from the GLC–mass spectroscopy method, it is apparent that no significantly measurable quantities of clindamycin palmitate can be found in the serum of subjects receiving 494–988 mg of clindamycin palmitate hydrochloride 0.25–1.5 hr after administration.

Although GLC methods have been used extensively for the detection and quantitation of antibiotics and other pharmaceuticals, the single-ion focused mass spectroscopy method represents the application of a new mass spectroscopy technique to antibiotic research. With suitable sample extraction procedures, single-ion focusing can be a very specific and highly sensitive means of characterizing and quantitating antibiotics.

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[x] To whom inquiries should be directed.

Controlled Drug Release from Polymeric Devices I: Technique for Rapid *In Vitro* Release Studies

YIE W. CHIEN[x], HOWARD J. LAMBERT, and DONALD E. GRANT

Abstract □ A simple system was developed which allows the rapid and reproducible quantification of parameters influencing the release of drug by solid polymeric devices. The apparatus utilizes only 150 ml of elution medium and maintains "sink" conditions with water-miscible (nonaqueous) cosolvent combinations. Constant diffusion layer thickness is controlled by constant stirring and fixed temperature conditions. Factors influencing the rate of release of ethynodiol diacetate, a synthetic progestin, from solid silicone polymer vaginal devices were evaluated. The cumulative amount of drug released was proportional to the square root of time. The drug diffusivity was calculated and found in excellent agreement with previously reported data for similar compounds in silicone matrixes. The presence of a matrix-controlled process was confirmed by the independence of the steady-state diffusion rate on drug solubility in the eluant.

Keyphrases □ Drug release, controlled—method for measuring rapid *in vitro* release from polymer devices, ethynodiol diacetate from silicone polymers □ Transport, drug—rapid *in vitro* method for measuring steady-state drug release flux, ethynodiol diacetate from solid silicone polymer vaginal devices □ Permeation, drug—ethynodiol diacetate through solid silicone matrix, rapid *in vitro* method for measuring steady-state drug release flux □ Ethynodiol diacetate—release from solid silicone vaginal devices, effect of concentration and solubility of drug, rapid *in vitro* method for measuring steady-state drug release flux □ Contraceptives—rapid *in vitro* method for measuring ethynodiol diacetate release from solid silicone vaginal devices □ Vaginal devices—method for measuring drug release from polymer matrix

Recent interest has centered on the idea of replacing daily administration of a drug with delivery devices that release a constant effective dose to target tissues *via* a controlled-release mechanism (1–10). The high permeability of silicone polymer to steroids has been applied to the development of drug-filled and drug-impregnated silicone devices for long-acting hormonal contraception (11–24).

It is apparent from the literature that the development of a suitable measurement system is needed to understand drug release mechanisms in *in vivo* systems and also to correlate *in vitro* and *in vivo* drug release rate profiles accurately. An *in vitro* apparatus for studying the release of medroxyprogesterone acetate from a silicone device was designed (25). Because of the low aqueous solubility of medroxyprogesterone acetate, a large quantity (60 liters/day) of distilled water was used for dissolution to approximate a sink condition. The sensitivity of the diffusion cell was ignored (26–28). The drug release rate was determined weekly by assaying the residual drug content or measuring the thickness of the depletion zone in the devices. The same mechanical concepts were also applied in constructing a diffusion system for studying the release of progesterone from a polyethylene matrix (29).

One prime concern in making permeability measurements is the ability to determine the rate of drug release reliably in as short a time as possible (26–28). The development of such a technique and system should also make possible the direct measurement of drug release flux. With these considerations in mind, a relatively simple and easily constructed drug release system was designed, and a rapid, reproducible technique was developed. The ring-shaped polymeric device was mounted in a holder and rotated at constant speed in the elution medium so that constant hydrodynamics were maintained. This procedure allowed for a constant thickness of diffusion layer on the immediate surface of the device and a homogeneous drug concentration in the elution medium. Additionally, a polymer-compatible, drug-stable,

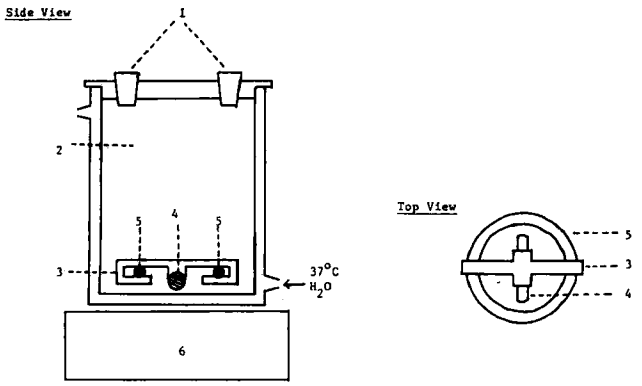

Figure 1—*Schematic representation of the* in vitro *system used to measure the release of drug from silicone devices. Key: 1, sampling holes with Teflon stopcocks; 2, water-jacketed cell; 3, Plexiglas holder for ring-shaped silicone devices; 4, Teflon-coated spin bar; 5, drug-impregnated silicone devices; and 6, magnetic stirrer. Up to six cells were connected in series and thermostated at 37°.*

and water-miscible macromolecular substance was mixed with the distilled water to increase drug solubility. A perfect sink condition was maintained throughout the experiment. The cell sensitivity was sufficiently high that hourly or daily measurements of drug release flux were possible. The drug release profile was followed closely by directly assaying the drug concentration in the elution medium. The developed system and technique provide a rapid methodology for reliably characterizing the pattern and rate of drug release from polymeric devices. This report defines the system and technique developed and compares the *in vitro* drug release profiles obtained with the results taken from the literature.

EXPERIMENTAL

Drug Release System—The system developed for studying the pattern of drug release is shown schematically in Fig. 1. A ring-shaped device was mounted in the arms of a Plexiglas holder. The holder was then rotated at a constant speed (360 rpm) in 150 ml of elution medium at 37°. At scheduled intervals, a given volume (25–150 ml) of elution medium was sampled and replaced with the same quantity of drug-free elution medium maintained at 37°. The sample was then assayed.

Drug Delivery Devices—The delivery devices were prepared[1] by mixing the required amount of ethynodiol diacetate or other steroid into a silicone elastomer[2] and then polymerizing with catalyst in a mold at room temperature to form a ring (6 × 50 mm to 6 × 63 mm).

Elution Medium—The elution medium was prepared by mixing a given volume of reagent grade polyethylene glycol 400[3] with distilled water. The drug solubility–polyethylene glycol 400 concentration profile, as expected from the following theoretical expression, is shown in Fig. 2:

$$\log C_s = \log C_{H_2O} + ef \qquad \text{(Eq. 1)}$$

where C_s and C_{H_2O} denote the solubilities of drug in the polyethylene glycol 400–water mixture and in the pure water system, respectively, e is the slope of solubility–concentration profile, and f is the volume fraction of polyethylene glycol 400 (% v/v) added. The solubility of ethynodiol diacetate (C_{H_2O} = 1.37 mg/100 ml) was enhanced remarkably with the addition of polyethylene glycol 400, so perfect sink condition was maintained.

[1] By Dow Corning Corp., Midland, Mich.
[2] Silastic.
[3] Matheson, Coleman and Bell.

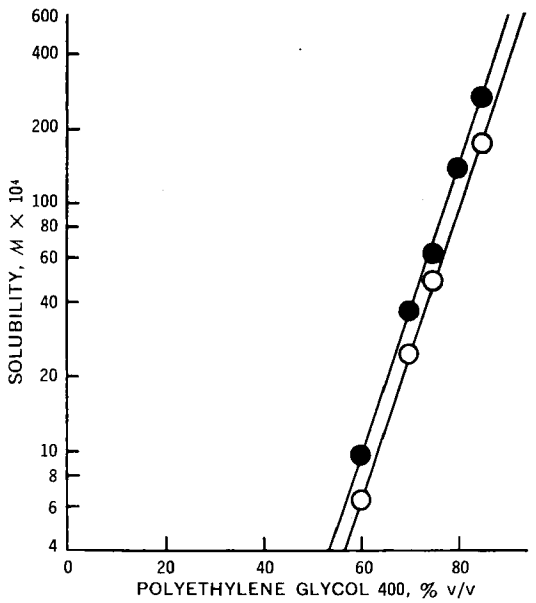

Figure 2—*Semilogarithmic relationship between the solubility of ethynodiol diacetate and the volume fraction of polyethylene glycol 400 in the elution medium at 37° (●) and 25° (○).*

The stability of ethynodiol diacetate and its compatibility with the silicone polymer also were examined for an observation period of 3 weeks. Both were stable and compatible.

Analytical Method—From 1 to 5 ml of sample solution was mixed with 10 ml of methanol, spectrophotometric grade, and 1 ml of 6 *M* hydrochloric acid solution. The mixture was boiled for exactly 5 min and then cooled to room temperature, and methanol was added to 25 ml. The drug concentration in such a solution was measured spectrophotometrically against a reference prepared from the same sample solution without acidic hydrolysis. The peak absorbance (at λ_{max} 236 nm) was recorded. No absorption peak was observed for the solution without acidic hydrolysis. The molar absorptivity determined was 19,140 M^{-1} for the acidic product (3,5-diene derivative) of ethynodiol diacetate. The analytical procedure for medroxyprogesterone acetate was the same as that for ethynodiol diacetate, except that no acidic hydrolysis was required and the same elution medium without drug was used as the reference. The λ_{max} and ϵ values for medroxyprogesterone acetate are 241 nm and 17,520 M^{-1}, respectively.

Determination of Drug Solubility—The solubility of ethynodiol diacetate at the study temperature (25 or 37°) was determined by vigorously mixing an excess amount of powdered drug

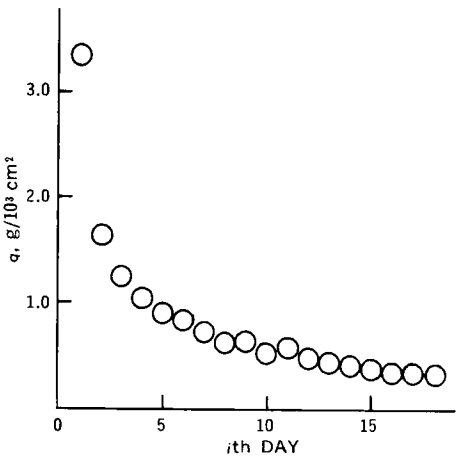

Figure 3—*Daily amount of drug release per unit area of device* (q) *on the ith day for a silicone device containing 12.79 g/10² cm³ of ethynodiol diacetate.*

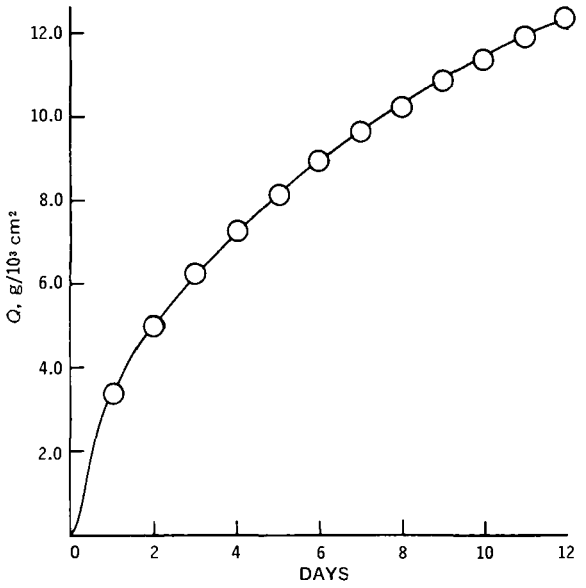

Figure 4—*Cumulative amount of drug release* (Q) *per unit area of device* versus *time for a silicone device containing 12.79 g/10² cm³ of ethynodiol diacetate.*

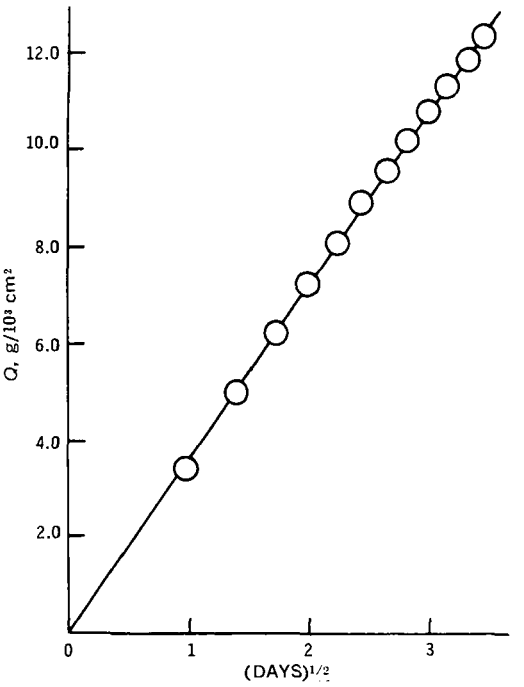

Figure 5—*Linear relationship between the cumulative amount of drug released per unit area of device* (Q) *and the square root of time* ($t^{1/2}$). *The rate of drug release calculated from the slope is 3.57 g/10³ cm²/day$^{1/2}$.*

in 10 ml of elution medium. At equilibrium (48 hr), samples were rapidly filtered through syringes equipped with a filter holder[4] containing a glass fiber membrane[5]. For the 37° measurements, the whole filtration apparatus was preheated. The clear filtrate was then assayed as previously described.

The solubility of ethynodiol diacetate in the silicone polymer was determined in the same manner as already described, except that a silicone liquid with 24 dimethylsiloxyl units was used. After filtration, one part of the clear filtrate was extracted with 10 parts of methanol with shaking at 37° for 24 hr. The solubility of ethynodiol diacetate in the silicone polymer at 37° was 1.4791 mg/ml.

RESULTS AND DISCUSSION

In the present study, a speed of 360 rpm for the silicone elastomer[2] was satisfactory. At this speed, the thickness of the hydrodynamic diffusion layer on the immediate surface of the device (26) was calculated, according to Eq. 2, to be from 63×10^{-4} to 70×10^{-4} cm, depending upon the kinematic viscosity of the elution medium used:

$$\delta_D = 1.62 D^{1/3} \omega^{-1/2} \nu^{1/6} \qquad \text{(Eq. 2)}$$

where δ_D is the thickness of the hydrodynamic diffusion layer around the device, D is the diffusion coefficient of the drug species examined, ω is the angular rotation speed, and ν is the kinematic viscosity of the elution medium. Apparently, the magnitude of δ_D may be decreased by the increase of the angular rotation speed. The effect of ω on the thickness of the hydrodynamic diffusion layer has been well established (26). The magnitude of δ_D should be held constant for an investigation of the real mechanism of matrix-controlled permeation and for a meaningful comparison between experimental observations.

The drug release profile obtained from such a system is shown in Fig. 3, where the amount of drug release daily *(q)* from the ring-shaped drug-impregnated silicone matrix is plotted against time. A large quantity of drug was released initially, and the daily amount of drug released then decreased with time. A plot of the cumulative amount of drug *(Q)* released from a unit area of matrix with time yields a curved *Q–t* profile (Fig. 4). The same type of observation was reported previously for both *in vitro* (23, 25, 29–31) and *in vivo* (12, 29) studies. The higher initial drug release has been attributed to release of drug molecules at the matrix surface (*i.e.*, burst effect) (32).

Theoretical treatment of the data obtained indicated that the release of drug from an insoluble, inert polymeric matrix, (*e.g.*, the silicone polymer in the present investigation) is best described by the equation developed by Higuchi (30) if diffusion is the rate-determining factor for the drug release process:

$$Q = \sqrt{D_m(2A - C_s)C_p t} \qquad \text{(Eq. 3)}$$

where Q is the cumulative amount of drug released per unit area of device (g/cm²); A is the amount of solid drug impregnated in a unit volume of device (g/cm³); C_s and C_p are the solubilities of the drug in the elution medium and the polymer phase, respectively; t is time; and D_m is the diffusivity of the drug species in the matrix.

The theoretical model defined in Eq. 3 indicates that the cumulative amount of drug released *(Q)* from a unit area of matrix

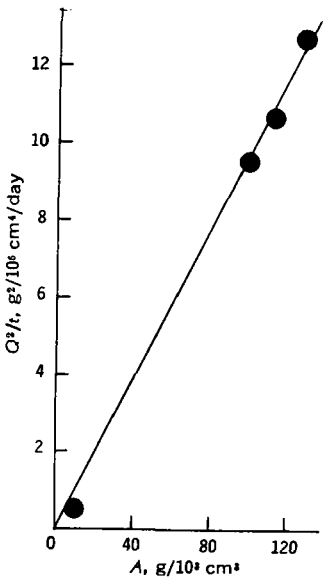

Figure 6—*Effect of the drug concentration* (A) *impregnated in the silicone devices on the square of the drug release rate* $(Q/t^{1/2})^2$. *The slope, defined as* $2D_mC_p$ *in Eq. 6, is calculated to be 96.67 g/10⁶ cm/day.*

[4] Millipore.
[5] Reeve Angel.

Table I—Effect of Drug Solubilities (C_s) on Rate of Drug Release from Silicone Devices Containing 98.8 g/10³ cm³ Ethynodiol Diacetate

Volume Fraction of Polyethylene Glycol 400, %	C_s, g/10³ cm³	Rate of Drug Release ($Q/t^{1/2}$) Initial[a], g/10³ cm²/day$^{1/2}$	Steady State[b], g/10³ cm²/day$^{1/2}$
65	0.78	1.597	2.99
70	1.39	2.607	3.115
75	2.43	3.024	3.09
80	4.45	3.478	3.04
85	8.00	3.651	3.05

[a] Initial rate of drug release is calculated from the 1st day drug release profile. [b] Steady-state rate of drug release is estimated from the slope of Q–$t^{1/2}$ profile up to 18 days.

should be a linear function of the square root of time ($t^{1/2}$). As demonstrated in Fig. 5, this linear relationship was obeyed when the drug release data in Fig. 4 were plotted following Eq. 3. The slope of the Q–$t^{1/2}$ profile is defined as:

$$Q/t^{1/2} = \sqrt{D_m(2A - C_s)C_p} \quad \text{(Eq. 4)}$$

Experimentally, the system was so designed that the amount of solid drug (A) in the matrix was much larger than the solubility of drug (C_s) in the elution medium ($A \geq 98.8$ g/10³ cm³ and $C_s \leq 8$ g/10³ cm³). Therefore, $2A \gg C_s$ may be established, and Eq. 4 may be reduced to Eq. 5 without inducing any significant error:

$$Q/t^{1/2} = \sqrt{2D_mAC_p} \quad \text{(Eq. 5)}$$

Taking the square of both sides of Eq. 5 results in:

$$Q^2/t = 2D_mC_pA \quad \text{(Eq. 6)}$$

On the basis of Eq. 6, linearity should exist between Q^2/t and A. Experimentally, this linearity was found to follow (Fig. 6); the slope of this line is $2D_mC_p$. When the solubility of drug in the polymer (C_p) is known, the magnitude of D_m, the diffusivity of drug in the matrix, may be estimated from this slope. In the present study, D_m was calculated to be 3.79×10^{-7} cm²/sec for ethynodiol diacetate. This result is very close to the 3.36×10^{-7} cm²/sec for medroxyprogesterone acetate (31) and the $3.0 \sim 3.3 \times 10^{-7}$ cm²/sec for chlormadinone acetate (23) determined by the lag time method using a similar silicone matrix. All three compounds are progestins. By using the semilogarithmic relationship between the self-diffusion coefficients and the number of the dimethylsiloxyl monomer units reported by McCall *et al.* (33), it is interesting to note that these steroids have diffusion coefficients in the silicone polymer approximately equal to the self-diffusion coefficient of a dimethyl silicone molecule containing 10 silicon atoms. One could interpret this finding to indicate that an opening in the polymer sufficiently large to permit a steroid molecule to jump from one hole to another would require the motion of a silicone chain segment of the order of 10 monomer units in length. By the same approach, Robb (34) concluded that the permeation of oxygen, nitrogen, and carbon dioxide required the motion of three silicon atoms.

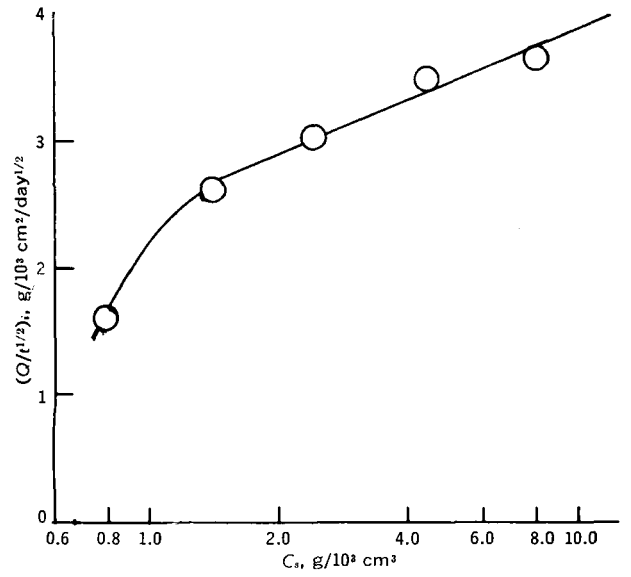

Figure 7—*Effect of the drug solubility* (C_s) *in the elution medium on the initial (1st day) rate of drug release.*

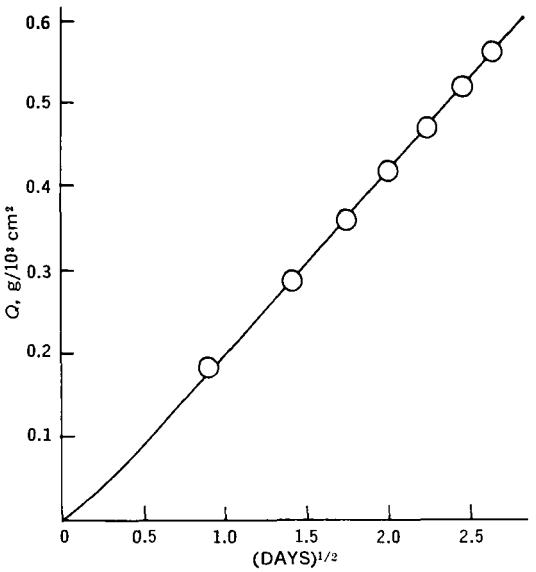

Figure 8—*Drug release profiles for medroxyprogesterone acetate measured in the present system.*

In developing Eq. 5, the C_s term in Eq. 4 was neglected on the basis of $2A \gg C_s$. Experimentally, a series of drug release studies were carried out in the elution medium with a wide range of drug solubilities (0.78 ~ 8.00 g/10³ cm³) to determine the effect on drug release profile (Table I). The data indicate that only the initial rate of drug release (the 1st day drug release) is dependent on the solubility of the drug in the elution medium (C_s). On the other hand, the steady-state rate of drug release is constant although the magnitude of C_s is enhanced 10-fold. The proportionality of initial drug release rate to drug solubility is also illustrated in Fig. 7, where a linear relationship is established after $C_s \geq 1.39$ g/10³ cm³. The linearity may be correlated with the dissolution kinetics of the drug concentration on the matrix surface.

The validity of Eqs. 4 and 5 and their correlation to the experimental data are further analyzed in Table II. Apparently, the omission of the C_s term results in a maximum error of only 2%. The experimental results correlate perfectly with the values calculated from the theoretical model of either Eq. 4 or 5.

The drug release pattern of medroxyprogesterone acetate from the silicone matrix was also examined in the same system. The reasons for including this drug in this investigation are simply that it has been studied extensively and literature reports are available for comparison. As seen in Fig. 8, the drug release profile for medroxyprogesterone acetate also followed the Q–$t^{1/2}$ relationship as did the ethynodiol diacetate reported in the present studies. Roseman and Higuchi (25) reported the same observation. The release of chlormadinone acetate was also described by the same theoretical model (23).

For comparison, the rate of drug release for medroxyprogesterone acetate, reported by Roseman and Higuchi (25), was cited in Table II. The data on drug solubility in the silicone polymer (C_p) and the drug diffusivity in the polymeric device (D_m) available in the literature (31) were also applied to estimate the theoretical rate of drug release (Table II). Both of these literature values are close to the experimental result (0.218 g/10³ cm²/day$^{1/2}$) and demonstrate the applicability of the drug release system. The comparisons point out that this system allows the rapid and direct characterization of the mechanism and rate of drug release from polymeric drug devices.

Table II—Comparison of Theoretical Rates of Drug Release with Experimental Data

Drug	Volume Fraction of Polyethylene Glycol 400, %	Rate of Drug Release, $g/10^3\ cm^2/day^{1/2}$			
		Theoretical[a]			
		A	*B*	Experimental	Ratio[b]
Ethynodiol diacetate	65	3.085	3.09	2.99	0.97
	70	3.081	3.09	3.115	1.01
	75	3.073	3.09	3.09	1.00
	80	3.056	3.09	3.04	0.99
	85	3.028	3.09	3.05	0.99
Medroxyprogesterone acetate	75	0.282[c]	0.241[d]	0.218	0.905

[a] *A* and *B* values are calculated from Eqs. 4 and 5, respectively, where $D_m = 3.27 \times 10^{-2}$ cm²/day, $A = 98.8\ g/10^3\ cm^3$, and $C_p = 1.4791\ g/10^3\ cm^3$. [b] Ratio of the experimental data over the theoretical *B* values. [c] Calculated from the drug release profile reported in Ref. 25. [d] Estimated from the data reported in Ref. 31 following Eq. 5.

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[x] To whom inquiries should be directed.