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* To whom inquiries should be directed.

Controlled Drug Release from Polymeric Delivery Devices IV: *In Vitro–In Vivo* Correlation of Subcutaneous Release of Norgestomet from Hydrophilic Implants

YIE W. CHIEN ˣ and EDWARD P. K. LAU

Abstract □ The *in vitro* and *in vivo* releases of norgestomet from hydrophilic implants were found to follow a matrix-controlled ($Q - t^{1/2}$) process. The sorption of drug onto the implants was observed to obey the same mechanism but with a much smaller magnitude of the $Q/t^{1/2}$ value. The effect of the extent of cross-linking on the magnitude of drug release ($Q/t^{1/2}$) profiles was analyzed both theoretically and experimentally. The release of norgestomet from hydrophilic implants was found to be an energy-linked process. Two energy terms were calculated; the activation energy for matrix diffusion was 7.71 kcal/mole, and the heat of drug crystal solvation was 25–28.6 kcal/mole.

Keyphrases □ Drug release—controlled, norgestomet from hydrophilic polymeric delivery devices □ Norgestomet—subcutaneous release from hydrophilic implants, matrix-controlled kinetic mechanism □ Implants—hydrophilic, subcutaneous release of norgestomet □ Delivery devices—polymeric, hydrophilic implants, subcutaneous release of norgestomet

The controlled release profiles of ethynodiol diacetate[1], a progestin, from silicone matrixes were reported previously (1). *In vitro* release of the drug from such silicone-type vaginal devices followed either of two kinetic mechanisms, matrix controlled or partition controlled, depending on whether the diffusion across the polymer phase or the partitioning across the polymer–solution interface was the rate-limiting step (2). An 8-week investigation on the intravaginal release of ethynodiol diacetate in rabbits (3) demonstrated that the matrix-controlled process was the predominant mode of drug release *in vivo*. Subsequently, the authors also investigated the controlled release of progestins from popularly used (Long–Folkman-type) polysiloxane[2] capsules (4). In contrast to the matrix-controlled ($Q/t^{1/2}$) mechanism seen in the drug release from silicone matrixes, they observed a constant (Q/t) drug release rate (5).

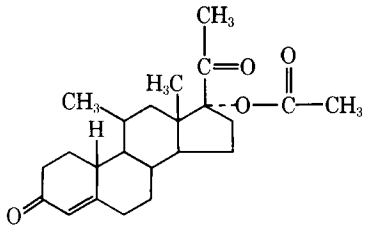
It was established that the carriers prepared from silicone polymer are permeable only to lipophilic drugs, *e.g.*, steroids. The rate of drug release is linearly proportional to the polymer solubility (partition-controlled process) (5) or to the square root of the polymer solubility (matrix-controlled process) (1, 2) of a given drug species when all other factors are constant. Apparently, the solubility of drug molecules in polymer plays a rate-limiting role in the controlled release of drug from the silicone-type drug delivery devices.

In addition to studying the lipophilic silicone polymer, researchers in this laboratory have had an ongoing interest in the development of a biocompatible, hydrophilic polymer (hydrogel) as the drug delivery carrier. First introduced by Wichterle and Lim (6) for prosthetic implants and contact lenses, this purified hydrogel is nontoxic, transparent, autoclavable, chemically stable, pliable, and moldable. The unique characteristics of this polymer (different from the silicone polymer discussed earlier) are its hydrophilicity, conductivity, and extreme wettability. Hydrogel will absorb and elute, in addition to neutral species, ionizable compounds with a molecular weight of 8000 or less (7). Through controlled alteration of the amount of cross-linking agent, the monomer-to-water ratio, and the polymerization conditions, a range of masses is obtainable from compact gel to cellular sponge, with varying physical properties.

The purposes of this study were to analyze the mechanisms and rates of the controlled release of

[1] SC-11800.
[2] Silastic.

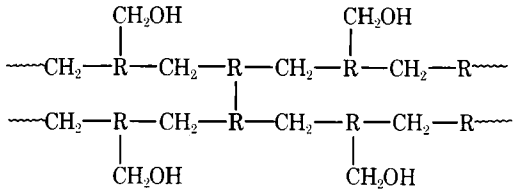
norgestomet (I) from hydrophilic implants and to investigate the correlations of *in vivo* and *in vitro* drug release profiles. Norgestomet is effective for the estrus synchronization in heifers.



I

EXPERIMENTAL

Drug Delivery Devices—The delivery devices were prepared[3] first by polymerization from the water-soluble monomers of hydroxyethyl methacrylate to an alcohol-soluble, linear polymer[4]. Addition of the cross-linking agent ethylene dimethacrylate and an oxidizing catalyst yielded the three-dimensional ethylene glycomethacrylate gel[5] (II) (7).



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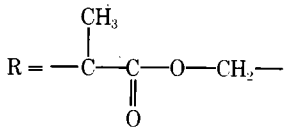

Various amounts of norgestomet may be impregnated in the hydrogel (II) by absorption by the dry polymer, incorporation into the gel plastic at the time of polymerization, or solution in the liquid linear polymer[4] (7).

Drug Release Systems—In Vitro *Studies*—In a dissolution flask, 300 ml of distilled water was maintained at 37°. At zero time, one rod of hydrogel (3 × 18 mm) was immersed with constant agitation (100 rpm) in this thermostated elution medium. The elution medium was sampled and renewed every 24 hr. The drug content in the samples was analyzed spectrophotometrically. The amount of norgestomet released from a unit surface area of hydrogel at a given day was calculated based on ϵ = 17,400 at λ_{max} = 242 nm.

In Vivo *Studies*—*In vivo* studies for three cross-links (*XL*) of hydrogel containing 5% norgestomet were conducted[6] in 39 cows. Cows were randomized into three lots of 13 each (A, B, and C). On Day 0, each cow in Lots A, B, and C was implanted in one of its ears with five implants of 1.2% *XL*, 4.8% *XL*, and 19.2% *XL*, respectively. The implants were placed in such a way as to minimize the possibility of their interfering with elution from each other. For analytical control purposes, two cows in each lot were implanted with a single nonmedicated hydrogel with corresponding cross-links. On Days 1, 2, 4, 8, and 16, one implant was removed from each cow and assayed for its residual drug content.

Hydrogel Sorption Studies—Ten rods of hydrogel (4.8% *XL*) containing no drug were immersed with shaking (80 oscillations/min) in 200 ml of aqueous solution of norgestomet (2×10^{-5} *M*) at 37°. Ten milliliters of sample was withdrawn every hour in the first 6 hr and then every day up to 5 days. After equilibration to 25°, the drug concentration in the sample was analyzed spectrophotometrically[7] and the amount of drug absorbed into the hydrogel (micrograms per square centimeter) was calculated as a function of time.

[3] HYDRO Med. Sciences, Inc., New Brunswick, N.J.
[4] Hydron S.
[5] Hydron.
[6] By Dr. Sam E. Curl, Texas Tech University, Lubbock, TX 79409
[7] Coleman 124 D double-beam spectrophotometer, Perkin-Elmer.

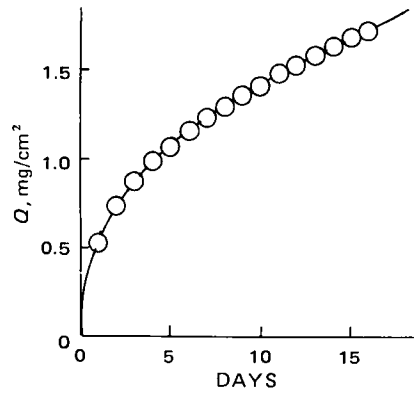

Figure 1—In vitro *cumulative amount of drug released (Q) per unit area of implant* versus *time for hydrogel implant (4.8% XL) containing 5% norgestomet.*

Determination of Solubility in Hydrogel—Five rods of hydrogel (4.8% *XL*) containing no drug were immersed with shaking (80 oscillations/min) in 200 ml of aqueous solution of norgestomet (2×10^{-5} *M*) at 37°. The drug concentration in the solution was monitored every day until a constant level was reached. Then the drug content absorbed into each rod of hydrogel was extracted with methanol for 3 days with constant shaking. The drug concentration in methanol was calculated and used to estimate the solubility of norgestomet in hydrogel. A solubility of 266.4 (±12.1) μg/cm³ was obtained.

RESULTS AND DISCUSSION

***In Vitro* Drug Release Studies**—The time course for the release of norgestomet from hydrogel implants at 37° is illustrated in Fig. 1. The cumulative amount of drug (Q) released from a unit surface area of implant is directly but not linearly proportional to the length of elution (in days). If the amount of drug (>36.3 mg/cm³) incorporated into a unit volume of hydrogel implant is greatly in excess of the polymer solubility (0.266 mg/ml) of drug, then most impregnated drug will be evenly dispersed in the polymeric matrix. In such a case, the release of drug from the hydrogel implant should follow the $Q - t^{1/2}$ relationship established by Higuchi (8), as demonstrated previously in the controlled release of ethynodiol diacetate from silicone vaginal devices (1–3):

$$Q = \sqrt{D_m(2A - C_p)C_p t} \qquad \text{(Eq. 1)}$$

where Q is the cumulative amount of drug released from a unit surface area of implant, D_m is the effective diffusivity of drug in polymeric matrix, A is the initial amount of drug incorporated in a unit volume of hydrogel, C_p is the solubility of drug in the hydrogel, and t is the time. In the present case, the drug content (A = 36.3 g/10³ cm³) incorporated into a unit volume of hydrogel is much higher than the solubility of drug in the hydrogel polymer (C_p = 0.266 g/10³ cm³); therefore, since $2A \gg C_p$, Eq. 1 may be simplified to:

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

According to Eq. 2, the cumulative amount of norgestomet released from the hydrogel, Q, should be linearly proportional to the square root of time ($t^{1/2}$). The nonlinear drug release profile ($Q - t$) shown in Fig. 1 is plotted in Fig. 2 according to Eq. 2. Apparently, the $Q - t^{1/2}$ relationship is also followed very well in the release of norgestomet from the hydrogel as ethynodiol diacetate was from silicone devices (1).

From the slope of the linear Q *versus* $t^{1/2}$ plot, the magnitude of drug release profile ($Q/t^{1/2}$) may be estimated. For the hydrogel implant with a degree of cross-linkage of 4.8%, the magnitude of the $Q/t^{1/2}$ value was found to be 0.396 mg/cm²/day$^{1/2}$. The influence of the extent of cross-linkage on the controlled-release profiles of norgestomet from hydrogel implants will be analyzed later.

***In Vivo* Drug Release Studies**—The release profile of norgestomet from a 4.8% cross-linked hydrogel device implanted subcu-

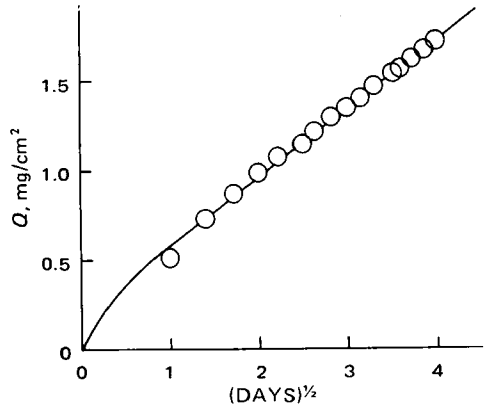

Figure 2—*Linear relationship between the* in vitro *cumulative amount of drug released (Q) per unit area of implant and the square root of time ($t^{1/2}$) following Eq. 2. The flux of drug release ($Q/t^{1/2}$) calculated from the slope is 0.396 mg/cm²/day$^{1/2}$.*

taneously in cows is shown in Fig. 3 according to Eq. 2. As demonstrated in the study of *in vitro* drug elution, the linear $Q - t^{1/2}$ relationship is also observed in the *in vivo* release of norgestomet. The agreement indicates that the same mechanism (matrix controlled) (1, 3) was followed in both *in vitro* and *in vivo* drug releases. The *in vivo* $Q/t^{1/2}$ value was also estimated from the slope of the $Q - t^{1/2}$ plot and found to be 0.504 mg/cm²/day$^{1/2}$. This magnitude of the $Q/t^{1/2}$ value is 27% higher than that estimated from the *in vitro* drug release profile (0.396 mg/cm²/day$^{1/2}$). This difference is obviously the result of the difference in the diffusional resistance between *in vivo* and *in vitro* cases (3).

Effect of Cross-Linking—In the process of hydrogel polymerization, varying amounts (1.2–19.2%) of ethylene dimethacrylate were added as a cross-linking agent for the cross-linking of a linear polymer[4] to a three-dimensional ethylene glycomethacrylate gel[5]. The addition of a cross-linking agent decreased the magnitude of $Q/t^{1/2}$ of norgestomet from the hydrogel (Table I). Both the *in vitro* and *in vivo* data for $Q/t^{1/2}$ were remarkably decreased as the extent of cross-linking increased.

In Eq. 2, only the matrix diffusivity (D_m), a rate-limiting parameter, appears to be sensitive to the degree of cross-linking (9), since it is directly proportional to the ratio of porosity (ϵ) over tortuosity (θ) (10) as follows:

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

since the addition of a cross-linking agent results in a greater degree of polymer cross-linkage leading to the reduction in the mobility of the polymer chain and, consequently, a decrease in porosity (ϵ) as well as an increase in tortuosity (θ) for the diffusion of

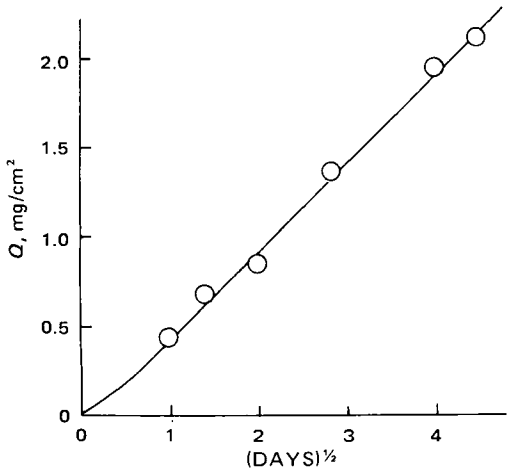

Figure 3—*Linear relationship between the* in vivo *cumulative amount of drug released (Q) per unit area of implant and the square root of time ($t^{1/2}$) following Eq. 2. The flux of drug release ($Q/t^{1/2}$) calculated from the slope is 0.504 mg/cm²/day$^{1/2}$.*

Table I—Effect of Extent of Cross-Linkage on the $Q/t^{1/2}$ Profiles of Norgestomet from Hydrogel Implants[a]

Cross-Linkage Extent, %	$Q/t^{1/2}$, mg/cm²/day$^{1/2}$	
	In Vitro	*In Vivo*
1.2	0.605	0.640
4.8	0.396	0.504
9.6	0.185	—
12.0	0.133	—
14.4	0.101	—
16.8	0.074	—
19.2	0.058	0.129

[a] Five percent drug per implant (total drug content = 6 mg).

drug in the polymer matrix. The term D is the intrinsic diffusivity of drug.

Equation 3 may be expressed alternatively to describe the influence of the extent of cross-linking (XL) on the effective matrix diffusivity (D_m):

$$D_m = kD/(XL) \qquad \text{(Eq. 4)}$$

since:

$$\epsilon/\theta = k/(XL) \qquad \text{(Eq. 5)}$$

where k is a proportionality constant. Substituting Eq. 4 for D_m in Eq. 2 gives:

$$Q/t^{1/2} = \sqrt{2kDAC_p}(XL)^{-1/2} \qquad \text{(Eq. 6)}$$

Equation 6 states that the magnitude of $Q/t^{1/2}$ values should be a direct function of the reciprocal of the square root of cross-linking agent added, $(XL)^{-1/2}$, with a slope defined by $(2kDAC_p)^{1/2}$. The relationship of $Q/t^{1/2}$ to $(XL)^{-1/2}$ is demonstrated in Fig. 4. Both *in vitro* and *in vivo* $Q/t^{1/2}$ values were linearly correlated with their corresponding $(XL)^{-1/2}$ data in the cross-linking range of 4.8–19.2% [$(XL)^{-1/2}$ = 4.56–2.28]. A higher effect on the magnitude of $Q/t^{1/2}$ value was observed when the cross-linking extent was below 4.8% [$(XL)^{-1/2}$ = 4.56]. The same kind of phenomenon was also observed in the diffusion of the gas molecules as small as nitrogen in natural rubber (9). The same type of trend was illustrated (insert in Fig. 4) when the effective diffusivity data were plotted against the reciprocal of the extent of cross-linking (Eq. 4).

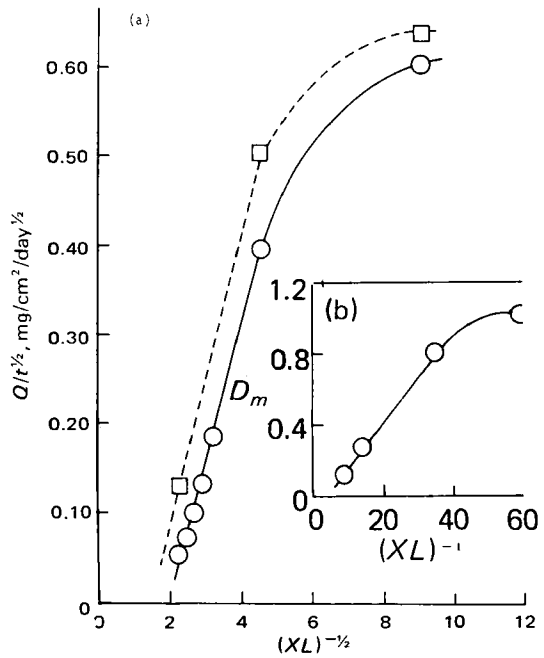

Figure 4—*(a) Relationship between the flux of drug release ($Q/t^{1/2}$) and the extent of cross-linking (XL) following Eq. 6. Key:* ○, *in vitro data; and* □, *in vivo data. (b) Relationship between* D_m *and* $(XL)^{-1}$ *(Eq. 4). (Data are from Ref. 9.)*

Table II—Effect of Extent of Cross-Linking (XL) on the Ratio of Porosity/Tortuosity (ϵ/θ) and the Effective Diffusivity of Drug in Polymer Matrix (D_m)

XL	ϵ/θ [a]	D_m [b], cm²/day
0.012	2.67	9.72×10^{-2}
0.048	0.67	2.42×10^{-2}
0.096	0.33	1.21×10^{-2}
0.120	0.27	9.72×10^{-3}
0.144	0.22	8.08×10^{-3}
0.168	0.19	6.93×10^{-3}
0.192	0.17	6.06×10^{-3}

[a] Calculated from Eq. 5, where $k = 3.20 \times 10^{-2}$. [b] Calculated from Eq. 4, where $k = 3.20 \times 10^{-2}$ and $D = 3.64 \times 10^{-2}$ cm²/day.

Figure 4 demonstrates that both *in vitro* and *in vivo* data followed the similar dependency of $Q/t^{1/2}$ on $(XL)^{-1/2}$.

The magnitude of the slope, $(2kDAC_p)^{1/2}$, of the linear region was estimated as 0.15 mg/cm²/day$^{1/2}$. By incorporating the values of D (3.64×10^{-2} cm²/day), A (36.3 g/10^3 cm³), and C_p (0.266 g/10^3 cm³), the magnitude of k, the proportionality constant relating ϵ/θ with $(XL)^{-1}$, may be computed. A value of 3.20×10^{-2} was obtained. Furthermore, the variation of ϵ/θ, the ratio of porosity to tortuosity, and of D_m, the effective diffusivity of drug in the hydrogel matrix, as a function of the extent of polymer cross-linking (XL) may be calculated from Eqs. 5 and 4, respectively (Table II). It is obvious that both the magnitudes of ϵ/θ and D_m values were decreased, except in the case with a cross-linkage of 0.012 (1.2% XL), as the extent of polymer cross-linking increased. Both the values of ϵ/θ and D_m for 1.2% XL were unrealistically high; *i.e.*, ϵ/θ should be less than unity (since $\epsilon \leq 1$ and $\theta \geq 1$) and D_m should also be smaller than D (3.64×10^{-2} cm²/day) (Eq. 3). These results are in agreement with observations discussed earlier (Fig. 4).

Effect of Temperature—The dependency of the drug release profiles on temperature is illustrated in Fig. 5. The higher the temperature, the greater the drug release $Q/t^{1/2}$ value (slope). This observation clearly indicates that the release of norgestomet from the hydrogel is an energy-linked process.

Inspection of Eq. 2 revealed that the magnitude of $Q/t^{1/2}$ values was directly proportional to the square root of the product of two energy-dependent parameters, C_P (polymer solubility) and D_m

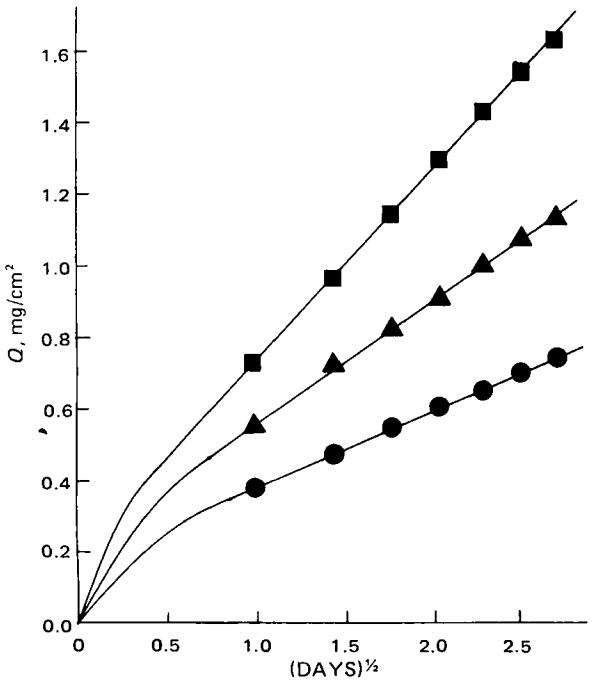

Figure 5—*Linear* $Q - t^{1/2}$ *relationship at various temperatures. Key:* ■, *45°;* ▲, *37°; and* ●, *25°. The* $Q/t^{1/2}$ *of drug release was calculated to be 0.522, 0.357, and 0.212 mg/cm²/day*$^{1/2}$, *respectively.*

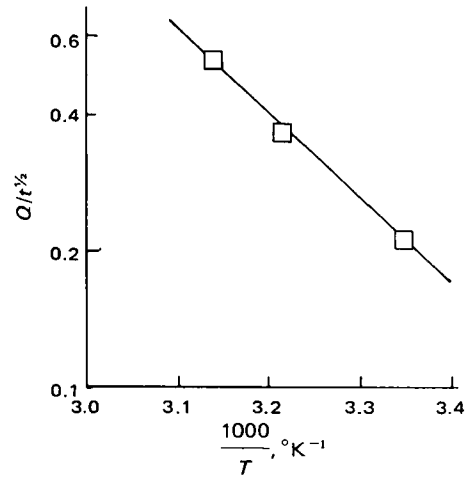

Figure 6—*Linear relationship between the flux of drug release* ($Q/t^{1/2}$) *and the reciprocal of temperature* (T^{-1}) *following Eq. 10. A value of 16.48 kcal/mole was obtained for the sum of* E_a *and* ΔH_f *[*$(T_m - T)/T_m$*].*

(matrix diffusivity), when the amount of drug ($2A$ term) incorporated was the same (a constant). Therefore, Eq. 2 may be expressed alternatively as:

$$\log (Q/t^{1/2}) = \tfrac{1}{2} \log (\text{constant}) + \tfrac{1}{2} \log D_m + \tfrac{1}{2} \log C_p \quad \text{(Eq. 7)}$$

It was known that (9):

$$\log D_m = \log D_0 - \frac{E_a}{2.303R} \frac{1}{T} \quad \text{(Eq. 8)}$$

where E_a is the energy of activation required for matrix diffusion, and (11):

$$\log C_p = -\frac{\Delta H_f}{2.303RT} \left(\frac{T_m - T}{T_m}\right) \quad \text{(Eq. 9)}$$

where ΔH_f is the energy required to increase the intermolecular distance in drug crystals, thus allowing drug molecules to dissociate from the crystal lattice and to dissolve into the polymer structure before molecular diffusion occurs, and T_m and T are the temperatures at which crystals melt and of the system examined, respectively.

Substituting Eqs. 8 and 9 for the D_m and C_p terms in Eq. 7, respectively, gives:

$$\log (Q/t^{1/2}) = \Sigma \log (\text{constant}) - \left[\frac{E_a}{4.606R} + \frac{\Delta H_f}{4.606R} \left(\frac{T_m - T}{T_m}\right)\right] \frac{1}{T} \quad \text{(Eq. 10)}$$

In the narrow temperature range (T = 298.15–318.15°K) investigated, it is assumed that the variation in $(T_m - T)/T_m$ term is quite small (T_m = 459.15°K) and may be approximated as a constant. If this first approximation is acceptable, then a linear relationship should be observed between log $(Q/t^{1/2})$ and T^{-1}. The result shown in Fig. 6 warrants this linearity. A value of 16.48 kcal/mole was calculated for $E_a + \Delta H_f [(T_m - T)/T_m]$. This energy term is a composite of E_a (activation energy for matrix diffusion) and ΔH_f (heat of crystal solvation) at a given temperature difference $[(T_m - T)/T_m]$.

The drug release profiles in Fig. 5 show a burst effect (12), with a higher initial release from the drug molecules accumulating on the matrix surface (1, 3). The values of lag time (t_{lag}) may be estimated from the negative time axis intercept on the initial stage of $Q - t$ (not $Q - t^{1/2}$) plots. The t_{lag} value is defined as:

$$t_{lag} = \frac{\delta^2}{3D_m} \quad \text{(Eq. 11)}$$

where δ is the effective thickness of a diffusion path.

Substituting Eq. 11 for the D_m term in Eq. 8 results in:

$$\log (t_{lag}) = -\log (\text{constant}) + \left(\frac{E_a}{2.303R}\right)\left(\frac{1}{T}\right) \quad \text{(Eq. 12)}$$

Equation 12 points out that a linear relationship exists between log (t_{lag}) and T^{-1} with a positive slope, which is defined by only the activation energy, E_a, for matrix diffusion. The linearity is

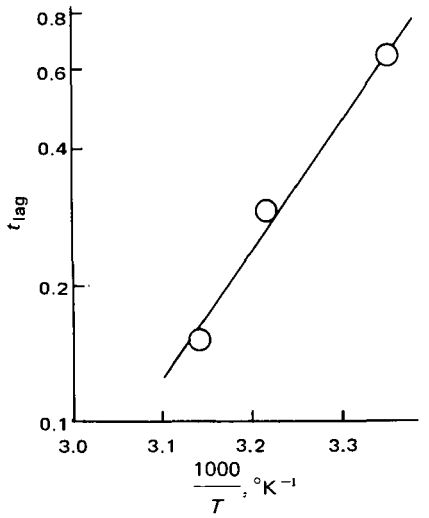

Figure 7—*Linear relationship between the lag time (t_{lag}) and the reciprocal of temperature (T^{-1}) following Eq. 12. From the slope, the activation energy (E_a) for diffusion was calculated to be 7.71 kcal/mole.*

demonstrated in Fig. 7. From the slope, the E_a value was estimated to be 7.71 kcal/mole. This value may then be applied to the estimation of the magnitude of ΔH_f at various values of the $(T_m - T)/T_m$ term. A range of 25–28.6 kcal/mole was obtained (Table III) for ΔH_f in the temperature range of 25–45°. The variation in both the magnitudes of ΔH_f and $(T_m - T)/T_m$ was quite small (only 12.5%) in this temperature range.

Sorption of Drug by Hydrogel Implants—In its dry state, the hydrogel is a compact and transparent polymer. In an aqueous solution, it tends to absorb water by virtue of its hydrophilicity and then to swell to a soft texture. A hydrogel implant with a cross-linking extent of 4.8% absorbed 54.6% of its weight of water, and its volume was increased 77.23% at the end of 7 days of immersion in water.

The sorption kinetics of norgestomet by hydrogel implants followed the same mechanism (Fig. 8) as in earlier analyses for the release of norgestomet from hydrogel implants. The profile of drug sorption ($Q'/t^{1/2}$) was calculated to be 4.92 mg/10^3 cm^2/day$^{1/2}$. Compared to the $Q/t^{1/2}$ of drug release (396 mg/10^3 cm^2/day$^{1/2}$),

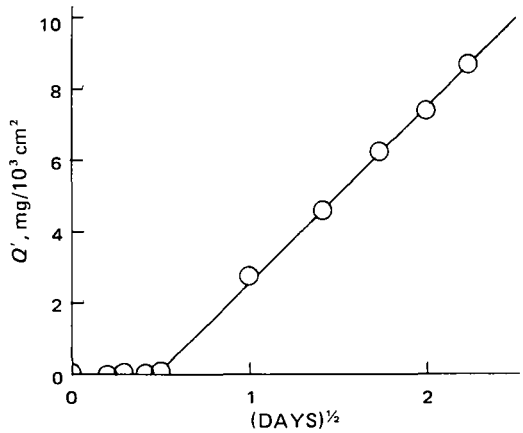

Figure 8—*Linear relationship between the cumulative amount (Q') of norgestomet adsorbed by a unit area of hydrogel implant* versus *time. The flux of drug release (Q'/t$^{1/2}$) was calculated from the slope and found to be 4.92 mg/10^3 cm^2/day$^{1/2}$.*

Table III—Calculation of the Heat of Crystal Solvation (ΔH_f) at Various Temperatures

Temperature	$(T_m - T)/T_m$[a]	ΔH_f[b], kcal/mole
25°	0.351	24.99
37°	0.325	26.98
45°	0.307	28.57

[a] T_m = 459.15°K. [b] ΔH_f was calculated from:

$$\Delta H_f = \frac{16.48 - E_a}{(T_m - T)/T_m} = \frac{8.77}{(T_m - T)/T_m}$$

since E_a = 7.71 kcal/mole.

this magnitude of drug sorption ($Q/t^{1/2}$) is insignificantly small (accounts for 1.24% only). This observation led to the conclusion that the release of norgestomet from hydrogel implants is an irreversible process under sink conditions.

It is concluded that, regardless of the difference in the physicochemical nature of polymer between hydrophilic hydrogel and lipophilic silicone delivery devices, the same theoretical model (Eq. 2) was followed for the release of drug molecules dispersing homogeneously throughout the polymeric matrixes. The same phenomenon was also observed in the delivery system prepared from polyethylene polymer (13).

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