$$\frac{dQ}{dt} = D_p C_p \left(Y_1^2 + \frac{2D_p C_p t}{A}\right)^{-\frac{1}{2}} \qquad \text{Eq. 28b}$$

Reinserting the constant Y_1 from Eq. (19) to give the mathematical expression for the <u>in vitro</u> rate of drug absorption from the Rate-Control vaginal device (contains a controlled-release silicone device laminated with a polymer coating membrane):

$$\frac{dQ}{dt} = (D_pC_p)\left\{ \left[\frac{D_p}{K_m}\left\{\frac{h_m}{D_m} + \frac{1}{K_s}\left[\frac{h_{aq}}{D_{aq}} + \frac{1}{K_v}\left(\frac{h_v}{D_v} + \frac{h_d}{D_dK_d}\right)\right]\right\}\right]^2 + \left(\frac{2D_pC_p}{A}\right)t\right\}^{-\frac{1}{2}} \quad \text{Eq. 28c}$$

Since the diffusional resistance, R, of each barrier is related to its permeability coefficient, P, as follows:

$$R = h/DK = 1/P.$$

Where, h, D, and K are, respectively, the thickness, diffusivity, and partition coefficient of each barrier.

Eq. (28) can be rewritten as:

$$\frac{dQ}{dt} = (D_pC_p)\left[\left\{D_p\left[R_m + \frac{R_{aq}}{K_m} + \frac{1}{K_mK_s}\left(R_v + \frac{R_d}{K_v}\right)\right]\right\}^2 + \left(\frac{2D_pC_p}{A}\right)t\right]^{-\frac{1}{2}} \quad \text{Eq. 28d}$$

Where, R_v, the diffusional resistance across the vaginal mucosa, is defined by:

$$R_v = (P_v)^{-1} = (P_1 + P_a)^{-1} = \left\{(f)\left[\frac{D_1K_v}{h_v}\right] + (1 - f)\frac{D_a}{h_v}\right\}^{-1} \quad \text{Eq. 29}$$

and R_m, R_{aq}, and R_d are the diffusional resistances across the polymer coating membrane, aqueous diffusion layer, and hydrodynamic boundary layer, respectively; f is the volume fraction of the lipid biophase; D_1 and D_a are the diffusivities of a drug in the lipid continum and aqueous pores, respectively; and h_v is the thickness of vaginal mucosa.

Eq. (28d) can be rewritten:

$$\frac{dQ}{dt} = \frac{X}{(Y^2 + Zt)^{\frac{1}{2}}} \quad \text{Eq. 28e}$$

Where, $X = D_pC_p$ Eq. 30a

$$Y = D_p\left[R_m + \frac{R_{aq}}{K_m} + \frac{1}{K_mK_s}\left(R_v + \frac{R_d}{K_v}\right)\right] \quad \text{Eq. 30b}$$

$$Z = 2D_pC_p/A \quad \text{Eq. 31}$$

X, Y, and Z are constants.

For cases where the polymer coating membrane, the aqueous diffusion layer, the vaginal mucosa and/or the hydrodynamic boundary layer are the rate-limiting steps, i.e., $Y^2 >> Zt$, Eq. (28d) becomes:

$$\frac{dQ}{dt} = C_p \left[R_m + \frac{R_{aq}}{K_m} + \frac{1}{K_m K_s}\left(R_v + \frac{R_d}{K_v}\right)\right]^{-1} \qquad \text{Eq. 32}$$

In the cases where the polymer coating membrane plays an important rate-limiting role; Eq. (32) can be further reduced to:

$$\frac{dQ}{dt} = \frac{C_p}{R_m} = \text{constant} \qquad \text{Eq. 33a}$$

or

$$\frac{dQ}{dt} = \frac{C_p D_m K_m}{h_m} \quad (\text{since } R_m = h_m/D_m K_m \qquad \text{Eq. 33b}$$

Because $K_m = S_m/C_p$ (Eq. 6);

$$\frac{dQ}{dt} = S_m D_m \left(\frac{1}{h_m}\right) \qquad \text{Eq. 33c}$$

A zero-order drug absorption profile should result. The intravaginal rate of drug absorption is thus dependent upon the solubility (S_m) and the diffusivity (D_m) of a drug in the rate-limiting membrane with a thickness of h_m.

Following the same mathematical derivations from Equations 10 through 28d, the mathematical expression for the *in vitro* rate of drug release from the Rate-Control vaginal device (contains a controlled-release silicone device laminated with a polymer membrane) is derived as:

$$\frac{dQ}{dt} = D_p C_p \left\{\left[D_p \left(R_m + \frac{R'_d}{K_m}\right)\right]^2 + \left[\frac{2D_p C_p}{A}\right] t\right\}^{-\frac{1}{2}} \qquad \text{Eq. 34}$$

Where, R'_d $(=h_d/D_d K'_d)$ is the diffusional resistance across the hydrodynamic boundary layer on the surface of silicone device, in which, K'_d, the partition coefficient for the interfacial partitioning between the hydrodynamic boundary layer and polymer coating membrane is defined by:

$$K'_d = \frac{C_d}{C'_m} \qquad \text{Eq. 35}$$

When the rate-controlling step is at polymer coating membrane or at hydrodynamic boundary layer, Eq. (34) is reduced to:

$$\frac{dQ}{dt} = [C_p]\ [R_m + \frac{R'_d}{K_m}]^{-1} = \text{constant} \qquad \text{Eq. 36}$$

Since $R_m = h_m/D_m K_m$

So, $$\frac{dQ}{dt} = \frac{C_p K_m D_m}{h_m + R'_d D_m} \qquad \text{Eq. 36a}$$

In the case where the Rate-Control vaginal device contains no polymer coating membrane on the external surface of the drug-releasing silicone device (Fig. 2), the mathematical expression for the in vitro rate of intravaginal drug absorption can be derived by following the same mathematical derivations from Equations 10 through 28d:

$$\frac{dQ}{dt} = [D_p C_p]\ \{D_p^2[R_{aq} + \frac{1}{K'_s}(R_v + \frac{R_d}{K_v})]^2 + [\frac{2C_p D_p}{A}]\ t\}^{-\frac{1}{2}} \qquad \text{Eq. 37}$$

Where, $$K'_s = \frac{C_s}{C'_p} = \frac{S_{aq}}{C_p} \qquad \text{Eq. 38}$$

K'_s is the partition coefficient for the interfacial partitioning between the vaginal mucosa and aqueous layer.

When C_p is small and/or A is relatively large, Eq. (37) is simplified to:

$$\frac{dQ}{dt} = C_p\ [R_{aq} + \frac{1}{K'_s}(R_v + \frac{R_d}{K_v})]^{-1} \qquad \text{Eq. 39}$$

A constant (zero-order) vaginal drug absorption profile is resulted by using a polymer matrix with a low C_p value or increasing the drug loading dose (A) in the polymer matrix.

When t increases substantially or if A is relatively small, Eq. (37) is reduced to:

$$\frac{dQ}{dt} = D_p C_p\ [\frac{2D_p C_p t}{A}]^{-\frac{1}{2}} \qquad \text{Eq. 40}$$

Integrating Eq. (40) gives:

$$\frac{Q}{t^{\frac{1}{2}}} = (2AD_p C_p)^{\frac{1}{2}} \qquad \text{Eq. 41}$$

A matrix-type (Q vs. $t^{\frac{1}{2}}$) vaginal absorption profile is resulted.

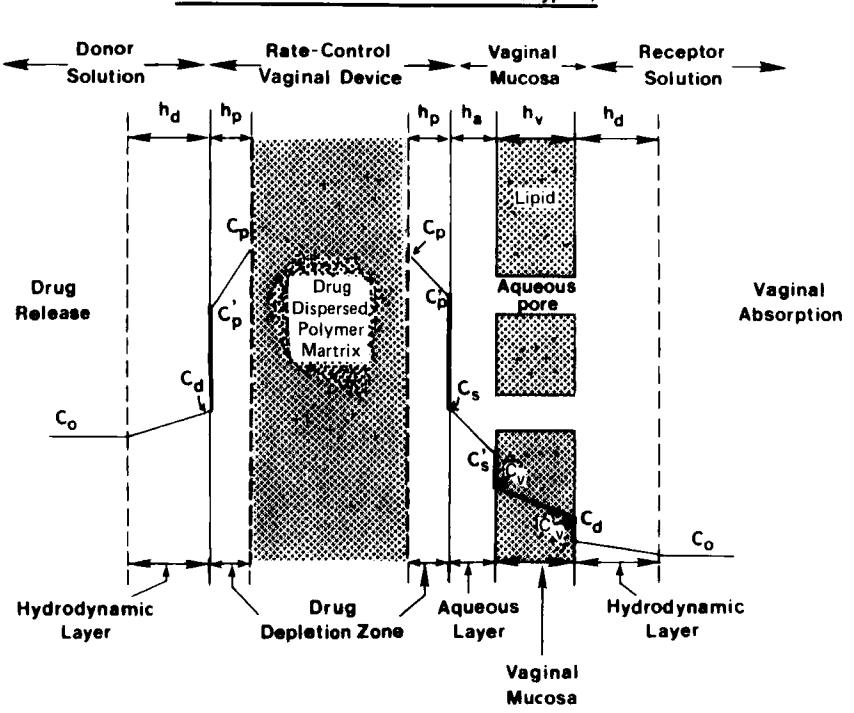

Figure 2: A theoretical model for the in vitro release and vaginal absorption of flurogestone acetate from a Rate-Control vaginal device (Type I, contains a medicated silicone device without a polymer coating membrane).

Following the same mathematical derivations from Equations 10 through 28d, the mathematical expression for the in vitro rate of drug release from a Rate-Control vaginal device (contains a controlled-release silicone device without a polymer coating membrane) is derived as:

$$\frac{dQ}{dt} = D_p C_p \left[(D_p R_d'')^2 + \left(\frac{2D_p C_p}{A}\right)t\right]^{-\frac{1}{2}} \qquad \text{Eq. 42}$$

Where, R_d'' $(=h_d/D_d K_d'')$ is the diffusional resistance across the hydrodynamic boundary layer on the surface of the silicone device in which K_d'' is the parition coefficient for the interfacial partitioning between the hydrodynamic boundary layer and polymer matrix.

When C_p is small and/or A is relatively large, Eq. 42 is simplified to:

$$\frac{dQ}{dt} = \frac{C_p}{R_d''} = \text{constant} \qquad \text{Eq. 43}$$

A zero-order (Q vs. t) release profile results.

When t increases substantially or if A is relatively small, Eq. 42 is reduced to:

$$\frac{dQ}{dt} = C_p D_p \left[\frac{2C_p D_p t}{A}\right]^{-\frac{1}{2}} \qquad \text{Eq. 40}$$

Integrating Eq. (40) gives:

$$\frac{Q}{t^{\frac{1}{2}}} = (2AC_p D_p)^{\frac{1}{2}} \qquad \text{Eq. 41}$$

Matrix-type release profile is resulted. Once again, the drug loading dose (A) in the polymer matrix determines the mechanism and the length of zero-order release profile. The higher the loading dose, the longer the duration of zero-order drug release.

EXPERIMENTAL

A. Materials

1. Chemicals and reagents - Flurogestone acetate (FGA)[1], estradiol[2], norethindrone[3], anhydrous sodium phosphate dibasic[4], anhydrous citric acid[4], polyethylene glycol (PEG) 400[4], glass-distilled acetonitrile[5] and methanol[5], acetone[5] and absolute ethanol[6], were used as received. HPLC-grade water[7] was freshly prepared and used throughout the study.

2. Silicone polymers - Silastic 382 (medical grade) elastomer[8], silicone fluid 360 (medical grade)[8], catalyst M (stannous octanoate)[8], silastic adhesive (silicone Type A, medical grade)[8], and silastic sheeting (medical grade, non-reinforced)[8] were used in the preparation of controlled-release silicone devices.

3. Non-medicated vaginal sponges - Cylinder-shaped polyurethane sponges, hard-grade 800 (gray # 375, 30 mm (h) x 42 mm (d)) or soft-grade 300

(white #373, 30 mm (h) x 40 mm (d))[9], were used in the preparation of Syncro-Mate vaginal pessaries or Rate-Control vaginal devices.

4. Dye solution - 0.5% Red Sudan III dye in absolute ethanol solution was used to study the distribution of drug in the sponges following drug solution disposition.

5. Animal model - The vagina freshly removed from the sheep[10] was used for permeation experiments.

B. Preparations:

1. Preparation of drug delivery devices:

1) Syncro-Mate pessary loaded with dye:

a. Burette-loaded sponges - An aliquot (0.5, 1, 1.5, or 2 ml) of the ethanolic dye solution was pipetted and delivered to the center of the bottom surface of each polyurethane sponge. The sponges were then laid flat on a paper towel with the thread side down and allowed to dry overnight (Fig. 3 A, B, C, and D).

b. Injection-loaded sponges - An aliquot (2 ml) of the ethanolic dye solution was injected into the center of each sponge (from the bottom surface) using a 5 cc. syringe and hypodermic needle. The sponges were laid flat with thread side down on a aluminum grid and allowed to dry overnight. (Fig. 3E).

c. Syringe-loaded sponges - An aliquot (2 ml) of the ethanolic dye solution was spread over the top surface of each sponge using a 5 cc. syringe and hypodermic needle. Sponges were laid flat with thread side up on a wire grid and dried overnight. (Fig. 3F).

After the sponges had been dried, they were cut open vertically for visual inspection (Fig. 3).

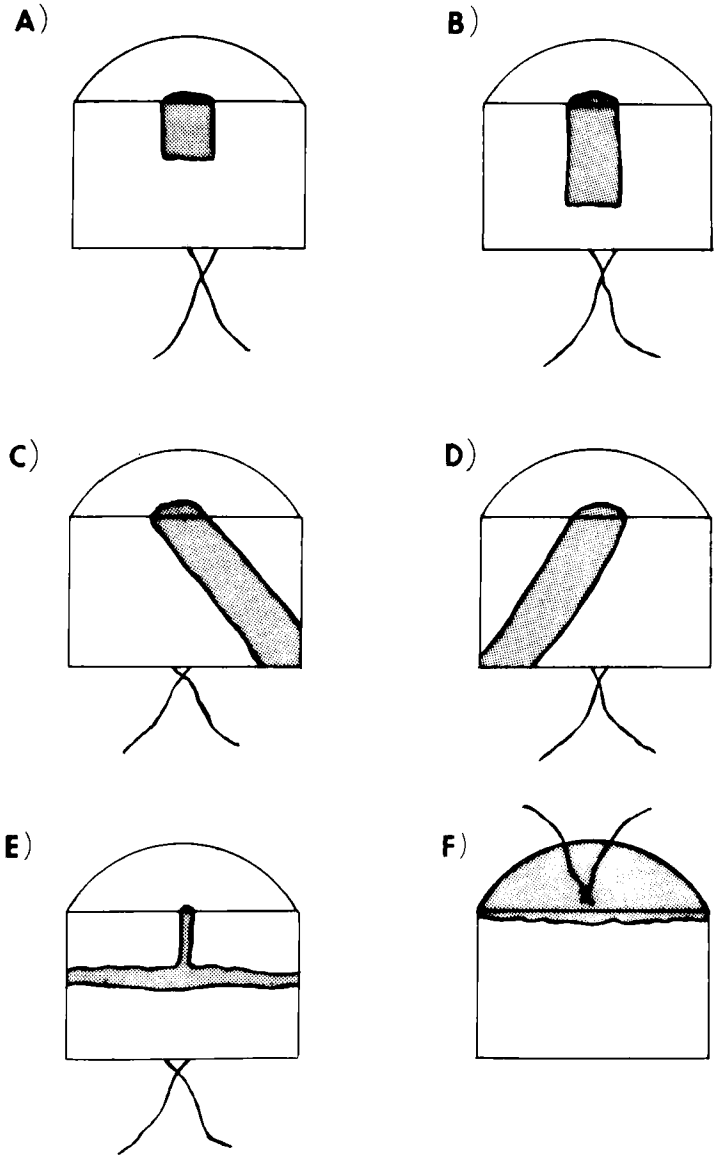

Figure 3: Distribution of a 0.5% ethanolic Sudan III solution in a Syncro-Mate vaginal pessary, after various methods of disposition: Burette-loaded sponges (A) 0.5 ml; (B) 1.0 ml; (C) 1.5 ml; (D) 2.0 ml; Syringe-loaded sponges; (E) 2.0 ml injected into the center of a rotating sponge; (F) 2.0 ml spread on the bottom surface of a sponge (with the threads).

2) Syncro-Mate pessary impregnated with FGA:

The polyurethane sponges (grade 800) were each impregnated, using syringe and hypodermic needle, with 2 ml of FGA solution (containing 5, 10, 15, or 20 mg/ml of FGA) in a combination of acetone and absolute ethanol (1:4) to produce the Syncro-Mate pessaries containing 10, 20, 30, or 40 mg of FGA. These pessaries were suspended on a horizontal bar and allowed to dry overnight.

3) Rate-Control vaginal device (Type I):

FGA (0.2 to 10%), Estradiol (2%) or Norethindrone (2%) was dissolved in acetone and then dispersed in silicone elastomer 382 (80 to 90%) and silicone fluid 360 (10%) which were thoroughly mixed using a laboratory stirrer[11] for 7 minutes. The resultant mixture was continuously stirred over a hot plate (at low setting) in the hood to remove acetone and then deaerated in a dessicator under a vacuum of about 25 mm Hg[12] for 5 minutes with intermittent release of vacuum to break the entrapped air bubbles. After cooling, catalyst M (0.04 ml/10 gm of elastomer base) was then added dropwise and thoroughly mixed for another minute. The mixture, after deaerated again under vacuum for additional 5 minutes, was spread over between two Teflon-covered glass plates (12" x 12"), which were then compressed to a constant thickness of 1 mm. The drug/elastomer blend was then allowed to cure at 60°C for 60 minutes[13]. After proper crosslinking, the resultant medicated silicone sheet was cut into circular discs (28 cm^2) for *in vitro* drug release and vaginal absorption studies.

4) Rate-Control vaginal device (Type II):

The same procedure as outlined above for Type I Rate-Control vaginal pessary was also followed, except that only FGA was used and the deaerated FGA/polymer blend was spread over a thin sheet of silicone membrane (with a thickness of 0.125 to 1.0 mm) using a spatula. Then, another thin sheet of silicone membrane was placed over to

form a 3-layered laminate, which was then pressed between two glass plates to a constant thickness of 1.0 mm (medicated layer). The 3-layered laminate was allowed to cure in the same manner as described earlier.

2. Preparation of elution solution:

The polyethylene glycol (PEG) 400 was added into the simulated vaginal fluid (SVF) to increase drug solubility and to maintain the sink condition required throughout the experiment. The 20% or 40% PEG 400/SVF solutions were prepared, respectively, by adding 200 or 400 ml of PEG 400 to a mixture containing 135 or 200 ml of 0.02M citric acid and 365 or 300 ml of 0.04M Na_2HPO_4, which was then q.s. to 1000 ml with water (pH 7.3 ± 0.5).

C. Simultaneous in vitro release and vaginal absorption studies:

1. Syncro-Mate pessary - A vagina, which was freshly removed from the sheep, was cut open vertically and the mucosa was separated from the wall. Once the donor and receptor compartments of the intravaginal release and permeation (IRP) system[14] (5) had reached the equilibrium temperature[15] of 38°C, the vaginal mucosa was sandwiched between the two compartments and clamped (Fig. 4). A unit of Syncro-Mate pessary (each contains 10-40 mg of FGA) was pre-moistened with 25 ml of elution solution and inserted into the flange opening to be in intimate contact with the vaginal mucosa. The elution solution (650 ml, which contains 20% or 40% PEG 400 in the SVF and pre-heated to 38°C) was introduced into the donor and receptor compartments, respectively, with the bar-shaped magnet rotating at a constant speed of 60 rpm. At scheduled intervals, aliquots of 1 to 100 ml of elution solution were withdrawn from each of the two compartments and assayed for FGA by the HPLC method outlined later. Experiments were conducted in triplicate. Release and vaginal absorption profiles of FGA were monitored simultaneously.

2. Rate-Control vaginal device - The same procedure as outline above for Syncro-Mate pessary studies was also followed, except that a 28 cm^2 circular disc-shaped medicated silicone device (Type I or Type II)

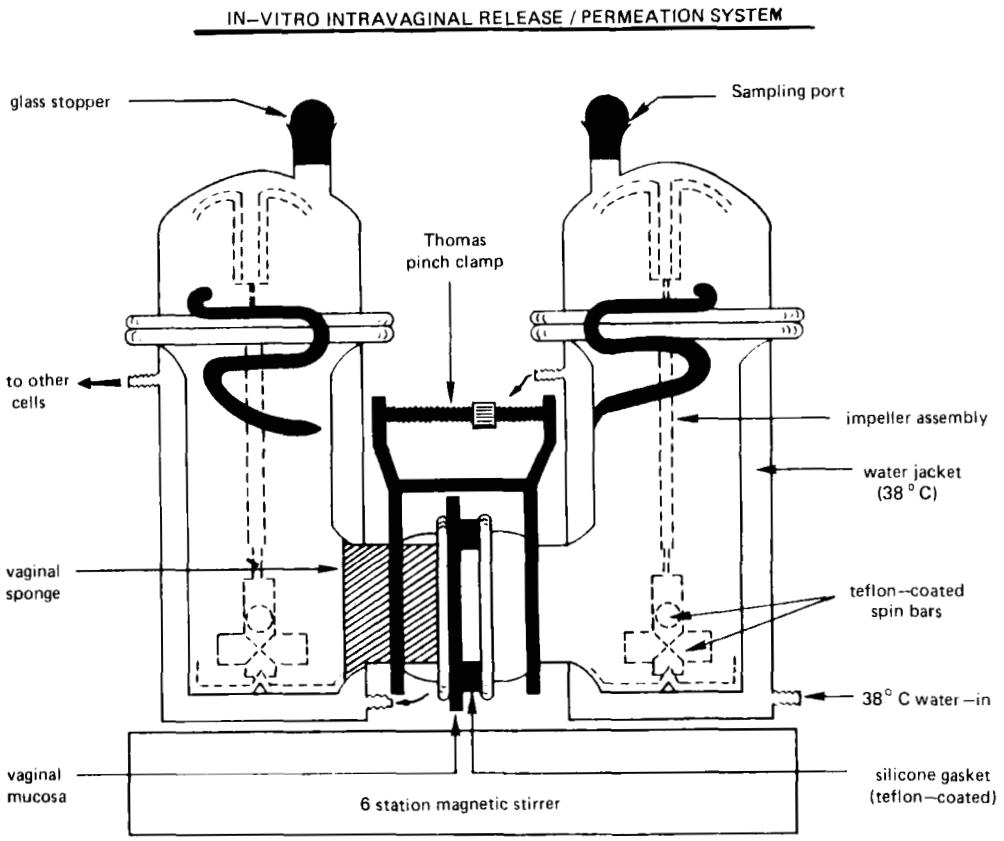

Figure 4: Schematic illustration of a unit of the in vitro intravaginal release and permeation (IRP) system. Each unit consists of a pair of donor (mucosal) and receptor (serosal) compartments and is maintained at 38°C by a circulating thermostated water through the water jacket. The solution hydrodynamics in each compartment is kept at constant by a matched pair of impeller assembly rotating at a synchronous rate, ranging from 60 to 330 rpm, by a six-station magnetic stirrer, for simultaneous release and absorption studies.

was positioned in an intimate contact with the vaginal mucosa and sandwiched between the two compartments (in which the controlled-release silicone disc and the serosal side of the vagina were each immersing in the donor and receptor solutions, respectively). Also, the SVF containing 20% PEG 400 was used as the elution solution with the magnets rotating at a constant speed of 330 rpm.

D. Analytical Procedure:

An aliquot (up to 200 µl) of samples was injected into a micro-processor-controlled high performance liquid chromatograph (HPLC)[16], which was equipped with a variable-wavelength detector, an automatic sampler, a variable-volume injector, a dual-head reciprocating pump and a dual solvent system (7). The 5 µ C_{18} resolve column (3.8 x 15 cm)[18] and the solvent temperature were both kept at ambient conditions. The mobile phase and the detector wavelengths used for the assay of FGA, estradiol, and norethindrone were MeOH-water (50:50) and 240 nm, acetonitrile-water (45.55) and 280 nm, and MeOH-water (50:50) and 240 nm, respectively. At a flow rate of 1 ml/min., specific peaks for FGA, estradiol and norethindrone were detected at retention times of about 4, 6, and 5 minutes, respectively.

F. Data Analysis:

The peak height for a drug was determined from the chromatogram and the drug concentration was calculated by comparing it to the standard curve. The cumulative amount (µg) of drug released was computed and plotted as a function of time (hours or days) or the square root of time ($hours^{1/2}$ or $days^{1/2}$) to determine the flux of drug release.

RESULTS AND DISCUSSION

1) Dye Distribution in Syncro-Mate Pessary

To examine the effect of drug impregnation methods on the drug distribution in the Syncro-Mate pessaries, a dye disposition study was initiated.

The distribution of dye in the sponges following disposition by various methods is shown in Figure 3. After the sponges were cut open, the results indicated that when the sponges are loaded by burette method, with a solution volume ranging from 0.5 ml to 2.0 ml, the dye does not distribute homogeneously throughout the sponge matrix; the dye tends to localize in the vicinity of application or just drips off to the side (Fig. 3A - D). When the dye solution was spread on the top of the sponge, the dye once again does not distribute uniformly in the sponge, but rather remains on the top (Fig. 3F). The best result was obtained when the dye solution was delivered into the center of the sponge by injection method with the sponge rotating during disposition, which seemed to produce a homogeneous distribution in the central plane of the sponge (Fig. 3E). Several experiments were carried out to determine the in vitro release and vaginal absorption profiles of FGA impregnated by various methods outlined above. The results confirmed that the sponges which are prepared by injection of the drug solution into the center of the sponge produce the best drug release and absorption profiles and the least sponge-to-sponge variation. So, for the following simultaneous in vitro drug release and vaginal absorption studies of FGA-impregnated Syncro-Mate pessaries, the injection method was used to load the sponges with 10, 20, 30 and 40 mg of FGA.

2) Simultaneous Release and Absorption Studies:

a) Syncro-Mate pessary - A relatively low rotation speed (60 rpm) was employed in the in vitro simultaneous release and vaginal absorption studies of FGA from the Syncro-Mate pessary to minimize the possibility of the sponge being pulled away from the intimate contact with the vaginal mucosa by centripetal force during the experiment (Figure 4). It was reported earlier, the effect of hydrodynamic boundary layer on the surface of the sponge can be neglected under the ideal mixing conditions, i.e., when Sherwood number is greater than 200 (8). The Sherwood number in the SVF containing 40% PEG 400 was found to be greater than 200, even at 60 rpm; so, a pseudo-steady-state release rate was achieved, which

was independent of the rotation speeds beyond 60 rpm (8). Therefore, the use of 60 rpm did not jeopardize the intrinsic release and absorption rate profiles of FGA from the Syncro-Mate pessaries.

The in vitro release and vaginal absorption profiles of FGA from the Syncro-Mate pessaries containing 40 mg of FGA are shown in Fig. 5. The results indicated that both the release and absorption profiles of FGA follow the typical matrix-control process as shown by the linear $Q - t^{1/2}$ relationship, which is different from the Q - t relationship observed earlier for the vaginal permeation of FGA from a saturated solution (5). Furthermore, it was noted that the flux of drug release, as indicated by the magnitude of the slope ($Q/t^{1/2}$), is about 18 times greater than the flux of vaginal absorption of FGA from the Syncro-Mate pessaries (818 vs. 46 $\mu g/cm^2/day^{1/2}$). The results suggested that only a very small fraction of the drug dose released is actually absorbed. The observations also implied that as the drug is released, under the in vivo conditions, from the pessary into the vaginal fluid, majority of the dose released could be washed away by the vaginal fluid. Since the drug concentration in the vaginal fluid is decreasing with time, the rate of absorption is also expected to be decreasing, so a non-linear absorption profile is resulted. The results also suggested that the release mechanism is mainly determined by the diffusion process in the solution-filled sponge matrix, while the absorption is controlled by the permeation across the vaginal mucosa. Also, the great discrepancy observed between the absorption and the release profiles under the in vitro conditions could produce an unpredictable in vivo absorption pattern. All the results discussed above suggested that designing of a new vaginal delivery device, which closely matches the drug release profile with vaginal absorption profile, would be highly desired. This type of vaginal device will permit one to predict the vaginal absorption profiles of drugs from their release profiles.

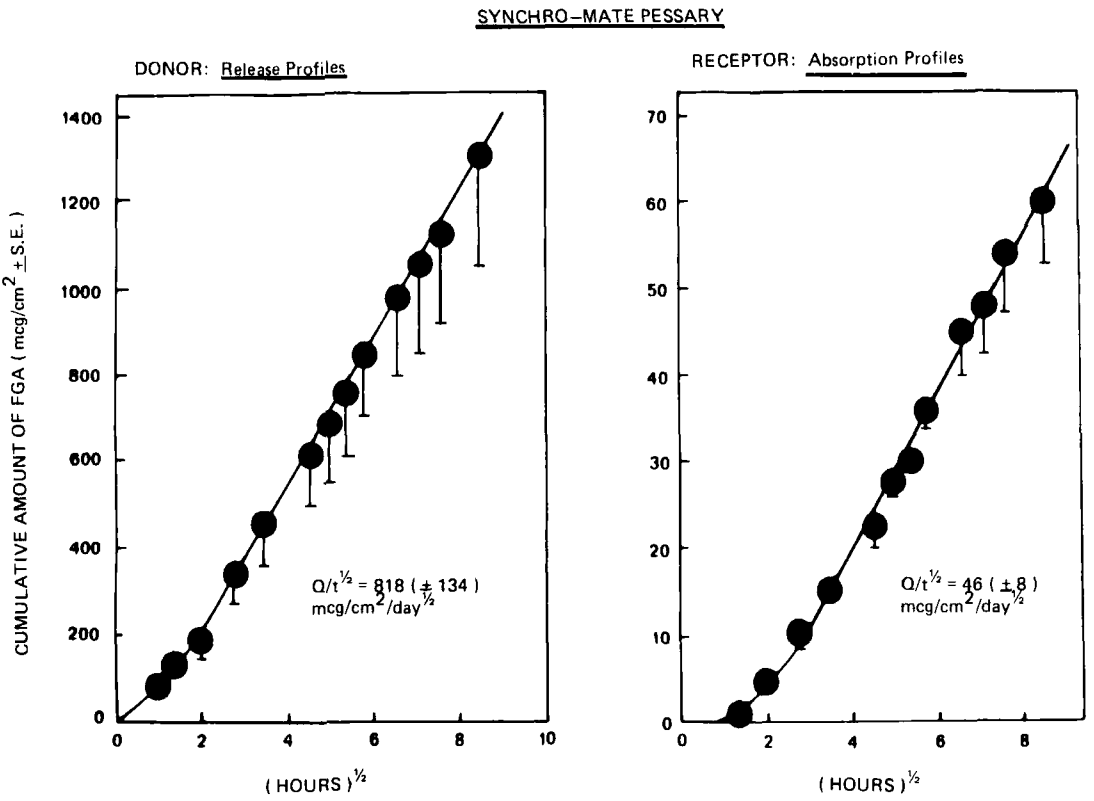

Figure 5: Simultaneous in vitro release and vaginal absorption profiles of FGA from the Syncro-Mate pessary (each contains 40 mg of FGA) in 650 ml of elution medium (Donor: 40% PEG 400/SVF, Receptor: 20% PEG 400/SVF) at 60 rpm. The release and absorption profiles of flurogestone acetate were both found to follow a linear $Q - t^{\frac{1}{2}}$ relationship. However, the release flux was found to be 18 times greater than the absorption flux (818 ± 134 vs. 46 ± 8 mcg/cm^2/day$^{\frac{1}{2}}$). Each data point represents the mean value ± standard error of 3 determinations.

Futhermore, if the controlling of the drug release rate resides in the delivery device, not in the vagina, it should lead to a lesser sheep-to-sheep variation and a greater predictability of the intravaginal drug absorption patterns.

The effect of FGA loading dose initially impregnated in the Syncro-Mate pessary on the in vitro release and vaginal absorption rate profiles of FGA was also studied. The flux of release or absorption, as indicated by the slope ($Q/t^{1/2}$) of the $Q - t^{1/2}$ linearity, should be linearly dependent upon the square-root of loading dose ($A^{1/2}$) as expected from the following relationship (5):

$$\frac{Q}{t^{1/2}} = \left[\frac{D\varepsilon}{\theta}(2A - \varepsilon C_s)C_s\right]^{1/2} \qquad \text{Eq. 44}$$

Where, D is the drug diffusivity in the sponge matrix with a porosity of ε and a tortuosity of θ.

Eq. (44) suggests that the magnitude of $Q/t^{1/2}$ values should increase as the drug loading dose in the sponge increases. The FGA dose levels ranging from 10 to 40 mg per sponge were investigated. As suggested by Eq. (44), the results confirmed that both the $Q/t^{1/2}$ values for the release and vaginal absorption of FGA are linear dependent upon the square root of 2A (Fig. 6). However, a poor correlation still exists between the release and absorption profiles. The release rate profile showed about 21 times greater dependency on the loading dose than did the absorption rate profile.

Apparently, the Syncro-Mate pessary inherently has several distinct disadvantages, including the poor intravaginal bioavailability as a result of low efficiency of drug absorption following the release, which suggests a great extent of drug loss or wastage due to the washing off of the drug by vaginal secretions. As the result of the matrix-type drug release, a higher dosage is required to insure an efficacious blood level at the end of 15-day treatment period. Additionally, the data suggested that the release and absorption profiles are extremely unpredictable as shown by the large value of standard deviations. To overcome these disadvantages, a new rate-control vaginal pessary was being considered for development.

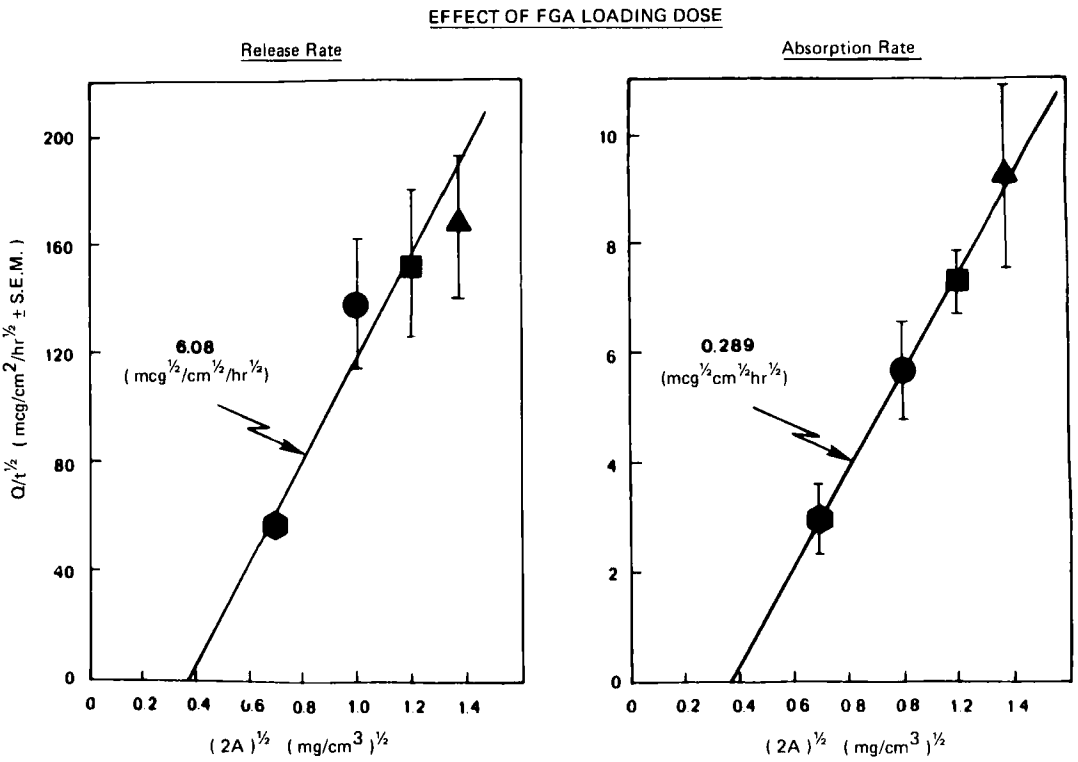

Figure 6: Effect of drug loading dose on the simultaneous release and absorption profiles of FGA from Syncro-Mate Pessary. A linear relationship was established between the fluxes of drug release and vaginal absorption, $(Q/t^{\frac{1}{2}})$ and the square-root of loading dose, $(2A)^{\frac{1}{2}}$. The dose dependency of release rate was found to be 20 times greater than the dose dependency of absorption rate (6.08 vs. 0.289 $mcg^{\frac{1}{2}}/cm^{\frac{1}{2}}/hr^{\frac{1}{2}}$). Each data point represents the mean value ± standard error of 3 determinations.

b) Rate-Control Vaginal device (Type II) - The release and absorption profiles of FGA from a Rate-Control vaginal device are shown in Figure 7. This new vaginal device was prepared by laminating a drug dispersing silicone device (1% FGA) between two polymer coating membranes. The quantity of drug released was found to be a linear function of time (Q vs. t relationship).

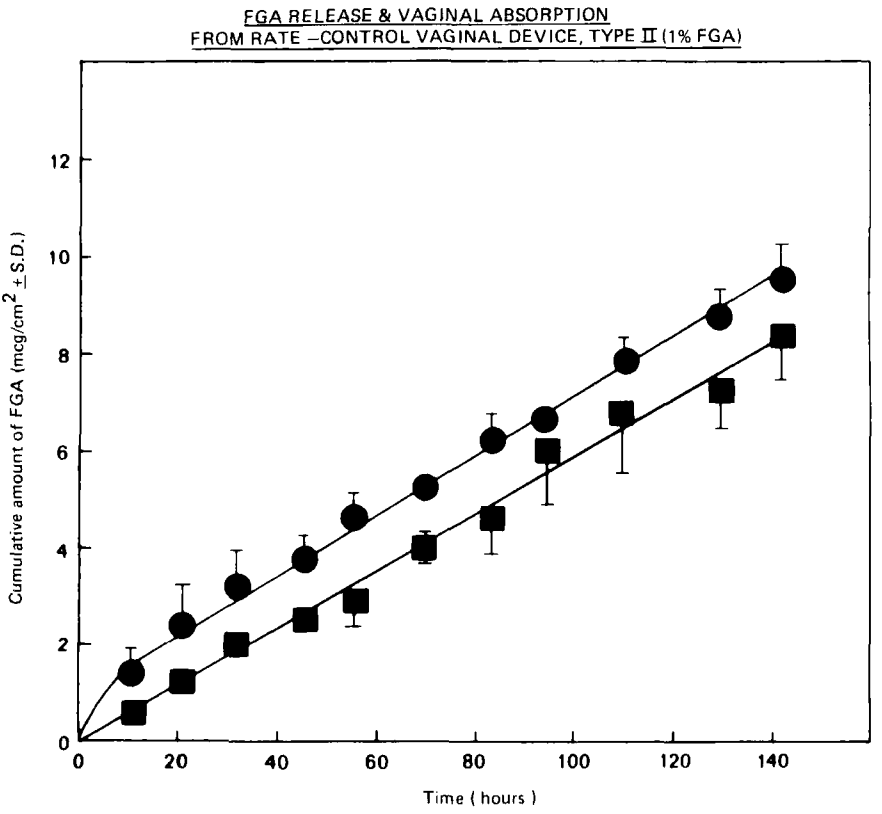

Figure 7: The time course for the in vitro release and vaginal absorption of FGA (Q) from the Rate-Control vaginal device (Type II, containing 1% FGA and 0.5 mm polymer coating membrane). A linear Q vs. t relationship was established with the release rate of 1.44 ± 0.20 mcg/cm^2/day (●) and absorption rate of 1.42 ± 0.26 mcg/cm^2/day (■). Each data point represents the mean value ± standard deviation of 3 determinations.

Mechanistically, when the coating membrane acts as the rate-limiting step for drug release, the absorption rate should be constant as defined by Eq. (33b). The steady-state in vitro release and vaginal absorption rates are defined by Eq. 36 and Eq. 32, respectively. It was rather encouraging to see that the release and absorption profiles of FGA are very much agreed with each other (1.44 ± 0.20 vs. 1.42 ± 0.26 μg/cm^2/day, Fig. 7), unlike the Syncro-Mate pessary

(818 ± 134 vs. 46 ± 8 $\mu g/cm^2/day^{\frac{1}{2}}$, Fig. 5). The agreement between drug absorption and release profiles could lead to a greater intravaginal bioavailability and a better predictability for in vitro-in vivo relationship. The observation for a negligible difference between release and absorption rate profiles suggested that the diffusional resistance of vaginal mucosa (R_v term in Eq. 32) is negligibly small.

However, the release and absorption rates of FGA from the devices coated with polymeric membrane (0.5 mm in thickness), unfortunately, were too low to provide a sufficient dose of FGA for an effective estrus synchronization in the sheep. It was reported that a daily dose of 0.3 ~ 0.4 mg of FGA would be required for inducing the estrus synchronization in sheep (2). Since, the drug-releasing surface of the controlled-release silicone device was limited by the size of vaginal sponge (as the supporting matrix), one of the alternate methods of increasing the rate of drug availability would be to decrease the thickness of the polymer coating membrane. Eq. (33c) suggested that the rate of intravaginal drug absorption from a membrane permeation-controlled drug delivery system should be inversely proportional to the thickness of the rate-controlling polymeric membrane. Experimentally, this linearity was followed fairly well for both the release and absorption rate profiles (Fig. 8). As the thickness of the polymer coating membrane decreased from 1.0 mm to 0.25 mm, there was a linear and proportional increase in the release and absorption rates of FGA. This observation agreed fairly well with Equations (33c) and (36a). The rates of vaginal absorption were also noted to be very much agreeable with the rates of drug release. Extrapolation of the data in Fig. 8 suggested that absorption rate of about 300 mcg/day (the FGA dose needed for an effective estrus synchronization in the sheep) can be achieved by using a silicone membrane with a thickness of only about 0.05 mm to coat a vaginal device with a

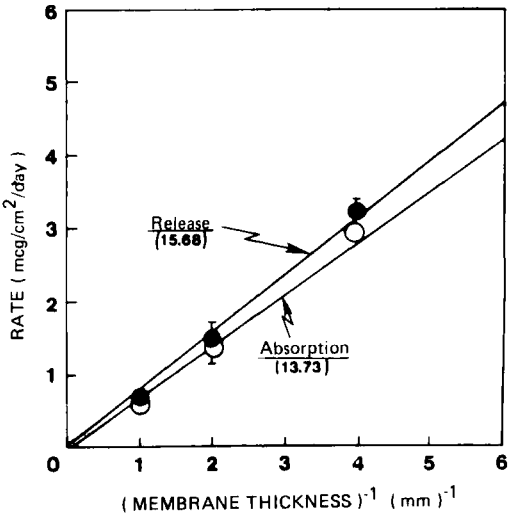

Figure 8: Effect of coating membrane thickness on the rates of in vitro release and vaginal absorption of flurogestone acetate from Rate-Control vaginal device (Type II, containing 1% FGA and 0.25, 0.50, and 1.00 mm coating membrane). The rates of release and vaginal absorption (Q/t) were observed to increase linearly with the reciprocal of the membrane thickness. Each data point represents the mean value ± standard deviations of 3 determinations. Keys: (●) Release rate profile, (○) Absorption rate profile

side surface of 39 cm^2. The thinnest silicone membrane that is commercially available in the marketplace for biomedical uses is only 0.125 mm, which is 25 times thicker than it is needed. An attempt was made in our laboratory without success to make a thin membrane, since the required mechanical strength of the membrane was found to be lacking at this thickness (0.05 mm).

c) Rate-Control Vaginal device (Type I) - Since a polymeric membrane of 0.05 mm in thickness was considered to be too thin a membrane to be fabricated, the theoretical model was further analyzed to see whether one can increase the rate of drug release and vaginal

absorption by eliminating totally the polymer coating membrane, while the desired zero-order rate profile can still be maintained. It was discovered that the drug release and vaginal absorption profiles from the Rate-Control vaginal device could still follow the zero-order kinetic process, under the conditions defined by Equations (39) & (43), even without a polymer coating membrane. This theoretical analysis encouraged the development of Type I Rate-Control vaginal device, which consists of no polymer coating membrane.

Eq. (39) and (43) suggested that the *in vitro* drug release and vaginal absorption profiles should follow a linear *Q vs. t* relationship. This is clearly shown experimentally in Fig. 9. From the *Q versus t* linearity, the rates of 18.56 ± 1.23 and 14.6 ± 0.54 mcg/cm^2/day were obtained, respectively, for the release and absorption of FGA. Once again the release and absorption rates are very close to each other (18.56 ± 1.23 vs. 14.6 ± 0.54 mcg/cm^2/day), indicating a fairly good intravaginal bioavailability and *in vitro-in vivo* predictability. The results suggested that to obtain a clinically efficacious daily dose of 0.3 - 0.4 mg, a surface area of the controlled-release silicone device between 18 to 24 cm^2 would be enough, which is certainly a smaller area than the circumference surface of the polyurethane sponge (39 cm^2). The *in vivo* release profiles of FGA from this Rate-Control vaginal device (Type I) and its clinical efficacy will be discussed in the next article of this series of reports.

When the drug loading dose of FGA in the Rate-Control vaginal device was reduced by 10 folds from 2% to 0.2%, however, the drug release and the vaginal absorption profiles were observed to shift from the *Q-t* relationship to a $Q - t^{1/2}$ linearity (Figure 10), as predicted from Equation (41). Chien et al (10), also reported a similar transition of drug release and vaginal absorption

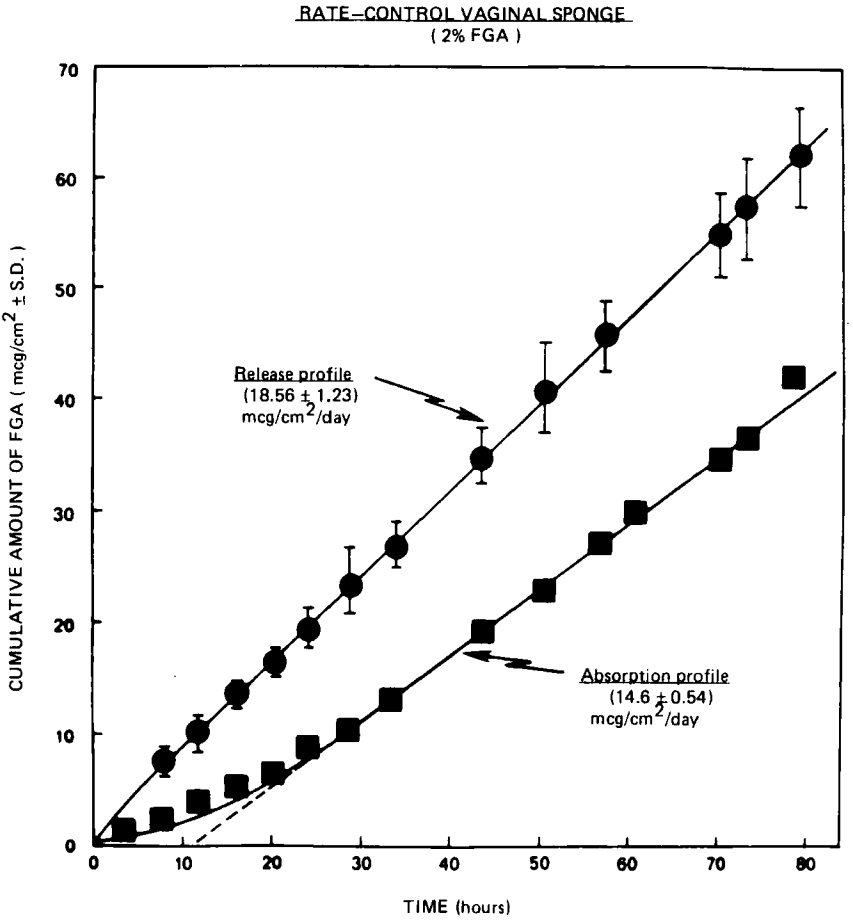

Figure 9: The time course for the in vitro release and vaginal absorption of FGA from Rate-Control vaginal device (Type I, containing 2% FGA). A linear Q vs. t relationship was established with the release rate of 18.56 ± 1.23 mcg/cm^2/day (●) and absorption rate of 14.6 ± 0.54 mcg/cm^2/day (■). Each data point represents the mean value ± standard deviation of 3 determinations.

mechanisms, i.e., the shift from a partition-control to a matrix-control process, when the intravaginal release profiles of ethynodiol diacetate from silicone devices were followed in the rabbits' vagina.

The release and absorption profiles of FGA from an intermediate dose (0.5%) were also studied and the results indicated that

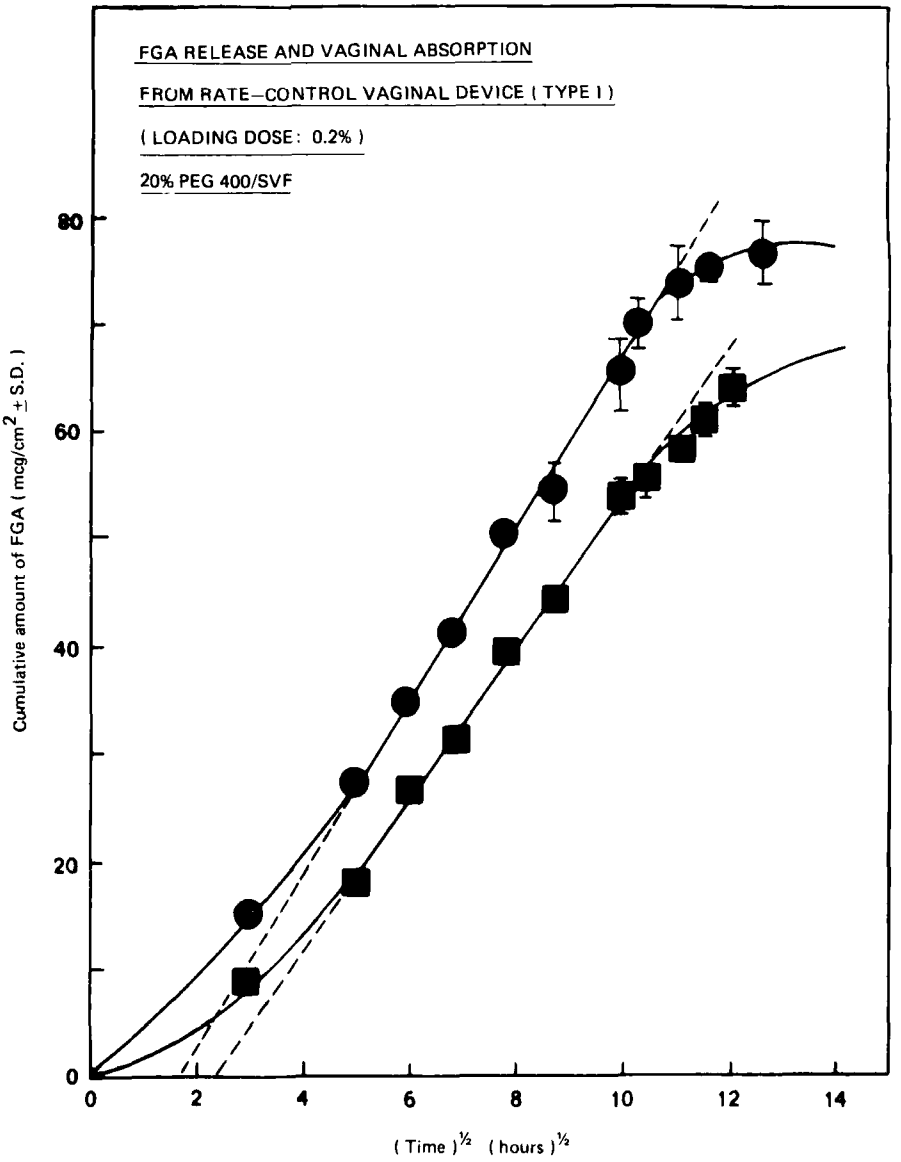

Figure 10: The time course for the in vitro release and vaginal absorption of FGA from Rate-Control vaginal device (Type I, containing 0.2% FGA). A linear Q vs. $t^{\frac{1}{2}}$ relationship was observed with the release flux of 7.14 ± 0.29 mcg/cm^2/hr$^{\frac{1}{2}}$ (●) and the absorption flux of 6.40 ± 0.11 mcg/cm^2/hr$^{\frac{1}{2}}$ (■). Each data point represents the mean value ± standard deviation of 3 determinations.

zero-order release and absorption profiles are observed initially, and then shift to the matrix ($Q - t^{\frac{1}{2}}$)-type release and absorption profiles at a later time (Figure 11).

d) Intravaginal Controlled Absorption of Other Steroids - In Eq. (41), it was assumed that a drug with a low polymer solubility and/or a high drug loading dose, a zero-order type of drug release and vaginal absorption profiles can be predicted. To validate this proposed physical model, the release and absorption profiles of other steroids with low polymer solubility and low partition coefficient, like estradiol and norethindrone, were also studied. The results clearly indicated that the release and absorption profiles of estradiol and norethindrone from the Rate-Control vaginal devices both follow Q - t linearity (Figure 12); and the release and absorption rates for both drugs are slightly greater than the results observed for FGA (Table I). The release rates, as determined by Eq. (43), should be directly proportional to their respective polymer solubility (C_p). The magnitude of Q/t values for the release of drugs from the Rate-Control vaginal devices, which were determined from the slopes of Q vs. t plots, was noted to increase from FGA to norethindrone as increasing the polymer solubility of the drugs (Table 1).

The magnitude of the rates of vaginal absorption was also observed to increase from FGA to norethindrone. However, it could be due to the difference in the permeability of vaginal mucosa, the increase was not as dramatic as the release rates. According to Eq. 39, the rate of vaginal absorption should be directly proportional to polymer solubility (C_p) and inversely proportional to the total diffusional resistance across the composite of aqueous layer, vaginal mucosa and hydrodynamic boundary layer. Although the polymer solubility increases in the order of: FGA < estradiol < norethindrone, the magnitude of the total resistance should also

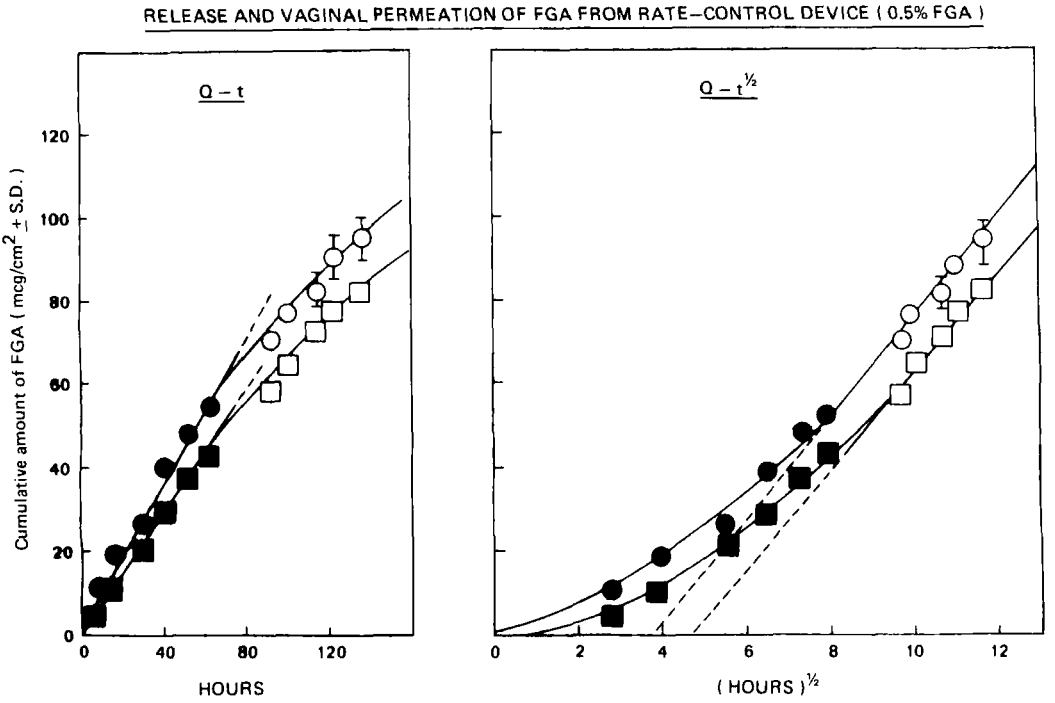

Figure 11: The time course for the in vitro release and vaginal absorption of FGA from Rate-Control vaginal device (Type I, containing 0.5% FGA). A linear Q vs. t relationship was observed for the initial 64-hour period, beyond which the drug release and vaginal absorption profiles shifted to the Q vs. $t^{1/2}$ linearity. A transition phase exists between the partition--control and the matrix-control processes for FGA release and absorption. Each data point represents the mean value ± standard deviations of 3 determinations. Keys: Release profiles - 0.78 ± 0.03 mcg/cm^2/hr (●, <64 hrs) and 14.18 ± 2.30 mcg/cm^2/hr$^{1/2}$ (○, >64 hrs), vaginal absorption profiles - 0.74 ± 0.01 mcg/cm^2/hr (■, <64 hrs) and 12.17 ± 1.24 mcg/cm^2/hr$^{1/2}$ (□, >64 hrs).

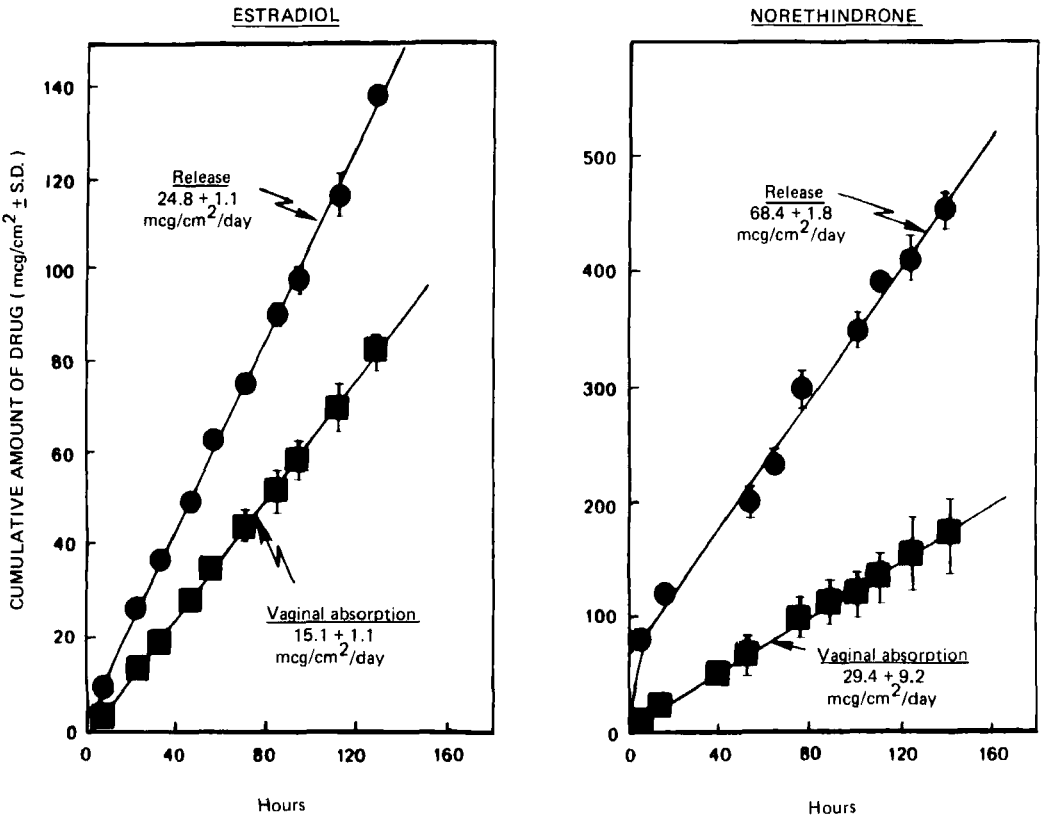

Figure 12: The time course for the in vitro release and vaginal absorption of estradiol and norethindrone from Rate-Control vaginal device (Type I, containing 2% estradiol or 2% norethindrone). A linear Q vs. t relationship was established. Each data point represents the mean value ± standard deviation of 3 determinations. Keys: Estraddiol - (●) release rate, 24.8 ± 1.1 mcg/cm^2/day; and (■) absorption rate, 15.1 ± 1.1 mcg/cm^2/day; norethindrone - (●) release rate, 68.4 ± 1.8 mcg/cm^2/day; and (■) absorption rate, 29.4 ± 9.2 mcg/cm^2/day.

increase steadily as the result of the increased resistance in the vaginal mucosa (since the resistance across the aqueous layer and hydrodynamic boundary layer are relatively constant for these steroids with relatively similar molecular weight). This increase in the total diffusional resistance tends to overweigh the increase

Table I: Comparison of in vitro release and absorption rates from Rate-Control vaginal device (Type I)

Steriod	Release Rate (mcg/cm^2/day)	Absorption Rate (mcg/cm^2/day)	Ratio[a)]	C_p (mcg/ml)
Flurogestone Acetate	18.56 ± 1.23	14.6 ± 0.54	0.787	3.1 ± 0.9
Estradiol	24.80 ± 1.10	15.1 ± 1.10	0.609	4.0 ± 0.7[b)]
Norethindrone	68.4 ± 1.80	29.4 + 9.20	0.430	11.0 ± 3.1[b)]

a) Ratio of absorption rate (A) over release rate (R)

b) Data from Reference 14.

in polymer solubility. In the in vitro release studies where the only resistance is the diffusion across the boundary layer, which is constant for all the steroids studied in this investigation, the same hydrodynamic conditions were maintained.

The ratio of the vaginal absorption rates to the release rates of various steriods from the Rate-Control vaginal device was also compared. The results indicated that the ratio decreases from 0.787 for FGA to 0.430 for norethindrone (Table I). The observed difference can be explained by comparing the mathematical expressions for vaginal absorption and release rates (Eq. 39 vs. 43). The ratio (γ') is thus defined by Eq. (45):

$$\gamma' = \frac{R_d'' K_s'}{[R_{aq} K_s' + R_v + R_d/K_v]} \qquad \text{Eq. 45}$$

since, $$R_d'' K_s' = \frac{R_d}{K_v} \qquad \text{Eq. 46}$$

Equation (45) becomes:

$$\gamma' = \frac{R''_d K'_s}{[R_{aq} K'_s + R_v + R''_d K'_s]} \quad \text{Eq. 47}$$

Since the diffusional resistances across the hydrodynamic boundary layer (R''_d) and aqueous layer (R_{aq}) are relatively constant for a particular drug, Eq. (47) can be rewritten as:

$$\gamma' = \frac{k_1}{[k_2 + R_v]} \quad \text{Eq. 48}$$

where, $k_1 = R''_d K'_s$ Eq. 49

and $k_2 = [R_{aq} K'_s + R''_d K'_s]$ Eq. 50

Eq. (48) indicates that for a given value of k_1 and k_2, the γ' value should be inversely proportional to the diffusional resistance across the vagina (R_v). In other words, the larger the magnitude of R_v, the lower the γ' value. The data in Table I indicated that the resistance due to the diffusion across the vagina increases in the following order: FGA < estradiol < norethindrone.

3) Transport Mechanism of FGA Through Vaginal Wall:

The permeability coefficient of the vaginal membrane (P_v) can be determined from the following relationship:

$$\frac{1}{P_v} = \frac{1}{P_{app}} - \left[\frac{1}{(P_{aq})_m} + \frac{1}{(P_{aq})_s}\right] \quad \text{Eq. 51}$$

Where $P_{aq} = \frac{D_{aq}}{h_{aq}}$ Eq. 52

Where, P_v is the intrinsic permeability coefficient for the vaginal membrane; P_{app} is the apparent permeability coefficient across the vagina, and $(P_{aq})_m$ and $(P_{aq})_s$ are the permeability coefficients across the aqueous diffusion layers on the mucosal and serosal sides of the vaginal membrane, respectively.

Assuming that the drug diffusion through the aqueous pores in the vaginal membrane is negligible, and based on the earlier data on P_{app} (0.311 cm/day)(5) and the following information:

a) For mucosal aqueous diffusion layer (40% PEG 400/SVF)

$(D_{aq})_m = 1.96 \times 10^{-6}$ cm^2/sec.

$(h_{aq})_m = 7.4 \times 10^{-4}$ cm.

b) For serosal aqueous diffusion layer (20% PEG 400/SVF)

$(D_{aq})_s = 6.95 \times 10^{-7}$ cm^2/sec.

$(h_{aq})_s = 1.4 \times 10^{-4}$ cm

the P_v value was calculated to be 0.314 cm/day, which is very close to the P_{app} value (0.311 cm/day). The observation suggested that during the course of vaginal absorption, the FGA molecules encounter the diffusional resistance across the vaginal mucosa, not the diffusional resistance across the hydrodynamic boundary layers on both the mucosal and serosal sides of the vaginal membrane.

CONCLUSION

Syncro-Mate pessaries prepared by injection technique (2 ml into the center) yielded the best distribution of dye in the sponges, and so the pessaries loaded with 10 - 40 mg of FGA, by the same technique, produced a reproducible drug release and vaginal absorption rate profiles. The simultaneous release and absorption profiles generated from these Syncro-Mate sponges were observed to follow Q - $t^{\frac{1}{2}}$ type relationship. However, the release flux was found to be about 18 times greater than the flux of vaginal absorption. The fluxes of release and absorption ($Q/t^{\frac{1}{2}}$) were found to increase linearly with the square root of loading dose. Since the in vitro fluxes of release and absorption from Syncro-Mate Pessaries were not constant and a very low bioavailability was yielded, a new Rate-Control vaginal device (contains a controlled release silicone device with or without a polymer coating membrane) was thus developed.

The new Rate-Control vaginal device with polymer coating membrane was observed to produce constant (Q - t) release and absorption profiles, as predicted from the theoretical model. However, the rates of absorption (Q/t) were found to be too small to be clinically effective for the estrus

synchronization of the sheep. Since the attempts to prepare a polymer coating membrane which is thin enough to release FGA at an efficacious rate from the Rate-Control vaginal device proved to be unfruitful, another type of Rate-Control device was fabricated from a controlled-release silicone device without the coating of a polymeric membrane. Theoretically, a zero-order profile could also be achieved, which was demonstrated experimentally, if the devices contained a FGA loading dose greater than 2%. The rate of vaginal absorption was predicted to be about 300 mcg/day from this new type of Rate-Control vaginal device with a surface area of 18 to 24 cm^2, which is considered to achieve the efficacious dose needed. On the other hand, the devices fabricated from 0.2% FGA was observed to follow a $Q - t^{\frac{1}{2}}$ relationship (at steady state), as predicted from the theoretical model. The vaginal absorption of FGA was found to be primarily controlled by the vaginal wall, not by the hydrodynamic boundary layer on the both sides of the vaginal membrane, under the hydrodynamic conditions of the present study.

In order to further validate the physical model developed, the *in vitro* release and vaginal absorption of other steriods, i.e., estradiol and norethindrone, from the Rate-Control vaginal devices were also studied. The profiles generated were observed to follow the predicted linear Q - t relationship. The *in vitro* release and vaginal absorption profiles for estradiol and norethindrone can be optimized by adding a polymer coating membrane to further control the release of the drugs, so an optimum dose cna be delivered.

The new Rate-Control vaginal device developed was found to be superior than the Syncro-Mate pessary currently marketed. Under the *in vitro* conditions, FGA was delivered at a slower, but a constant rate; and better bioavailability could be accomplished. The clinical effectiveness and *in vivo* vaginal absorption rate were evaluated and the results will be reported in the next paper of this series.

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FOOTNOTES

1. Searle Laboratories, Skokie, Illinois.
2. Roussel Uclaf, Paris, France.
3. Sigma Chemical Company, St. Louis, Missouri.
4. Fisher Scientific Co., Fairlawn, New Jersey.
5. Burdick & Jackson Lab. Inc., Muskagon, Michigan.
6. Pharmko, Publick Industries Co., Linfield, Pa.
7. Nanopure, Sybron/Barnstead, Boston, Massachusetts.
8. Dow Corning Corporation, Midland, Michigan.
9. Synkron Corporation, Paris, France.
10. Dealeman Meats, Warren Township, New Jersey.

11. Model #43800-00, Cole-Parmer, Chicago, Illinois.
12. Vacuum pump Model # SASSNXGTC-4143, Cole-Parmer, Chicago, Illinois.
13. Series 200, Fisher-isotemp oven, Fisher Scientific Co., Springfield, New Jersey.
14. Bellco Glass, Inc., Vineland, New Jersey.
15. Waterbath Model 80, Fisher Scientific Co., Springfield, New Jersey.
16. HP Model 1084B HPLC, Hewlett-Packard, Palo Alto, California.
17. Resolve C-18 column, Waters Associates, Milford, Massachusetts.

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