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Medicated Tampons: Intravaginal Sustained Administration of Metronidazole and *In Vitro–In Vivo* Relationships

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Abstract □ The technical feasibility of utilizing tampons as a drug delivery system for prolonged intravaginal drug administrations was studied. Several commercially available brands of tampons were examined. The methodology for the incorporation of various doses of metronidazole, an antitrichomonas agent, in tampons was described. The sustained-release profile of metronidazole from these medicated tampons was characterized. Intravaginal administration of metronidazole *via* the medicated tampons was investigated in rhesus monkeys and human volunteers, and *in vitro–in vivo* correlations were established. The biopharmaceutics of intravaginal absorption of metronidazole *via* medicated tampons was analyzed in comparison with a vaginal solution formulation.

Keyphrases □ Metronidazole—intravaginal sustained administration in medicated tampons, *in vitro–in vivo* relationships □ Tampons—intravaginal sustained administration of metronidazole, *in vitro–in vivo* relationships □ Intravaginal administration—sustained metronidazole in tampons, *in vitro–in vivo* relationships

Tampons are made of cotton and/or cellulose and are commonly used for intravaginal insertion to absorb menstrual discharge (1). Numerous brands of vaginal tampons are commercially available. Their characteristics of high fluid absorbability and retention have been recommended for the absorption of extensive vaginal discharge in trichomonas-infected women.

Metronidazole[1] has been shown to be an effective antiprotozoal agent with a broad spectrum of activity against anaerobes (2–6). It is selectively absorbed by and produces cytotoxicity in anaerobes (6–8). Its efficacy in the treatment of *Trichomonas vaginalis* has been well documented (9). The idea of developing a medicated tampon to combine the therapeutic efficacy of metronidazole and the high fluid absorbability of tampon for trichomonas-infected women is thus generated.

Additionally, a high incidence of toxic shock syndrome was recently reported in menstruating women who used tampons, especially one brand[2] (10). Continuing epidemiological and microbiological studies at the Center for Disease Control have firmly related the pathogenesis of toxic shock syndrome to the infection of *Staphylococcus aureus* isolated from the vaginas of patients who suffered from toxic shock syndrome (98 *versus* 7% in the unmatched controls). On the other hand, no *S. aureus* could be recovered from the unused tampons, including those from tampon boxes used by the patients (10). The incidence of toxic shock syndrome further suggests the need to develop a medicated tampon, which administers an antistaphylococcal agent in the vagina in a controlled manner for a prolonged period of time, to protect the user from *S. aureus* infection.

The objective of this investigation is to evaluate the technical feasibility of using the tampon as an intravaginal drug delivery system. In this report, the methodology for

[1] Flagyl (SC-10295), Searle Laboratories, Division of G. D. Searle & Co., Skokie, IL 60077.

[2] Rely tampons.

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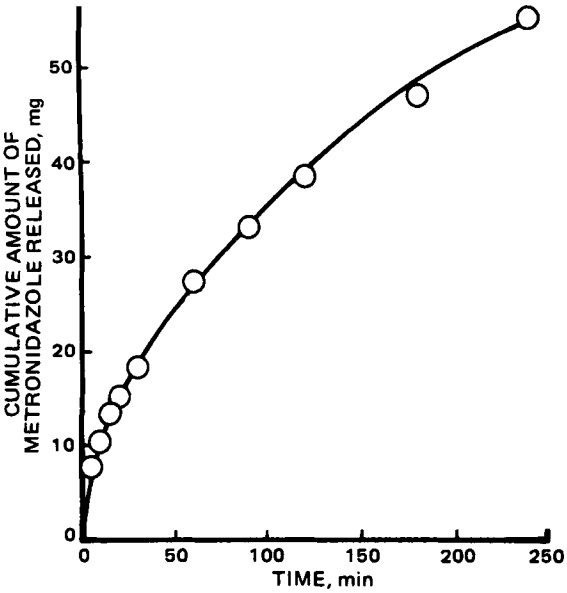

Figure 1—*Time course for the release of metronidazole from medicated Tampon I (A = 20.25 mg/cm³) into 200 ml of simulated vaginal fluid (pH 4.5) at 37° for 4 hr.*

the incorporation of various doses of metronidazole in several well-known brands of tampon is described, and the sustained-release profile of metronidazole from these medicated tampons is characterized. Sustained intravaginal administration of metronidazole *via* the tampon was also examined in both rhesus monkeys and human volunteers. *In vitro–in vivo* correlations were established and the biopharmaceutics of intravaginal absorption of metronidazole was also analyzed.

EXPERIMENTAL

Materials—Both metronidazole[1] and various commercial brands[3–5] of tampon (I–IV) were used as obtained. All the reagents or solvents used were analytical reagent grade.

Impregnation of Tampons with Metronidazole—Impregnation of tampons with metronidazole was achieved by preparing a concentrated metronidazole solution in acetone–methanol combinations and placing an aliquot of this solution onto the tip of the tampons. The solution was allowed to diffuse throughout the tampon body and the solvent was then evaporated under controlled conditions. This process was repeated until the desired amount of metronidazole was impregnated.

***In Vitro* Elution Studies of Medicated Tampons**—A polyethylene tube (6-cm length; 1.6-cm o.d.; 1.5-cm i.d.) with 20 evenly distributed openings (2.5 mm in diameter) was fabricated as the tampon holder for *in vitro* drug elution studies to simulate the constriction produced by the vaginal wall on the tampon *in situ*. All *in vitro* elution studies of medicated tampons were conducted under sink conditions in 200 ml of simulated vaginal fluid (0.026 *M* citric acid and 0.024 *M* sodium citrate in distilled water at pH 4.5) in a 250-ml reagent bottle thermostated at 37° in a waterbath (with a shaking rate of 80 oscillations/min). A 1-ml aliquot was withdrawn at each scheduled interval for up to 4 hr. After appropriate dilution, the concentration of metronidazole in the simulated vaginal fluid was determined spectrophotometrically[6] at its λ_{max} value of 316 nm. Several long-term (*e.g.*, 24 hr) drug elution studies were also carried out to ensure that 100% release of the impregnated metronidazole could be achieved from various brands of tampons.

Intravaginal Release Studies of Medicated Tampons—Five female, mid-cycle rhesus monkeys, weighing 4.7–6.5 kg, were used for crossover intravaginal release studies. Each monkey was tranquilized with 3 mg im of phencyclidine hydrochloride[7]. After tranquilizing, the animal was placed on its stomach on a V-board with the legs hanging freely over the end. The vagina was then sufficiently distended with a speculum to permit the easy insertion of a medicated tampon (1.5 cm in length). After insertion, each animal was placed in a primate chair[8] until the tampon was removed. The tampon was removed at 2, 4, 8, 16.5, or 25.5 hr after insertion by gently pulling on the string (which is attached to the tampon). The residual amount of metronidazole in each tampon was then analyzed spectrophotometrically following a 4-hr extraction with 40 ml of methanol.

Table I—*In Vitro* Release of Metronidazole from Various Brands of Tampon

Brands[a]	Surface Area, cm^2	Volume of Liquid Retained[b], ml/tampon	$Q/t^{1/2}$ [c], $\mu g/cm^2/min^{1/2}$
I	22.93	32.2	79.4
II	21.34	35.5	76.9
III	27.26	30.0	37.4
IV	28.99	24.0	51.6

[a] Each tampon was impregnated with 60 mg of metronidazole. [b] Volume of simulated vaginal fluid absorbed by 10-min soaking of tampon at room temperature. [c] *In vitro* release profile determined in simulated vaginal fluid at 37°.

Pharmacokinetics of Intravaginal Absorption—*[^{14}C]Metronidazole*—[^{14}C]Metronidazole, 1-(2[U-^{14}C]hydroxyethyl)-2-methyl-5-nitroimidazole[9], with a radiochemical purity >98% was used. The labeled drug was diluted with unlabeled metronidazole to yield a specific activity of 1.13 μCi/mg.

[^{14}C]Metronidazole-Tampon—Following the method described earlier, Tampon I was impregnated with 48.3 μCi (42.75 mg) of [^{14}C]-metronidazole.

Intravaginal Absorption of [^{14}C]Metronidazole from Medicated Tampons—One rhesus monkey was selected from the group that was used in the earlier intravaginal release studies. The animal was tranquilized and the [^{14}C]metronidazole-impregnated tampon was inserted in the manner as described previously. A urinary catheter[10] and a venous catheter[11] were also inserted. The patency of the venous catheter was maintained with a slow infusion of saline. The animal was secured in a

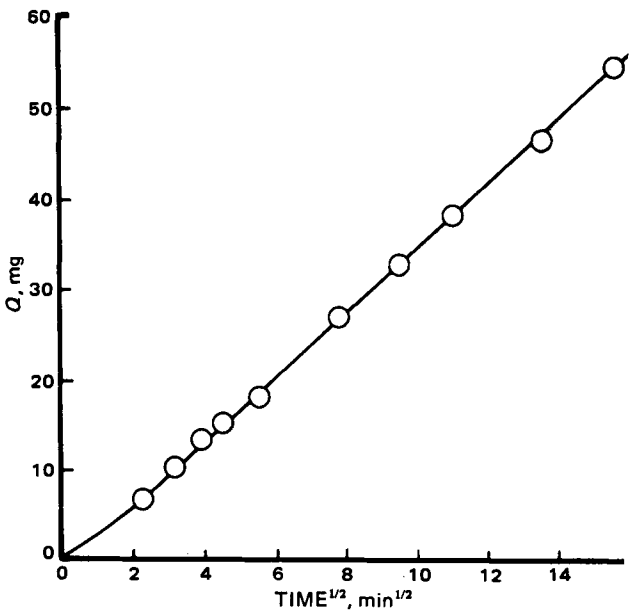

Figure 2—*Linear relationship between the cumulative amount of metronidazole (Q) released from medicated Tampon I and the square root of time ($t^{1/2}$) as defined in Eq. 1. The data from Fig. 1 were plotted.* $Q/t^{1/2} = 79.4\ \mu g/cm^2/min^{1/2}$.

[3] Tampax menstrual tampons (I), Tampax Inc., Palmer, MA 01069.
[4] Kotex tampons, (II), Kimberly-Clark Corp., Neenah, WI 54956.
[5] Playtex self-adjusting tampons (III) and Playtex self-adjusting tampons with deodorant (Playtex-D) (IV), International Playtex Co., Division Rapid-American Corp., Dover, DE 19901.
[6] Coleman Model 124D Spectrophotometer, Perkin-Elmer, Scientific Products, McGaw Park, IL 60085.
[7] Sernylan, Bio-Centric Laboratories, Inc., St. Joseph, MO 64502.
[8] XPL-515-SASR, Plas Laboratories, Scientific Div., Plastics Manufacturing and Supply Inc., Lansing, MI 48906.
[9] Amersham Corp., Arlington Heights, IL 60005.
[10] Bardex Foley Catheter, 10 French.
[11] B-D Longdwel, 20 gauge, with 2-inch catheter needle.

Table II—Apparent Diffusivities of Metronidazole and Porosity–Tortuosity Ratio in Various Brands of Tampons

Brands	$(D_m C_s)^{1/2}$ [a], $mg^{1/2}/cm^{1/2}/min^{1/2}$	$D_m \times 10^6$, cm^2/sec	ϵ/θ [b]
I	28.0×10^{-3}	1.03	0.213
II	29.5×10^{-3}	1.14	0.236
III	24.6×10^{-3}	0.79	0.164
IV	33.5×10^{-3}	1.47	0.304

[a] Slope of the linear $Q/t^{1/2}$ *versus* $(2A - C_s)^{1/2}$ plots, where C_s = 12.7 mg/ml. [b] The ratio of porosity over tortuosity as calculated from Eq. 3 using a D value of 4.84×10^{-6} cm^2/sec, which was determined polarographically from the following relationship: $D = [(i_d)/0.605nCm^{2/3}t^{1/2}]^2$. *p*-Nitrophenol ($D = 9.18 \times 10^{-6}$ cm^2/sec) was run simultaneously as reference.

primate chair[8] until the tampon was removed and then transferred to a metabolism cage for continuous urine collections. Two milliliters of blood were collected at 3, 6, 8, 24, 26, 28, 30, 72, 96, and 120 hr. Urine was collected at 24, 48, 72, 96, and 120 hr.

Intravaginal Absorption of [^{14}C]*Metronidazole in Solution*—Three female rhesus monkeys, weighing 4.5–5.0 kg, were tranquilized with 1 mg/kg of phencyclidine hydrochloride[7]. After tranquilizing, catheters were placed in the saphenous vein[11] and urinary bladder[10]. A slow infusion of saline was initiated to maintain patency of the saphenous vein catheter. The animals were then placed on their backs on a V-board with the legs in a vertical (lithotomy) position and the pelvic area was supported and slightly elevated. A solution of 1 mg/kg of [^{14}C]metronidazole in 0.5 ml of distilled water was then quantitatively instilled into the vagina with a micropipet.

The animals were maintained in a tranquilized state by periodic administration of phencyclidine hydrochloride (1 mg/kg/90 min) for the first 5 hr after drug administration. Then, the animals were transferred to primate chairs[8] and remained there until 24 hr after drug administration. At this time the catheters were removed, the vaginal vault was thoroughly rinsed with 50 ml of saline, and the animals were transferred to metabolism cages for continuing urine and plasma collection.

Radioactivity Measurements—Aliquots (100–500 μl) of plasma, urine, or tampon extracts were added to 4 ml of water in scintillation vials. Ten milliliters of liquid scintillation solution[12] was added and the mixture was agitated to form a gel. Each sample was then assayed for carbon 14 content by liquid scintillation spectrometry[13].

RESULTS AND DISCUSSION

***In Vitro* Release Studies of Medicated Tampons**—The release profile of metronidazole from a medicated tampon in simulated vaginal fluid (pH 4.5) under a sink condition is shown in Fig. 1. Mechanistic analyses of this nonlinear drug release profile suggested that the release of metronidazole from tampons is under a matrix-controlled process and follows the same Q *versus* $t^{1/2}$ release pattern as demonstrated earlier in the release of norgestomet from hydrogel-type drug delivery device (11). The linear Q–$t^{1/2}$ relationship observed can be defined mathematically by:

$$Q = [D_m(2A - C_s)C_s t]^{1/2} \quad \text{(Eq. 1)}$$

where Q is the cumulative amount of metronidazole released from a unit surface area of a tampon; D_m is the effective diffusivity of metronidazole in the tampon matrix; A is the initial amount of metronidazole impregnated per unit volume of tampon; C_s is the solubility of metronidazole in the simulated vaginal fluid; and t is the time. As demonstrated in Fig. 2 a Q *versus* $t^{1/2}$ linearity was followed. The slope of this linearity is thus defined as:

$$Q/t^{1/2} = [D_m(2A - C_s)C_s]^{1/2} \quad \text{(Eq. 2)}$$

The $Q/t^{1/2}$ profiles for various brands of tampons are compared in Table I. It is noted that Tampons I and II released metronidazole at very much the same magntiude of $Q/t^{1/2}$, which was slightly more than twice the value of $Q/t^{1/2}$ for Tampon III; and the *in vitro* release of metronidazole from Tampon IV (Tampon III with deodorant) was observed to be 40%

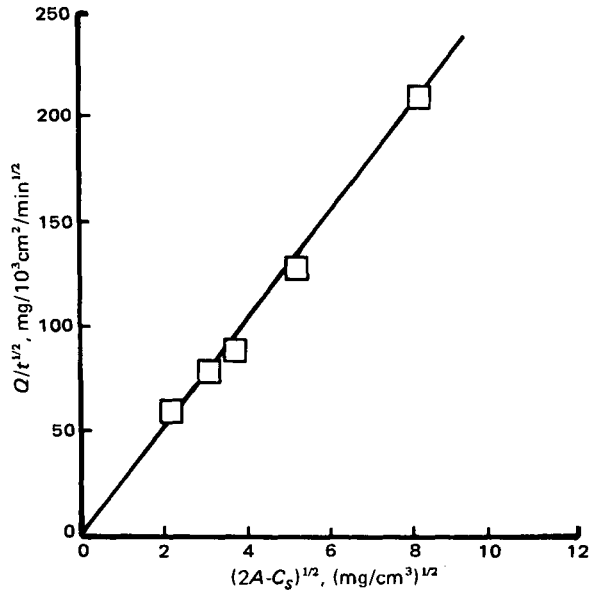

Figure 3—*Linear relationship between the values of* $Q/t^{1/2}$ *and* $(2A - C_s)^{1/2}$ *as defined in Eq. 2.*

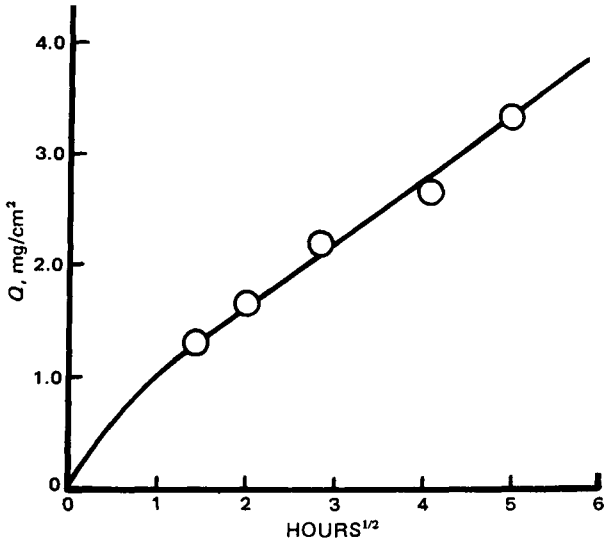

Figure 4—*Intravaginal release of metronidazole from Tampon I (A = 20.25 mg/cm^3) in five rhesus monkeys for up to 25 hr.* $Q/t^{1/2}$ *= 74.9 μg/cm^2/min$^{1/2}$.*

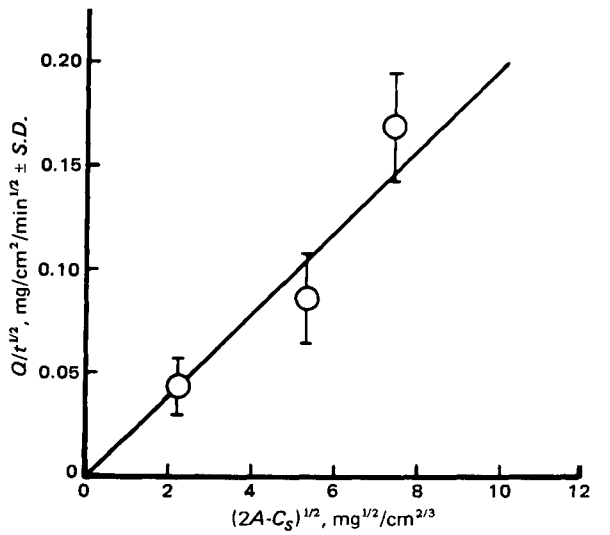

Figure 5—*Linear dependency of the intravaginal* $Q/t^{1/2}$ *data determined in rhesus monkeys on the* $(2A - C_s)^{1/2}$ *values of metronidazole in Tampon I.*

[12] PCS liquid scintillation solution, Amersham/Searle Corp., Arlington Heights, Ill.

[13] Mark II Spectrometer, Searle Analytic Inc., Des Plaines, Ill.

Table III—*In Vitro*—*In Vivo* Correlation on the Sustained Release of Metronidazole from Tampons

Types	Release Conditions	$Q/t^{1/2}$, $\mu g/cm^2/min^{1/2}$
I[a]	*In vitro* elution	79.4
	Monkey vagina	74.9
III[b]	*In vitro* elution	37.4
	Human vagina	45.9

[a] A = 20.25 mg/cm^3. [b] A = 6.59 mg/cm^3.

faster than Tampon III. No correlation could be estalished between the values of $Q/t^{1/2}$ and the extent of liquid retention of the tampons.

The effect of the dose of metronidazole initially impregnated in a tampon on the sustained-release profile of metronidazole was also studied. Equation 2 suggests that the magnitude of $Q/t^{1/2}$ values should increase as the drug content (A) in the tampon increases. A dose level ranging from 60 to 360 mg/tampon was investigated. As suggested by Eq. 2, the results confirmed that $Q/t^{1/2}$ values show a linear dependency on the square root of $(2A - C_s)$ values (Fig. 3). These data indicate that the dosage administered intravaginally to a subject can be controlled by incorporating an appropriate amount of metronidazole in the tampon.

The slope of this linear $Q/t^{1/2}$ *versus* $(2A - C_s)^{1/2}$ relationship is defined by $(D_m C_s)^{1/2}$. If the aqueous solubility (C_s) of metronidazole is known or predetermined, the effective diffusivity (D_m) of metronidazole in a tampon matrix can be calculated. A D_m value ranging from 0.79 to 1.47 × 10^{-6} cm^2/sec was determined (Table II). Using the relationship:

$$D_m = D\frac{\epsilon}{\theta} \qquad \text{(Eq. 3)}$$

and the solution diffusivity (D) which was determined independently by dc polarography (12), the ratio of porosity (ϵ) over tortuosity (θ) can be estimated (Table II). It appears that the value of ϵ/θ varies from one brand of tampon to another (ranging from 0.164 to 0.304). The higher values of D_m and ϵ/θ for Tampon IV than for Tampon III are, apparently, due to the addition of deodorant in Tampon IV. The pretreatment by a fragrance (as the deodorant) with an o/w-type surfactant, such as polysorbate 20, should result in the enhancement of wettability of the tampon cotton and/or the reduction of drug–cotton interaction, leading to a higher porosity-tortuosity (ϵ/θ) ratio and, hence, a greater diffusivity (D_m) in the tampon matrix. It is also noticed that a lower liquid retention was obtained for Tampon IV than for Tampon III (Table I).

Intravaginal Release Studies of Medicated Tampons in Rhesus Monkeys—The intravaginal release profile of metronidazole from medicated tampons in rhesus monkeys is illustrated in Fig. 4. As expected from Eq. 1, the results indicated that the intravaginal release profile of

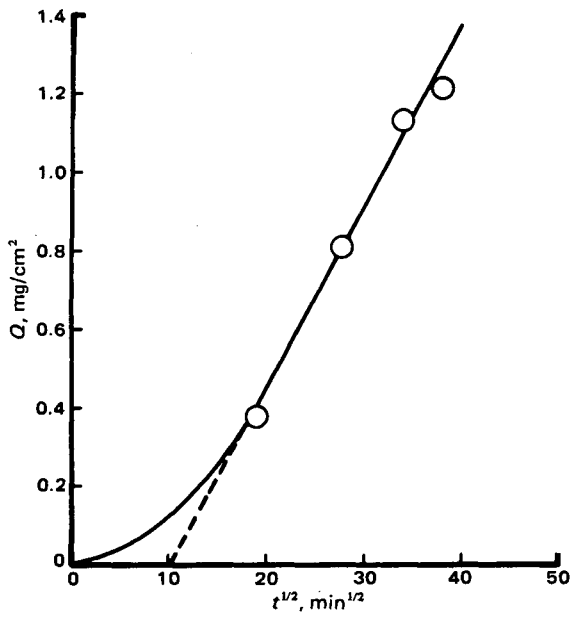

Figure 6—*Intravaginal release of metronidazole from Tampon III (A = 6.59 mg/cm^3) in a human volunteer for up to 24 hr. Q/t$^{1/2}$ = 45.9 μg/cm^2/min$^{1/2}$.*

Table IV—Effect of the Days in Menstrual Cycles on the Sustained Release of Metronidazole [a]

Days[b]	$Q/t^{1/2}$, mg/min$^{1/2}$	
	8 pm → 8 am	8 am → 8 pm
1	0.301	0.595
7	0.215	0.452
14	0.366	0.647
21	0.344	0.444

[a] For each 12-hr insertion, each volunteer receives one tampon (III) impregnated with 60 mg of metronidazole. [b] Days after the termination of menstruation.

metronidazole also follows the linear Q *versus* $t^{1/2}$ relationship. A $Q/t^{1/2}$ value of 74.9 μg/cm^2/min$^{1/2}$ was calculated. This intravaginal release rate of metronidazole (74.9 μg/cm^2/min$^{1/2}$) was found to be very close to the *in vitro* release rate (79.4 μg/cm^2/min$^{1/2}$) determined in the 4-hr drug elution studies (Fig. 2 and Table III).

Tampon I was also impregnated with 3 dosage levels of metronidazole and examined in rhesus monkeys to test the applicability of Eq. 2 to the *in vivo* condition. Results (Fig. 5) were in agreement with the *in vitro* observations (Fig. 3). Assuming that metronidazole has a solubility (C_s) in vaginal secretions similar to that in the simulated vaginal fluid (12.7 mg/ml), the effective diffusivity (D_m) can be calculated from the slope of $Q/t^{1/2}$ *versus* $(2A - C_s)^{1/2}$ plot. A value of 7.21 × 10^{-7} cm^2/sec is the result. It is only slightly lower than the value of 10.3 × 10^{-7} cm^2/sec determined in *in vitro* studies (Table II).

Intravaginal Release Studies of Medicated Tampons in Human Volunteers—The intravaginal release profile of metronidazole from medicated tampons in human volunteers is illustrated in Fig. 6. In this study, Tampon III was medicated and tested in one volunteer for a duration from 6 hr up to 24 hr. An intravaginal release rate of 45.9 μg/cm^2/min$^{1/2}$ was achieved. This release rate was found to be only slightly higher than the 37.4 μg/cm^2/min$^{1/2}$ measured in the 4-hr *in vitro* elution study (Table III).

Considering the cyclic variation in vaginal physiology, the effect of physiological phases in a menstrual cycle on the intravaginal release of metronidazole from medicated tampons was examined in one volunteer. The data in Table IV suggest that the intravaginal release rate of metronidazole first decreases right after menstruation and then increases toward the middle of the cycle just prior to ovulation. This behavior is very similar to the cyclic pattern observed in rhesus monkeys on the intravaginal absorption of hydrophilic and hydrophobic n-alkanols (13).

A higher rate of intravaginal release was also consistently observed in those medicated tampons inserted in daytime (8 am–8 pm) as compared to those inserted at night (8 pm–8 am). The observation may be related to the higher physical activity shown in the daytime, which may give a greater secretion of vaginal fluid.

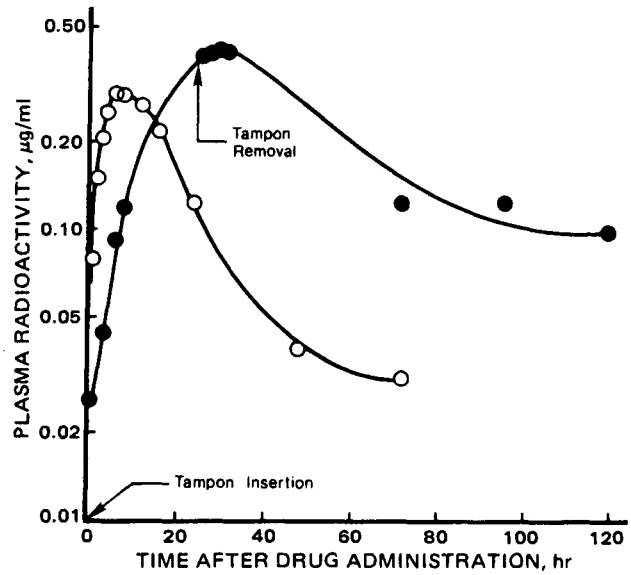

Figure 7—*Comparative plasma profiles of total radioactivity in rhesus monkeys administered with [^{14}C]metronidazole in solution dose (○; 5 mg; n = 3) and via medicated Tampon III (●; 42.75 mg; n = 1), where n is the number of subjects tested. The tampon was inserted for 25 hr while solution was administered for 24 hr.*

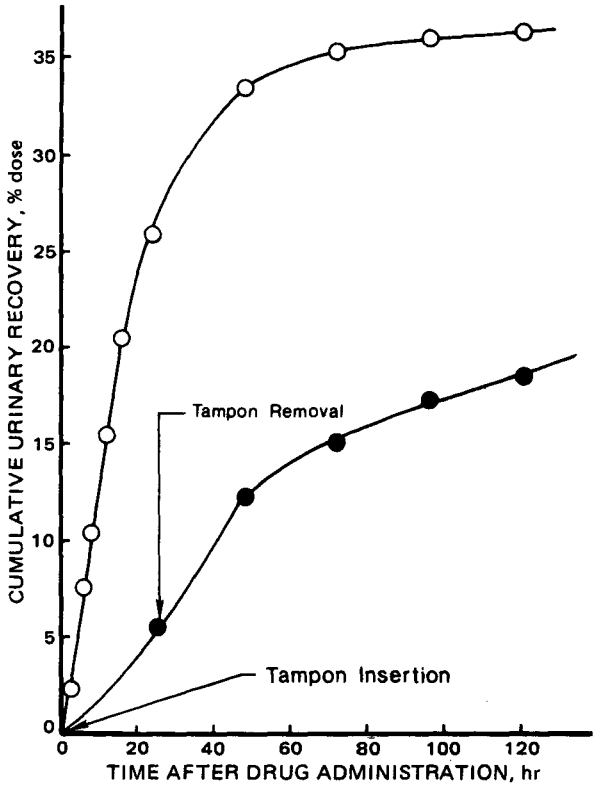

Figure 8—*Cumulative urinary recovery of total radioactivity (percent of the applied dose) after the intravaginal administrations of [^{14}C]-metronidazole in rhesus monkeys through solution dose (○) and medicated Tampon III (●). Conditions are the same as in Fig. 7.*

***In Vitro–In Vivo* Correlations**—The correlations between the *in vitro* data and intravaginal release profiles, as shown in Table III, are very encouraging. The results suggest that the 24-hr intravaginal release of metronidazole from medicated tampons in both rhesus monkeys and human volunteers can be predicted from the 4-hr *in vitro* drug elution study.

Comparative Plasma Profiles of Metronidazole—To study the comparative systemic bioavailability by intravaginal drug administration *via* medicated tampon and solution formulation, one unit of Tampon III was medicated with 48.3 μCi (42.75 mg) of [^{14}C]metronidazole and then inserted into the monkey vagina for 25 hr. Analysis of the ethanol extract of the removed tampon (by double 50-ml extractions) indicated that 10.4 mg of [^{14}C]metronidazole still remained in the tampon. Complete combustion of the extracted tampon to [^{14}C]carbon dioxide and water further demonstrated that an additional 1.2% (0.51 mg) of the original radioactivity was present in the tampon[14]. These results suggest that altogether, 74.5% (31.84 mg) of the [^{14}C]metronidazole incorporated into the tampon was released in the rhesus monkey during the 25-hr insertion period. This result is in agreement with the data obtained from similar experiments conducted with unlabeled metronidazole utilizing a UV spectrophotometric assay technique.

The plasma profile of total radioactivity following the 25-hr intravaginal administration of [^{14}C]metronidazole in the rhesus monkey *via* medicated tampon is compared with that following the intravaginal administration of [^{14}C]metronidazole in a solution formulation for 24 hr (Fig. 7). Results show that the peak plasma carbon 14 concentration occurs at 6 hr during administration of the solution dose, whereas after the vaginal tampon medication the peak is reached at a much later time (30 hr after insertion or 5 hr after tampon removal). These observations suggest a delayed intravaginal uptake of metronidazole by the sustained release mechanism of the medicated tampon as compared to the drug administration in solution dose. On the other hand, 5 hr after the removal of the tampon, the plasma radioactivity eliminates at basically the same rate as that following solution administration. These results suggest that the use of tampons as the intravaginal drug delivery device does not change the elimination kinetics of metronidazole from the body.

Comparing the areas under the plasma carbon 14 concentration curves (0–120 hr, corrected for the difference in the doses applied), it was estimated that the systemic bioavailability of metronidazole administered by the medicated tampon is only 27.2% of the solution dose. The low relative systemic bioavailability (27.2%) may occur if the majority of metronidazole released from the medicated tampon remains in the vaginal tract to exert a localized therapeutic activity. This possibility is confirmed by the observation that the peak plasma carbon 14 concentration is reached at 5 hr after removal of the medicated tampons (Fig. 7).

Comparative Urine Excretion Profiles of Metronidazole—Figure 8 compares the rate and extent of the urinary excretion of radioactivity after intravaginal administration of [^{14}C]metronidazole in solution formulation (5 mg) and medicated tampon (42.75 mg) to rhesus monkeys. Apparently, the rate and extent of urinary recovery of the radioactivity were significantly reduced when [^{14}C]metronidazole was administered *via* the medicated tampon. The observed reduction in the rate of urinary recovery is in agreement with the result observed in the plasma profiles (Fig. 7). This could well be the outcome of the sustained release of metronidazole from the medicated tampon, which prolongs the uptake of drug by the vagina.

Only 18.5% of the released dose was recovered in the urine during the 5-day observation period. [The majority (13%) was excreted in the 4-day period following removal of the tampon.] This is considerably lower than the 36.3% recovered from the solution dose during the same period (Fig. 8). By comparison with the vaginal absorption of the solution dose, it is estimated that the medicated tampon produces a relative systemic bioavailability of 51%, which is almost twice the value (27.2%) calculated from the plasma data (Fig. 7). This difference suggests that metronidazole molecules administered by sustained release medicated tampon may become more locally available *via*, possibly, binding to the vaginal wall. The bound metronidazole is then excreted *via* the perieum venous plexus, which drains the vaginal tissue and rectum, flows into the pudentum vein, and ultimately into the vena cava, resulting in a lower systemic bioavailability (13).

[14] Sample Oxidizer, Packard Model 306, Packard Instruments Corp., Lincolnwood, Ill.

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