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In Vitro-In Vivo Correlation on the Subcutaneous Release of Progestins from Silicone Capsules

Yie W. Chien

Biopharmaceutics Section Development Department Searle Laboratories[1]

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A sink *in vitro* drug elution system was applied to characterize the mechanisms and rates of drug release of progestins from silicone capsules. A zero order (constant) drug release profile was observed. The rate of drug release was found to be a linear function of the partition coefficient of drug from silicone polymer to elution medium. The subcu taneous implantation of such delivery device in heifers resulted an *in vivo* release rate in agreement with the value predetermined on the basis of *in vitro* data. The *in vivo* drug release rates observed for all the four progestins investigated were found to be computable from the physico-chemical parameters following a theoretical expression. The thermodynamics of the drug release process was also analyzed and found to be in agreement with experimental observations.

Introduction

In 1966, Long and Folkman[2] were issued a patent describing silicone capsules as carriers for drugs and other drug-like agents. Since then, a great deal of interest has been generated in the use of silicone capsules as drug delivery devices for the controlled release of L-dopa,[3] narcotic-antagonists,[4] tranquilizer,[5] atropine and histamine,[6] antimalarial and antischistosomal agents,[7] contraceptive drugs,[8] as well as antibacterial agents.[9]

Several investigators[10,11] have examined the *in vitro* release mechanisms of steroids from silicone capsules and found that steroids diffused into distilled water or normal saline at a constant rate for long periods of time. Sink condition was not taken into consideration.

In view of the sink condition maintained *in vivo* by an active hemoperfusion, it is logical that an *in vitro* drug release system should also be maintained under sink condition (in which the drug concentration is maintained at a level less than 10% of drug solubility in the elution medium used throughout the observation). In this way, a realistic drug release mechanism may be better visualized. Recently, the author[12,13] introduced a sink *in vitro* drug elution system that allows a rapid characterization of drug release mechanisms. In this system, a sink condition was maintained throughout the measurement by enhancing the low aqueous solubility of the steroid several hundredfold with the addition of water miscible co-solvent. In the present study, the controlled release of progestins from silicone capsules was also studied in the

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[1] Location: *Skokie, Illinois 60076, U.S.A.*

[2] D.M. Long, Jr. and J. Folkman, U.S. Patent 3279996 (October 18, 1966). "Polysiloxane Carrier for Controlled Release of Drugs and Other Agents."

[3] P. Siegel and J. Atkinson, *J. Appl. Physiol.*, **30**, 900 (1971).

[4] Anonymous, *Chemical Week*, September **1**, 39, (1971).

[5] M. Nakano, *J. Pharm. Sci.*, **60**, 571 (1971).

[6] P. Bass, R. Purdon, and J. Wiley, *Nature*, **208**, 591 (1965).

[7] K.G. Powers, *Parasitology*, **51**, (Sec. 2), 53 (1965).

[8] H. Tatum, *Contraception*, **1**, 253 (1970).

[9] J.G. Wepsic, U.S. Patent 3598127 (August 10, 1971)

[10] P.J. Dzuik and B. Cook, *Endocrinology*, **78**, 208 (1966).

[11] F.A. Kincl, G. Benagiano, and I. Angee, *Steroids*, **11**, 673 (1968).

[12] Y.W. Chien, H.J. Lambert, and D.E. Grant, *J. Pharm. Sci.*, **63**, 365 (1974).

[13] Y.W. Chien and H.J. Lambert, *J. Pharm. Sci.*, **63**, 515 (1974).

same system. This paper reports our results obtained on the mechanisms and rates of progestins released from silicone capsules and also analyzes the correlations between the *in vivo* drug release rates observed and the rates calculated from physico-chemical parameters determined in *in vitro*

Experimental

The system for drug release studies and the polyethylene glycol 400–water co-solvent system for drug elution developed earlier[12] were utilized in the present investigation. As demonstrated earlier for ethynodiol diacetate, the solubility of Norgestomet in such an elution medium is also exponentially proportional to the concentration of polyethylene glycol 400 added (Fig. 1).

Capsules were prepared from medical grade Silastic tubing (O.D., 0.183″; I.D., 0.132″) by sealing one end with a Silastic Medical Grade Adhesive Type A. The capsules were then filled with Norgestomet crystals and sealed. Each seal was placed overnight in a water vapor-saturated hood for proper crosslinking.[11] In the case of *in vitro* studies, 16 cm long capsules were made and mounted as a ring in the arms of a Plexiglas holder. The holder was then rotated at 81 rpm in 150 ml of elution medium at 37°. At intervals, 50 ml of elution medium were sampled and replaced with the same quantity of drug-free elution medium maintained at 37°. The sample was properly diluted with methanol and assayed for drug content with an ultraviolet spectrophotometer at $\lambda_{\max}$ of 240 nm. In the case of *in vivo* studies, 2-cm-long silicone capsules were prepared and implanted subcutaneously (on the center of the dorsal surface of one ear) in heifers. At the end of 4, 8, 16, and 32 days, the capsules were removed, cut open, and soaked in 25 ml of methanol (spectral grade) with constant shaking for 2 days. The residual drug content in each capsule was then determined, and the extent of drug release was calculated.

The solubility of Norgestomet in the silicone polymer was determined in the same manner as described earlier[12] and found to be 0.1655 mg/ml at 37°.

The partition coefficient, K, of Norgestomet from the polymer to the elution medium was calculated[14] by the following relation:

$$K = \frac{C_s}{C_p} \qquad \text{Eq. 1}$$

where C_s and C_p are the solubilities of drug in the elution solution and in silicone polymer, respectively.

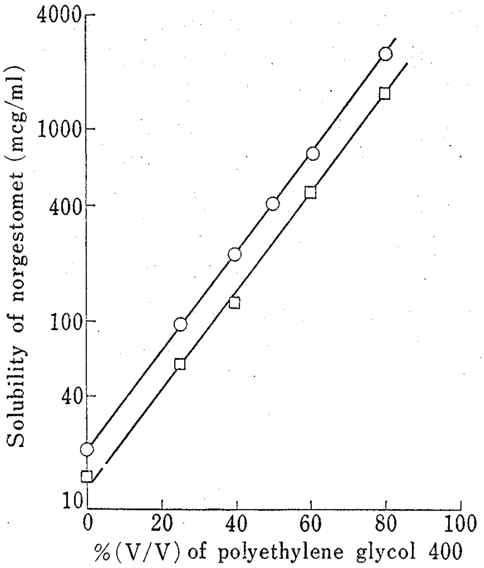

Fig. 1. Enhancement of the Aqueous Solubility of Norgestomet by Polyethylene Glycol 400 at ○ 37° and □ 25°

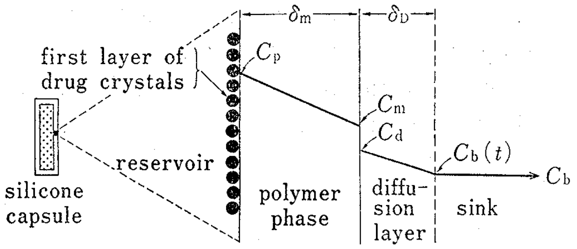

Fig. 2. Schematic Representation of the Drug Release Pattern from Crystalline Drug-filled Silicone Capsule

All terms are defined in the Text.

Theoretical Consideration

The release of drug from silicone capsules is schematically visualized in Figure 2. A reservoir of crystalline progestin is enveloped in a capsule of silicone polymer with a

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14) T.J. Roseman and W.I. Higuchi, *J. Pharm. Sci.*, 59, 353 (1970).

wall thickness of δ_m. The drug molecules in the first layer of crystals contacting the inner wall of silicone capsule must dissociate from the crystal state, dissolve into the polymer structure, diffuse through it, and finally partition into the elution medium surrounding the capsule. A thickness (δ_D) of hydrodynamic diffusion layer,13) in which drug molecules diffuse by natural convection under a concentration gradient, is present on the immediate surface of the device.15) In the present analysis, the thickness of the hydrodynamic diffusion layer ($\leq 154.6 \times 10^{-4}$ cm) is much smaller than the surface area of the silicone capsule (23.2 cm^2) available for the diffusion of drug species. Therefore, the diffusion of drug molecules to and from the capsule across the hydrodynamic diffusion layer may be treated as one-dimensional diffusion to a plane surface.13,16)

With the assumption that: (a) diffusion is the primary mode of drug release dynamics, (b) the diffusion coefficient is constant, (c) dissolution of drug crystals into silicone polymer is the first step of drug release process, and (d) a pseudo steady-state exists, the rate of drug diffusion from the drug/polymer interface to the polymer/solution interface, under Fick's law of diffusion, may, therefore, be expressed as:

$$\frac{dQ_m}{dt} = \frac{D_m(C_p - C_m)}{\delta_m} \qquad \text{Eq. 2}$$

where D_m is the effective diffusivity of the drug species in the polymer structure, δ_m is the apparent thickness of the polymer phase traveled, C_p is the solubility of drug in the polymer phase, and C_m is the drug concentration on the polymer/solution interface ($C_p \geq C_m$). On the other hand, the rate of drug diffusion across the hydrodynamic diffusion layer (with a thickness of δ_D) may be described by

$$\frac{dQ_D}{dt} = \frac{D_s[C_d - C_b(t)]}{\delta_D} \qquad \text{Eq. 3}$$

where D_s is the diffusivity of drug in the elution medium, and C_d and $C_b(t)$ are the drug concentrations at the solution/polymer interface and in the bulk of elution medium at a given time, respectively. C_d is smaller than or equal to C_s, the drug solubility in a given elution medium.

At a steady state, the rate of drug diffusion across the polymer structure (dQ_m/dt) should be equal to the rate of drug diffusion across the hydrodynamic diffusion layer (dO_D/dt), and

$$D_m\delta_D(C_p - C_m) = D_s\delta_m[C_d - C_b(t)] \qquad \text{Eq. 4}$$

Since the partition coefficient for the partitioning of drug species from the polymer phase to the elution medium (at the polymer/diffusion layer interface) is assumed as:

$$K = \frac{C_d}{C_m} \qquad \text{Eq. 5}$$

Substituting KC_m for C_d in Eq. 4 and then rearranging Eq. 4 to get:

$$C_m = \frac{D_m\delta_D C_p + D_s\delta_m C_b(t)}{D_m\delta_D + D_s\delta_m K} \qquad \text{Eq. 6}$$

Replacing Eq. 6 for C_m term in Eq. 2 results in:

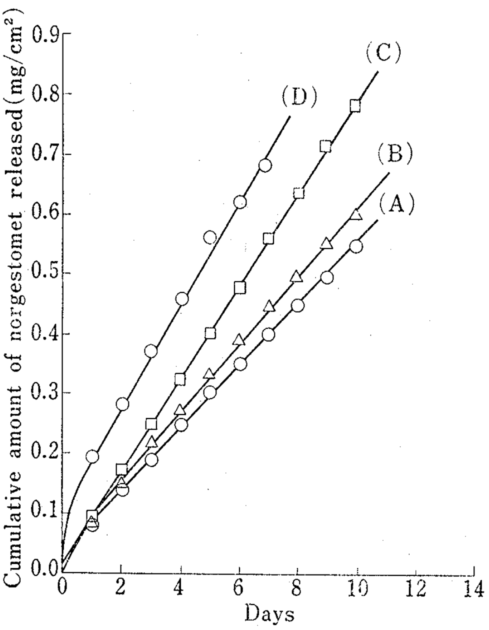

Fig. 3. Cumulative Amount of Norgestomet Released from a Unit Surface Area of Silicone Capsule (Q) as a Function of the Days of Elution

The slope of the lines is a function of the partition coefficient (K) (from silicone polymer to elution medium). The magnitudes of the slopes (and K) are: (A) 52.34 (0.629); (B) 56.52 (1.444); (C) 74.58 (11.89); (D) 83.83 (16.205) mcg/cm^2/day.

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15) W. Nernst, *Z. Physik. Chem.*, **47**, 52 (1904).
16) W.G. Perkins and D.R. Begeal, *J. Chem. Phys.*, **54**, 1683 (1971).

$$\frac{dQ_m}{dt}=\frac{D_m D_s[C_p K-C_b(t)]}{D_m\delta_D+D_s\delta_m K} \qquad \text{Eq. 7}$$

Integration of Eq. 7 yields:

$$Q_m=\frac{D_m D_s C_p K}{D_m\delta_D+D_s\delta_m K}t-\frac{D_m D_s}{D_m\delta_D+D_s\delta_m K}\int_0^t C_b(t)dt \qquad \text{Eq. 8}$$

If a sink condition is maintained throughout the experiment, *i.e.*, $C_b\simeq 0$ and $C_s\gg C_b(t)$, Eq. 8 is simplified to:

$$Q=\frac{D_m D_s C_p K}{D_m\delta_D+D_s\delta_m K}t \qquad \text{Eq. 9}$$

Results and Discussion

(A) *In Vitro* Release of Norgestomet

Eq. 9 indicates that a constant drug release profile should be obtained from such a delivery device. The results in Figure 3, where the cumulative amount (Q) of drug released in various elution media is plotted as a function of the days of elution following Eq. (9), demonstrate this linear Q-t relationship. The slope of the resultant line is defined as:

$$Q/t=\frac{C_p K D_s D_m}{K D_s\delta_m+D_m\delta_D} \qquad \text{Eq. 10}$$

Table I. Comparison of $KD_s\delta_m$ with $D_m\delta_D$

Progestins	$KD_s\delta_m$ (cm^3/day $\times 10^2$)	$D_m\delta_D$ (cm^3/day $\times 10^2$)
Progesterone	0.0088	0.8271
Norgestomet	0.0272	0.1340
Chlormadinone acetate	0.0236	0.1418
Medroxyprogesterone acetate	0.0107	0.1859

The two extreme conditions that may possibly exist are that the $KD_s\delta_m$ term is either much larger or smaller than the $D_m\delta_D$ term. If $KD_s\delta_m \ll D_m\delta_D$ (See Table I) occurs, then, Eq. (10) will reduce to Eq. (11) to define the rate of drug release under the diffusion layer-limiting partition-controlled process:[13]

$$Q/t=\frac{KD_s C_p}{\delta_D} \qquad \text{Eq. 11}$$

Eq. (11) indicates that the rate of drug release (Q/t) is a linear function of K (partition coefficient), D_s (solution diffusivity), and C_p (polymer solubility) of a drug species and is inversely proportional to δ_D (diffusion layer thickness). The drug release profiles in Figure 3 illustrate that the magnitude of the release rate (slope, Q/t) of norgestomet increases (from 52.34 to 83.83 mcg/cm^2/day) when the partition coefficient of drug (K) is enhanced (from 0.629 to 16.205). This observation indicates that the partitioning process at the polymer-solution interface is important as expected from Eq. (11). As predicted from Eq. (11), a linear relationship was observed between Q/t and K. This linearity is shown in Figure 4.

(B) *In Vitro-In Vivo* Correlation on the Release of Norgestomet

Based on the solubility (19.03 mcg/ml) of norgestomet in a simulated physiological solution (isotonic phosphate buffer at pH 7.3), the partition coefficient was calculated, following Eq. 1, to be 0.115. This value was used to estimate *in vivo* drug release flux from the linear Q/t-K relationship (Fig. 4). By this calculation, a 2 cm long silicone capsule was developed to provide 151.8 mcg/day (*i.e.*, 52.4 mcg/cm^2/day) of norgestomet required for estrus synchronization in heifers. The implantation of these capsules in heifers for 32 days gave the drug release profile (Fig. 5) as defined by Eq. (9). The *in vivo* rate of drug release was calculated

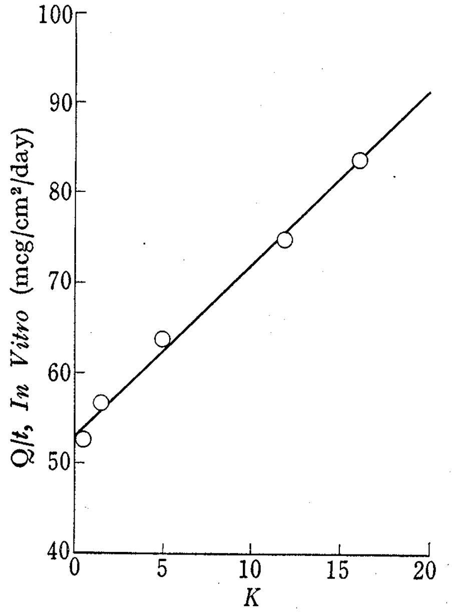


Fig. 4. Relationship between the Rate of Drug Release (Q/t) and the Partition Coefficient of Drug(K)

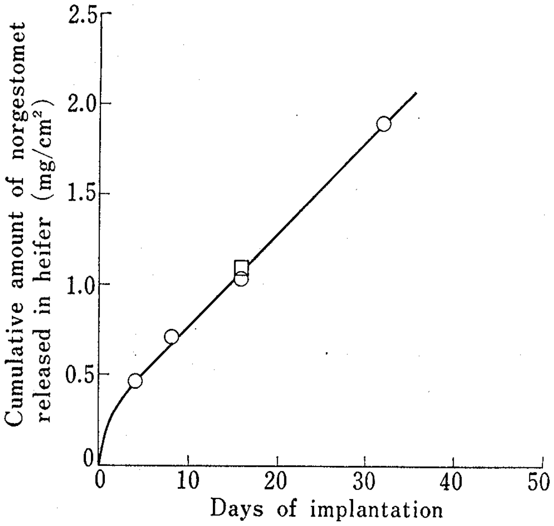


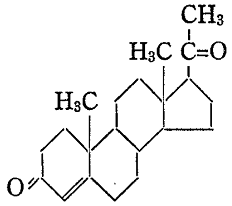
Fig. 5. Drug Release Profile of Norgestomet from Silicone Capsules subcutaneously Implanted in Heifers as a Function of the Length of Implantation

The open circle data were the results from a study in Colorado, and the open rectangle data point was the statistical mean of a Japanese experiment ($n=12$). The rate of drug release (Q/t) was calculated from the slope to be 45.72 mcg/cm²/day.

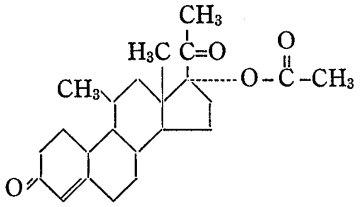
to be 45.72 mcg/cm²/day. The agreement of the *in vivo* rate (45.72 mcg/cm²/day) observed with the rate (52.4 mcg/cm²/day) predetermined from the *in vitro* Q/t-K linearity demonstrates the applicability of the simplified Eq. (11) and the validity of the drug release model defined by Eq. (9).

(C) *In Vitro-In Vivo* Correlation on the Release of Progestins

To further investigate the validity of Eq. (9) in defining the drug release profile from silicone capsules, the *in vivo* release profile of other progestins reported by Lifchez and Scommegna[17] was analyzed. In these studies, data were collected from the silicone capsules implanted subcutaneously in rats. They were recalculated and plotted in Figure 6. Apparently, the linear Q-t relationship (Eq. 9) was also followed in these progestins as Norgestomet discussed earlier in Figure 5. The *in vivo* drug release rates were estimated to be 64.5 mcg/cm²/day for progesterone ($\delta_m=0.8$ mm), 25.3 and 18.1 mcg/cm²/day for chlormadinone acetate ($\delta_m=0.42$ and 0.80 mm, respectively), and 14.9 and 9.2 mcg/cm²/day for medroxyprogesterone acetate ($\delta_m=0.42$ and 0.80 mm, respectively). The effect of capsule thickness on the magnitude of drug release rate is obvious, but smaller, due to the existence of an *in vivo* diffusion layer (*e.g.*, $\delta_D \simeq 0.58$ mm)[18] on the immediate surface of the implanted capsules. As illustrated in the following, progesterone, chlormadinone acetate, and medroxyprogesterone acetate are structurally related to norgestomet:



progesterone (I)



norgestomet (II)

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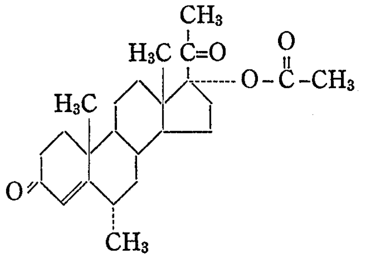
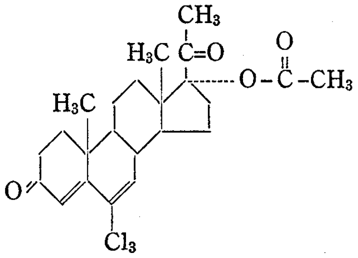
[17] A.S. Lifchez and A. Scommegna, *Fertility and Sterility*, **21**, 426 (1970).
[18] T.J. Roseman, *J. Pharm. Sci.*, **61**, 46 (1972).



medroxyprogesterone acetate (III)



chlormadinone acetate (IV)

As predicted by Eq. (10), the rate of drug release (Q/t) should be proportional to C_p (polymer solubility), K (partition coefficient from polymer toward solution), D_s (solution diffusivity), D_m (matrix diffusivity), δ_m (capsule wall thickness), and δ_D (diffusion layer thickness). If this drug release model is also followed in the biological environment, then the drug release flux should be calculable, following Eq. (10), if the physical variables are known or predetermined. The values for C_p, D_m, δ_m *etc.* may be collected from literature or experimentally determined without difficulty. However, the information on the magnitudes of K and D_s in the tissues where the implants are placed was unavailable. They were therefore, approximated from the data measured in either distilled water or isotonic phosphate buffer (pH 7.3).[12–14,18,19] In addition, a δ_D value of 580 microns[18] reported in the literature was adopted. These values (Table II) were inserted into Eq. (10) to calculate the expected *in vivo* drug release rates (Q/t) for progesterone, norgestomet, chlormadinone acetate, and medroxyprogesterone acetate. Results are shown in Table III. The estimated rates are found 4-to 7-fold lower than the observed values (compare columns 2 with 3). This difference indicates that the combination of K and D_s values under *in vivo* condition may be approximately 4-to 7-fold greater than that measured in *in vitro* studies using distilled water or phosphate buffer solution.

The 4-to 7-fold difference between expected and observed *in vivo* drug release rates may also indicate that the magnitude of *in vivo* diffusion layer (δ_D=580 microns) we applied to the computation of the expected drug release rates is several times higher than what the real value should be. The δ_D value around a device implanted subcutaneously may be much thinner than that around an intravaginal device (580 microns).[18] In other words, the subcutaneously implanted device has a much better tissue-device contact than does the intravaginally inserted one; therefore, a smaller δ_D value should be expected for the device implanted subcutaneously. This is demonstrated in the data tabulated in the 4th column of Table III where a δ_D value of 80 microns was applied into the calculation of drug release rates. Apparent-

TABLE II. Rate-Limiting Physico-Chemical Parameters for the Release of Progestins from Silicone Capsules

Progestins	Physico-Chemical parameters					
	K	D_s (cm²/day×10²)	D_m (cm²/day×10²)	C_p (mcg/ml)	δ_D[a] (cm)	δ_m[b] (cm)
Progesterone[c]	0.022	4.994	14.26	513	0.058	0.080
Norgestomet	0.115	3.64	2.31	165.53	0.058	0.065
Chlormadinone	0.122	2.419	2.445	82	0.058	0.042
acetate[d]	0.122	2.419	2.445	82	0.058	0.080
Medroxyprogesterone	0.037	3.603	3.205	87	0.058	0.042
acetate[c]	0.037	3.603	3.205	87	0.058	0.080

a) data from Reference (14)
b) data from Reference (17)
c) data on K, D_s, D_m and C_p were calculated from Reference (18). Please refer to text for their definition.
d) Data on D_s, D_m and C_p were calculated from Reference (19). K was re-examined in this laboratory.

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19) J. Haleblian, R. Runkel, N. Mueller, J. Christopherson, and K. Ng, *J. Pharm. Sci.*, 60, 541 (1971).

Table III. Comparison between Observed and Calculated Rates of Drug Release

Progestins	Rate of drug release (mcg/cm²/day)		
	Observed	Calculated[a]	
		$\delta_D = A$	$\delta_D = B$
Progesterone	64.5[b]	9.62	65.40
Norgestomet	45.72[c]	9.93	35.03
Chlormadinone	25.3[d]	3.84	18.49
acetate	18.1[b]	3.58	13.70
Medroxyprogesterone	14.9[d]	1.94	11.88
acetate	9.2[b]	1.89	10.24

a) calculated from the data in Table II following Eq. (10). $A=580$ microns, $B=80$ microns
b) $\delta_m = 800$ microns
c) $\delta_m = 650$ microns
d) $\delta_m = 420$ microns

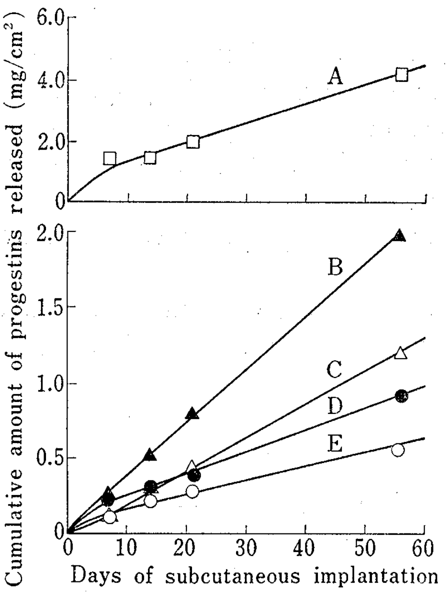

Fig. 6. The *in Vivo* Drug Release Profiles of Progesterone (A), Chlormadinone Acetate (B, C), and Medroxyprogesterone Acetate (D, E) from Silicone Capsules Implanted subcutaneously in Rats

Data were calculated from Reference (17) and two thicknesses of capsule wall were vsed: 0.42mm (solid data points) and 0.80 mm (open data points). Drug release rates (Q/t) were calculated to be; (A) 64.5, (B) 25.3, (C) 18.1, (D) 14.9, and (E) 9.2 mcg/cm²/ day.

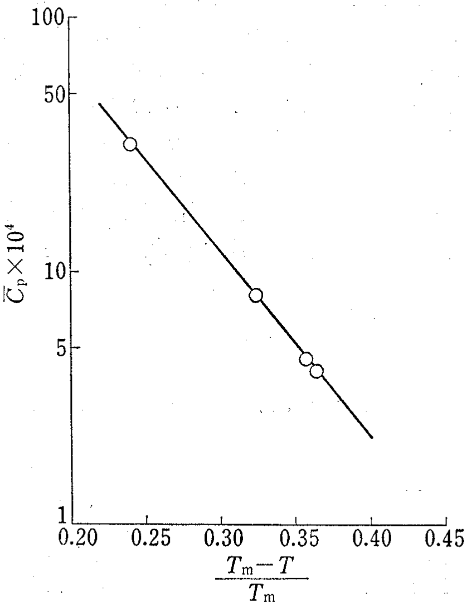

Fig. 7. Linear Relationship of log $\bar{C}_p$ and $(T_m - T)/T_m$ as Defined by Eq. 12

From the slope ($\Delta H_f/2.303RT$) of the linearity, the ΔH_f value at 37° was estimated to be 10.354 kcal/mole.

ly, a much better agreement between expected and observed *in vivo* drug release fluxes was obtained.

Both 580 microns and 80 microns are arbitrary. At the present stage of the art, we are not able to measure reliably the real thickness of the *in vivo* diffusion layer around an implanted drug delivery device. The same kind of difficulty will be expected as what we encountered in the measurement of the *in vivo* magnitudes of K (partition coefficient) and D_s (solution diffusivity) discussed earlier. Aside from the biological complexity, however, the comparisons made above suggested that we may expect that a proportionality exists between *in vivo* and *in vitro* drug release profiles. This proportionality should be useful as a working factor in the future developments on a drug delivery system to translate *in vitro* drug release profiles into those which may be expected *in vivo.*

In conclusion, in the development of a silicone capsule as the long-acting delivery device for a given drug, a biological drug release study should also be conducted to evaluate the *in vitro-in vivo* correlation on both the mechanisms and the rates of drug release. The *in vitro-in vivo* relation illustrated in this report should be beneficial to the future formulation studies in the development of a suitable long-acting delivery system to deliver effectively a drug at a programmed rate to maintain a desirable therapeutic level for a predetermined duration of medication.

(D) Thermodynamics of Drug Release

As discussed earlier, if the dissolution of drug crystals into the polymer structure (with a solubility of C_p) is the first step for the release of drug from silicone capsules, then the mole fraction solubility, $\bar{C}_p$, of a progestin in a real solution of polymer-progestin mixture should follow the relationship of:[20]

$$\log \bar{C}_p = -\log \gamma_p - \frac{\Delta H_f}{2.303RT}\left(\frac{T_m - T}{T_m}\right) \qquad \text{Eq. 12}$$

where ΔH_f is the energy required to increase the intermolecular distances in crystals, thus allowing drug molecules to dissociate from the lattice and dissolve into the polymer structure. T_m and T are the temperatures at which crystals melt and of the system (310.15°K in this case), respectively. As expected from Eq. 12, a linearity of $\log \bar{C}_p$ to $(T_m - T)/T_m$ is observed and shown in Figure 7. From the slope, ΔH_f was calculated to be 10.354 kcal/mole at 37°. In addition, the activity coefficient (γ_p) of progestins in silicone polymer was calculated from the intercept and found to be 0.245.

The entropy, ΔS_m, gained by the dissociation of drug molecules from crystal lattice and their dissolution into the polymer structure may be calculated from the following relation:

$$\Delta S_m = \frac{\Delta H_f}{T_m} \qquad \text{Eq. 13}$$

Table IV. Membrane Permeation Thermodynamics of Crystalline Progestins

Progestins	T_m[a] (°K)	$\bar{C}_p$[b] (Mole fraction)	$T_m - T/T_m$ (T=310.15 °K)	ΔS_m[c] (cal/mole/deg)
Progesterone	403.15	31.79×10^{-4}	0.231	25.68
Norgestomet	459.15	7.96×10^{-4}	0.325	22.55
Medroxyprogesterone acetate	482.15	4.39×10^{-4}	0.357	21.47
Chlormadinone acetate	487.15	3.94×10^{-4}	0.363	21.25

a) CRC: "Handbook of Chemistry and Physics," 48 th ed. (1967—1968), The Chemical Rubber Co., Cleveland, Ohio 44128.
b) calculated from the C_p data in Table II
The molar concentration of the polymer fraction in the solution of drug-polymer mixture is 0.5124 M.
c) calculated from $\Delta S_m = \Delta H_f/T_m$ where ΔH_f=10.354 kcal/mole

and the results are tabulated in Table IV. The data suggest that the dissociation of progestin molecules from their crystal structure resulted in gains of 21.25 to 25.68 entropy units of molecular freedom. This gain in entropy enables these progestins to facilely diffuse through silicone capsules.

The results obtained in this investigation should provide a better understanding of the choice of a progestin analog in a homogeneous series for a long-acting drug delivery system.

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[20] A.N. Martin, "Physical Pharmacy," Lea & Ferbiger, Philadelphie, 1960, Chapter 14.

More investigations on the validity of Eq. 12 and its relation to the controlled release of drugs from a delivery system have been conducted in this laboratory on other series of drug analogs. Their results will be reported later.

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