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# Sustained Drug Delivery Systems II: Factors Affecting Release Rates from Poly(ϵ-caprolactone) and Related Biodegradable Polyesters

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**Abstract** □ The release rates of several steroids from films and capsules of homopolymers and copolymers of ϵ-caprolactone, DL-lactic acid, and glycolic acid were measured *in vitro* and *in vivo* for up to 200 days. Relatively constant release rates from capsules (reservoir devices) were observed only under certain conditions. Factors that influence the drug release kinetics were evaluated. Release from poly(ϵ-caprolactone) and poly(ϵ-caprolactone-co-DL-lactic acid) was diffusion controlled. Release from poly(DL-lactic acid-co-glycolic acid) was associated with polymer degradation. Release from poly(DL-lactic acid) was very slow when diffusion controlled.

**Keyphrases** □ Polyesters, biodegradable—poly(ϵ-caprolactone), poly(DL-lactic acid), copolymers, steroid release, films, capsules □ Drug delivery systems—kinetics, biodegradation, diffusion, films, capsules □ Poly(ϵ-caprolactone)—homopolymers, copolymers, release rates, films, capsules □ Sustained-release systems—biodegradable polyesters, poly(ϵ-caprolactone), films, capsules

Polymer systems for sustained subdermal drug delivery may be based on principles of drug diffusion and/or polymer degradation. The diffusion coefficients of steroids in poly(ϵ-caprolactone) and poly(ϵ-caprolactone-co-DL-lactic acid) are comparable to values reported for poly(dimethylsiloxane) and, *a priori*, these polymers may be used in diffusion-controlled delivery systems that biodegrade after drug exhaustion (1, 2). In contrast, diffusion in poly(DL-lactic acid) is much slower (2); consequently, diffusion, leaching, and biodegradation may contribute to the drug delivery rates reported in studies of this polymer (3–5).

This paper describes the release rates of several steroids from films and capsules of homopolymers and copolymers of ϵ-caprolactone, DL-lactic acid, and glycolic acid *in vitro* and *in vivo* and factors that determine the observed kinetics.

## EXPERIMENTAL

**Synthesis**—Poly(ϵ-caprolactone), poly(DL-lactic acid), their copolymers, and poly(DL-lactic acid-co-glycolic acid) were prepared by bulk polymerization of the purified monomers at 130° *in vacuo* in the presence of stannous octoate (50–500 ppm). The polymers were purified by precipitation from methylene chloride with methanol, followed by rapid and thorough washing with water in a blender[1]. Copolymer composition was determined by NMR spectroscopy.

Films were prepared by casting a common solution of the steroid and polymer in methylene chloride onto a glass plate and spreading with an adjustable applicator[2]. When a thickness greater than 100 μm was required, thinner films were stacked and compression molded at 100–130° to ensure even drug distribution. Sandwiched films, *i.e.*, a drug–polymer layer completely encased by drug-free polymer, were prepared by casting a polymer–drug solution on a drug-free polymer film. The resulting double-cast film was cut to leave smaller squares, over which a drug-free film was cast. The triple film then was cut between the squares.

Polymer tubing was prepared by melt extrusion or, when limited material was available, by rolling polymer film around a short polytef tube and annealing *in vacuo* while mechanically rotating the tube about its axis. Capsules were prepared by heat sealing the tubing with warm pliers. Steroids were micronized[3] (<5 μm) and dispersed in a vehicle using a tissue grinder (10 min) prior to capsule filling.

**Release Rate Measurement**—Films or capsules were immersed totally in distilled water (80–400 ml) at 37°. Mixing was accomplished using a rotating shaker[4] maintained at 135 rpm. Increasing the shaker speed to 195 rpm did not change the release rate. The aqueous reservoir was changed daily (capsules) or more frequently (films); where release rates were very fast, a flow system was used to keep the aqueous drug concentration low. In most cases, the frequency of solution change was such that the drug concentration did not exceed 10% of its aqueous solubility and typically was <1%. Drugs were either tritium or carbon 14 labeled, and release rates were determined by radioassay.

*In vivo* release rates were determined by radioassay of the feces and/or urine after subdermal implantation of the films or capsules in female New Zealand White rabbits or Charles River rats *via* incisions about the dorsal midline.

## THEORETICAL

The diffusion-controlled release of a drug from a monolithic film or slab of unit area into an infinite aqueous sink may be described by Eqs. 1 and 2. Equation 1 applies when the drug is dissolved completely in the polymer (6); Eq. 2 applies when the drug solubility is exceeded and the

[1] Waring.
[2] Boston-Bradley.
[3] Wig-L-Bug, Crescent Dental Manufacturing.
[4] Eberbach.



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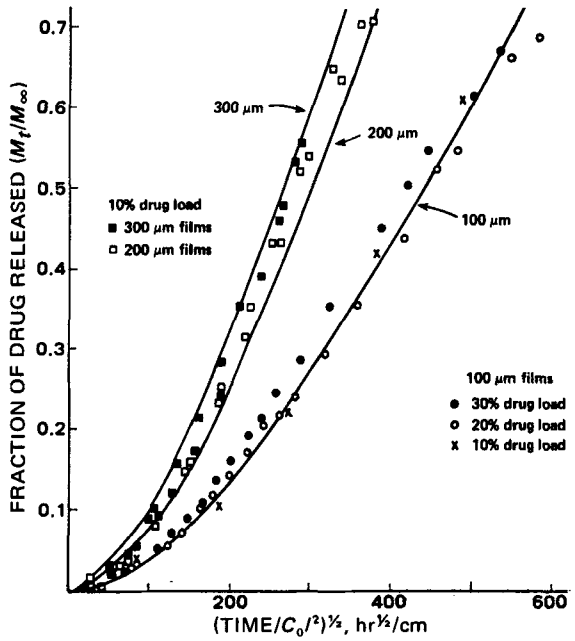


**Figure 1**—*Fraction of progesterone released from poly(ϵ-caprolactone) films with different thicknesses and drug loads, plotted as a function of* $(time/C_0l^2)^{1/2}$. *Solid lines were predicted from Eq. 3 using values for the constants listed in the text. The 100-μm films were cast; the 200- and 300-μm films were compression molded.*

solid drug particles are distributed uniformly in the film and are small relative to the average diffusion distance (7):

$$M_t/M_\infty = (4D_et/\pi l^2)^{1/2} \quad \text{for } M_t/M_\infty \leq 0.6 \quad \text{(Eq. 1a)}$$

$$M_t/M_\infty = 1 - 8\exp(-\pi^2 D_e t/l^2)/\pi^2 \quad \text{for } 0.4 \leq M_t/M_\infty \leq 1.0 \quad \text{(Eq. 1b)}$$

$$M_t/M_\infty = [4D_eC_st(2C_0 - C_s)/C_0^2l^2]^{1/2} \quad \text{for } C_0 > C_s \quad \text{(Eq. 2a)}$$

$$M_t/M_\infty = [8D_eC_st/C_0l^2]^{1/2} \quad \text{for } C_0 \gg C_s \quad \text{(Eq. 2b)}$$

where $M_t$ is the cumulative drug released at time $t$, $M_\infty$ is the total drug content (equals $C_0l$), $C_s$ is the drug solubility in the polymer, $C_0$ is the initial drug concentration, $l$ is the film thickness, and $D_e = D\epsilon/\tau$, where $D_e$ is the effective diffusion coefficient and $\epsilon$ and $\tau$ are the volume fraction and the tortuosity of the polymer, respectively.

The case where the drug solubility in the polymer is exceeded, *i.e.*, $C_0 > C_s$, was expanded to include the effect of an aqueous boundary layer (8, 9). The modified kinetic expression is:

$$M_t/M_\infty = (A^2 + Bt)^{1/2} - A \quad \text{(Eq. 3)}$$

where $A$ equals $2D_eh_aK/D_al$, $B$ equals $8D_eC_s/C_0l^2$, $K$ is the partition coefficient $(C_s/C_{aqueous})$, $h_a$ is the aqueous boundary layer thickness, and $D_a$ is the aqueous drug diffusion coefficient. At longer times, when $Bt \gg A$, Eq. 3 reduces to Eq. 2b.

In contrast to monolithic devices, diffusion-controlled drug release rates from a reservoir device are time invariant, provided the difference in drug concentrations ($\Delta C$) on each side of the membrane remains constant. The latter condition is met when solid drug remains within the device and either a perfect sink or constant drug dissipation prevails outside. For a capsule (hollow cylinder) of unit length (centimeters), the drug diffusion rate through the walls (ends neglected) is given by (10):

$$dM/dt = 2\pi D_eK\,\Delta C/\ln(\text{o.d./i.d.}) = 2\pi D_eC_s/\ln(\text{o.d./i.d.}) \quad \text{(Eq. 4)}$$

## RESULTS AND DISCUSSION

**Poly(ϵ-caprolactone) Films**—*In vitro* progesterone release rates were measured using different initial drug concentrations [$C_0$ = 10, 20, and 30% (w/w)] and film thicknesses ($l$ = 100, 200, and 300 μm). Release was rapid, complete within 24 hr, and consistent with a diffusion-controlled process attenuated by an aqueous boundary layer (8, 9). Illustrative results are plotted in Fig. 1 as the drug fraction release ($M_t/M_\infty$) *versus* $(t/C_0l^2)^{1/2}$ to normalize the effects of film thickness and drug concentration predicted by Eqs. 2a, 2b, and 3. The fact that the rates from the 100-μm films, $C_0$ = 10, 20, and 30% (w/w), conform to a single line when plotted in this manner shows that Eq. 1 is not valid, *i.e.*, $C_0 > C_s$. Although the crystallinity of poly(ϵ-caprolactone) prevented visual confirmation of undissolved progesterone, partition measurements showed that progesterone solubility in poly(ϵ-caprolactone) is only 1.69% (w/w) (2).

The initial curvature of the Fig. 1 plots ($t$ < 15 min) is inconsistent with Eqs. 2a and 2b, unless it is associated with equilibration of the freshly immersed polymer film with the aqueous environment. It is probably the result of an aqueous diffusion barrier, and Eq. 3 is applicable. The experimental data with the 100-μm films could be reproduced by this equation (solid line, Fig. 1) using the following constants: $D_e = 8.3 \times 10^{-9}$ cm²/sec, $D_a = 7 \times 10^{-6}$ cm²/sec, $C_s = 1.69 \times 10^{-2}$ g/g, $K$ = 1200, and $h_a$ = 19 μm.

The value of $D_a$, the aqueous diffusion coefficient of progesterone, is estimated using the Sutherland–Einstein equation (11, 12); values of $K$ and $C_s$ are known (2), and $h_a$ and $D_e$ were chosen to fit the experimental data. The derived $h_a$ value is comparable to estimates made in similar studies (8, 9, 11). The $D_e$ value is only slightly greater than the value of $3.6 \times 10^{-9}$ cm²/sec derived from diffusion cell measurements of the progesterone diffusion rate across an unloaded poly(ϵ-caprolactone) film (2).

The release rates from 200- and 300-μm films (10% drug load) were the same within experimental error when normalized for film thickness but significantly greater than the rate from 100-μm films (Fig. 1). The experimental results for the 200- and 300-μm films were reproduced by Eq. 3 using the given values of $D_a$, $C_s$, $K$, and $h_a$ but with a higher $D_e$ of 20.5 $\times 10^{-9}$ cm²/sec. This change in $D_e$ with film thickness reflected different film preparation methods. For practical reasons, the thinner films were solvent cast and the 200- and 300-μm films were compression molded. When the 100-μm films also were compression molded, the estimated diffusion coefficient increased to the value observed with the thicker films (Fig. 2).

The dependence of $D_e$ on the film preparation method is attributed to the fact that poly(ϵ-caprolactone) is a partially crystalline polymer (13). Thus, the film preparation method will affect the polymer morphology, which, in turn, can affect significantly the volume fraction, tortuosity, drug solubility, and intrinsic diffusivity of the polymer (14). The degree to which the experimental results conform to the theoretical model is surprisingly good in view of the assumptions made, particularly the assumption that the tortuosity and volume fraction are independent of $C_0$ and the drug fraction released.

*In vivo* progesterone release from poly(ϵ-caprolactone) films ($2 \times 1 \times 10^{-2}$ cm) was at least as fast as its excretion rate. Thus, when triplicate films containing 10% $^3$H-progesterone were implanted in the dorsal area of two rabbits, the observed tritium urinary excretion rate was essentially identical to that observed when progesterone was injected subdermally as a sesame oil suspension: 16 hr, 49 ± 4%; 40 hr, 78 ± 4%. This result is consistent with the observed *in vitro* rates and shows that drug diffusion away from the polymer is not impaired by any foreign body reaction.

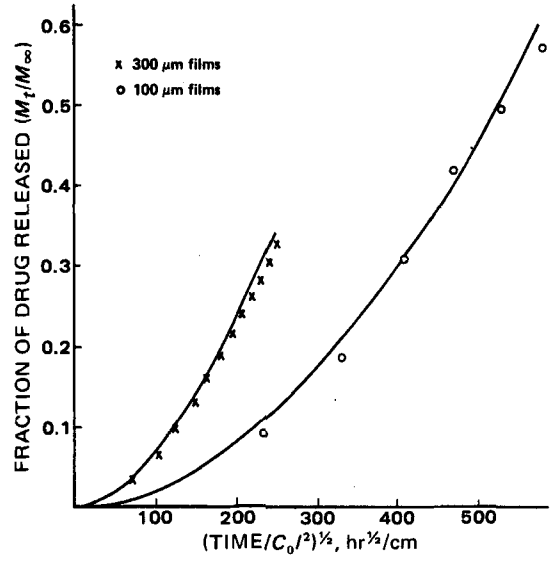


**Figure 2**—*Fraction of progesterone released from poly(ϵ-caprolactone) films, compression molded, 10% drug load. Solid lines were predicted from Eq. 3 using values for the constants listed in the text, except for* $D_e = 24.6 \times 10^{-9}$ *cm²/sec and* $h_a$ = 34 μm.

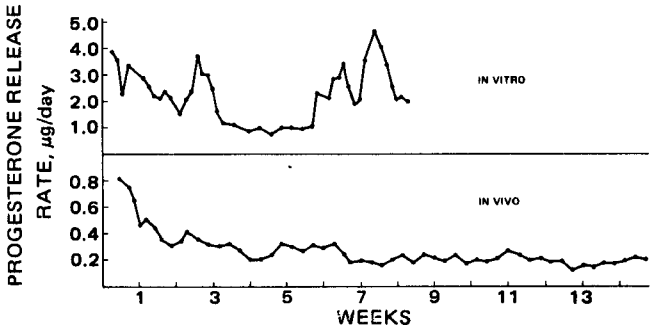


**Figure 3**—In vitro *and* in vivo *progesterone release rates from poly(DL-lactic acid) films, 100-μm thickness, 10% drug load.*

**Poly(DL-lactic Acid) Films**—Progesterone release from poly(DL-lactic acid) films was much slower and more erratic than from poly(ϵ-caprolactone) films. Figure 3 shows the daily progesterone release rate from poly(DL-lactic acid) films ($C_0$ = 10%, $l$ = 100 μm) under both *in vitro* and *in vivo* conditions.

The much slower release from poly(DL-lactic acid) is consistent with the fact that both the solubility and diffusion coefficients of progesterone in this polymer are much lower (2): poly(DL-lactic acid), $D_e = 5.1 \times 10^{-12}$ cm²/sec and $C_s = 0.65 \times 10^{-3}$ g/g; and poly(ϵ-caprolactone), $D_e = 3.6 \times 10^{-9}$ cm²/sec and $C_s = 1.69 \times 10^{-2}$ g/g. However, the fact that the *in vitro* release rate from poly(DL-lactic acid ) was so erratic and not proportional to $t^{1/2}$ suggested that leaching and/or polymer degradation might be largely responsible for the observed rate. To increase the contribution of diffusional release, the progesterone concentration was increased to 30% (w/w) and the films thickness was reduced to 3 μm. Since this thickness was no greater than the size of drug crystallites in the film, drug-free 3-μm films were cast on each side of the film to prevent leaching by direct contact between the undissolved drug and the aqueous reservoir.

With this film, the release rate was considerably more rapid, although it was still much slower than rates from 100-μm poly(ϵ-caprolactone) films. Plots of $M_t$ *versus* $t^{1/2}$ were approximately linear after an induction period of 1 day *in vitro*, and similar results were obtained in *in vivo* monitoring of urinary excretion (Fig. 4). In this case, the induction period must be attributed to drug equilibration among the three layers of the sandwiched film. A simple calculation using Eq. 3 shows that the aqueous boundary layer can be neglected because of the time range covered. The smaller slope of the *in vivo* plot arises because drug release measurements were restricted to urinary excretion with no correction for metabolic losses by other routes.

Since the low permeability of poly(DL-lactic acid) is partly a reflection of its high glass transition temperature (57°), the effect of temperature on the release rate was of interest. When the *in vitro* temperature was raised from 37 to 60°, the progesterone release rate from the composite films increased 250-fold.

**Copolymer Films**—Progesterone release rates from films (100 μm,

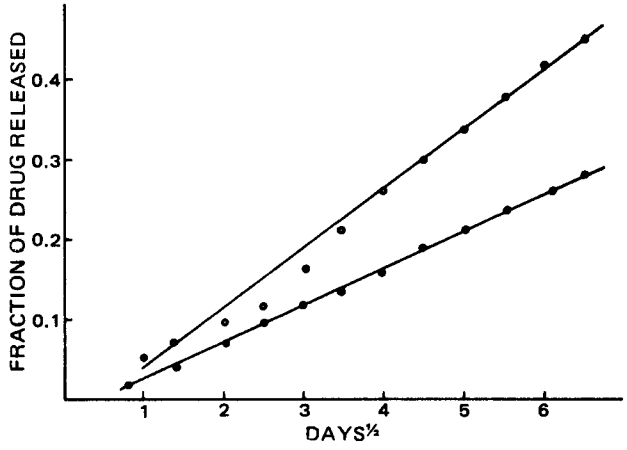


**Figure 4**—In vitro (○) *and* in vivo (●) *progesterone release rates from sandwiched poly(DL-lactic acid) films.*

**Table I—Predicted Rates and Duration of Release of Steroids from Poly(ϵ-caprolactone) Capsules** [a]

| Drug | Release Rate, μg/day/cm 1.0-mm i.d. | Release Rate, μg/day/cm 2.0-mm i.d. | Duration, days 1.0-mm i.d. | Duration, days 2.0-mm i.d. |
|---|---|---|---|---|
| Progesterone | 56 | 271 | 70 | 58 |
| Testosterone | 35 | 170 | 111 | 92 |
| Norethindrone | 9.3 | 45 | 422 | 352 |
| Norgestrel | 8.7 | 42 | 452 | 377 |

[a] Assumptions are: 2.4-mm o.d., 50% steroid in diluent, and $D_e$ values derived from diffusion cell measurements (2).

10% drug load) of a 60:40 copolymer of ϵ-caprolactone and DL-lactic acid and a 90:10 copolymer of ϵ-caprolactone and glycolic acid were comparable to rates from poly(ϵ-caprolactone). In contrast, rates from copolymers of DL-lactic acid and glycolic acid were orders of magnitude slower. Four copolymers with 7, 14, 19, and 21 mole % of glycolic acid were evaluated *in vitro* as 100-μm films loaded with 10% progesterone. During the first 20 days, the cumulative drug released from each film was proportional to $t^{1/2}$ and, based on Eqs. 2*a* and 2*b*, the rates corresponded to $DC_s$ values of $0.24 \times 10^{-15}$, $0.51 \times 10^{-15}$, $0.86 \times 10^{-15}$, and $1.08 \times 10^{-15}$ g/cm/sec, respectively[5]. These values are essentially the same as those of poly(DL-lactic acid) determined from diffusion cell measurements (2).

After 20 and 30 days, the release rate from the two copolymers with the highest glycolic acid content (21 and 19 mole %) began to increase substantially until a new linear relationship between the drug fraction released and $t^{1/2}$ was established (Fig. 5). Since this transition coincided with the mechanical deterioration and fragmentation of the films, it can be attributed to polymer hydrolysis and exposure of a larger surface area. The linear relationship after fragmentation may well be fortuitous.

The copolymer films with less glycolic acid (7 and 14 mole %) were changed little during 50 days, and the initial progesterone release rate was essentially unchanged.

Since other studies (1) established that the bioerosion onset can be tailored by the choice of copolymer composition and molecular weight, poly(DL-lactic acid-co-glycolic acid) delivery systems with various kinetic

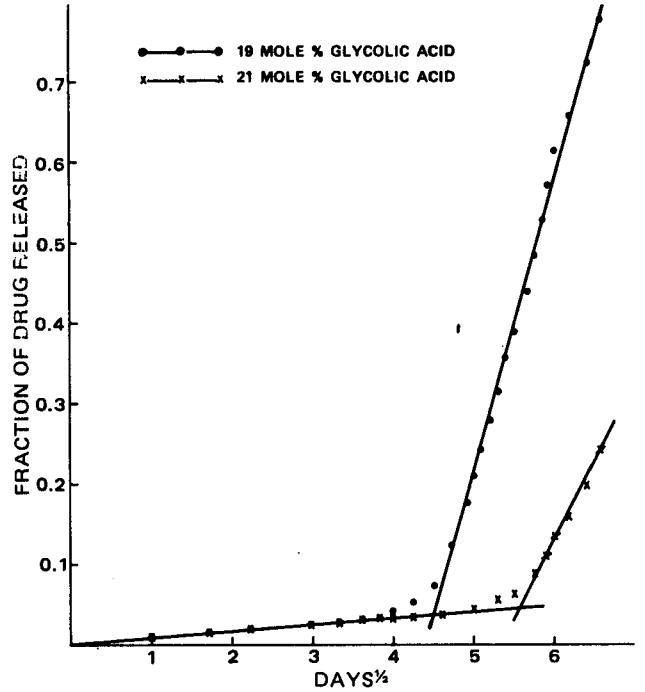


**Figure 5**—In vitro *progesterone release rates from poly(DL-lactic acid-co-glycolic acid) films, 100-μm thickness, 10% drug load.*

[5] The progesterone solubility in these copolymers was not determined, but the condition that $C_0 > C_s$ could be inferred from the progesterone solubility in the homopolymers.

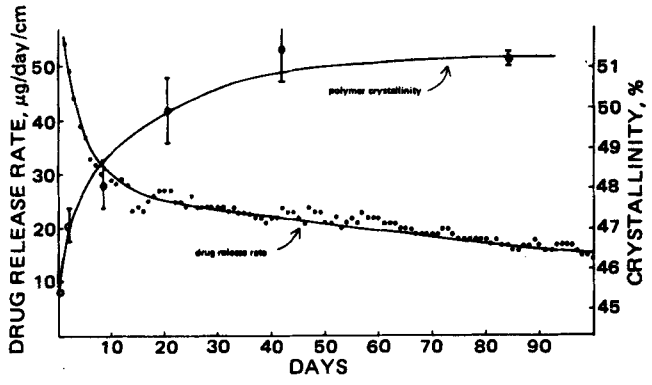


**Figure 6**—In vitro *norgestrel release rates from a poly(ϵ-caprolactone) capsule, o.d./i.d. = 2.41 mm/2.06 mm, and polymer crystallinity change under the same conditions.*

profiles probably can be designed by using copolymer blends.

**Poly(ϵ-caprolactone) Capsules**—*A priori*, the permeabilities of poly(ϵ-caprolactone) and its copolymers are such that diffusion-controlled delivery of efficacious amounts of a contraceptive agent for 1 year or longer is feasible. Table I summarizes rates and durations of release of four hormonal steroids from poly(ϵ-caprolactone) capsules, calculated from Eq. 4 using known (2) $D_e$ and $C_s$ values, two different inner diameters, and an outer diameter of 2.4 mm. An outer diameter of 2.4 mm was the maximum size compatible with subdermal insertion. It also was assumed that the drug was present as a 50% dispersion in an inert carrier. The carrier maximizes contact between the drug reservoir and the inner surface of the capsule and is necessary to maintain a constant concentration gradient and release rate (15).

The calculated rates fall within the range that is believed necessary for fertility control by sustained administration of the more potent progestins, *e.g.*, norethindrone and norgestrel (16). Furthermore, while the duration of release (load/rate) is independent of capsule length and not very sensitive to changes in the outside diameter–inside diameter ratio, manipulation of the percent dispersion provides a means of varying the duration from several months to years.

In practice, the higher steroid release rates in Table I could not be achieved for any significant period. Typically, the kinetics were characterized by a rapid and substantial rate decline during the first 20 days, followed by a much slower, smaller decline over the next 100–200 days. An example of this behavior *in vitro* is shown in Fig. 6. Two reasons for the failure to achieve a constant release rate seemed plausible: a permeability reduction produced by morphological changes in the polymer and, alternatively, a reduction in the concentration gradient across the polymer wall produced by a declining rate of steroid dissolution in the dispensing agent and/or polymer.

A declining drug dissolution rate might arise because of: (*a*) depletion

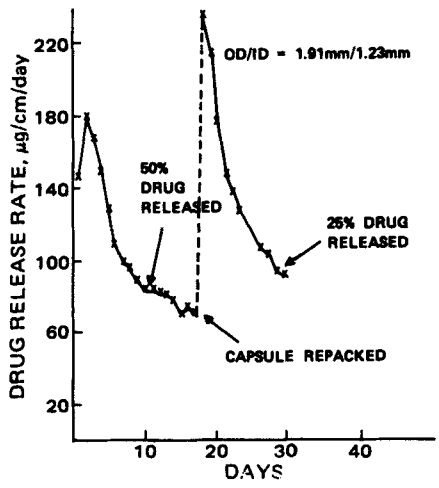


**Figure 7**—*Effect of repacking on release rate of ethinyl estradiol from poly(ϵ-caprolactone) capsules* in vitro.

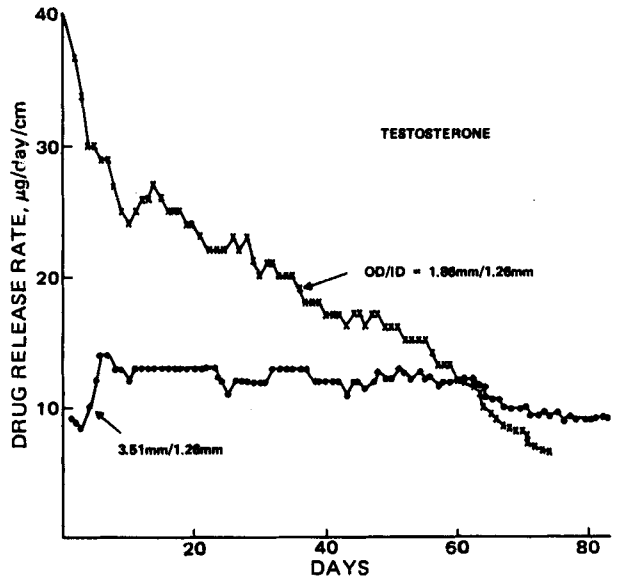


**Figure 8**—In vitro *testosterone release rates (15% dispersion in sesame oil) from poly(ϵ-caprolactone) capsules as a function of the ratio of the inner and outer diameters of the capsule.*

of the smaller drug particles during the initial time period, (*b*) aggregation of drug particles, or (*c*) drug recrystallization, producing an increase in the crystal size. A classical burst effect (10) was ruled out because the kinetics were unchanged if there was no time delay in immersing the freshly packed capsule in the aqueous reservoir. A series of experiments suggested that the larger release rate decline observed in the first 20 days was a reflection of a decreasing drug dissolution rate while the smaller, long-term decline was associated with a polymer crystallinity increase.

The larger decline was observed a second time when the partially depleted capsule was opened and repacked with freshly micronized drug, and the experiment was resumed (Fig. 7). On the other hand, the diffusion rates of progesterone and testosterone through a 100-μm poly(ϵ-caprolactone) membrane in water at 37° did not change when measured daily over 10 days using a diffusion cell and *efficient stirring*. Most importantly, it was possible to eliminate the initial release rate decline by increasing the capsule outside diameter–inside diameter ratio (Figs. 8 and 9). These results are consistent with the idea that dissolution of these steroids becomes slower and will determine the kinetics unless the outside diameter–inside diameter ratio is sufficiently large that diffusion through

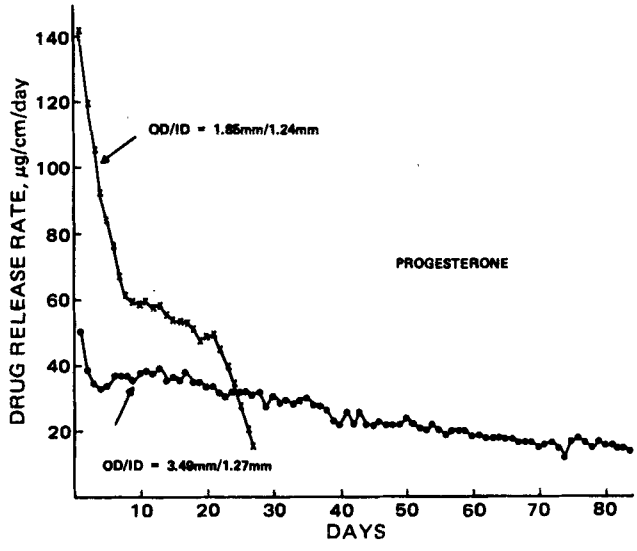


**Figure 9**—In vitro *progesterone release rates (15% dispersion in sesame oil) from poly(ϵ-caprolactone) capsules as a function of the ratio of the inner and outer diameters of the capsule.*

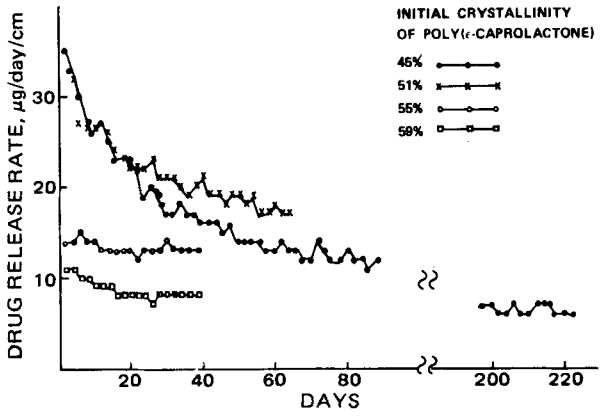


**Figure 10**—*Norgestrel release rates from capsules of poly(ε-caprolactone) with different degrees of crystallinity: untreated (45%), annealed (51%), and pretreated (55 and 59%).*

the polymer wall is the rate-determining step. Although increasing the outside diameter–inside diameter ratio eliminates the initial release rate drop, this result obviously is at the expense of the maximum rate.

Morphology is potentially relevant to the constancy of the release rate because poly(ε-caprolactone) is a semicrystalline polymer subject to slow hydrolysis *in vitro* and *in vivo* (1). The resulting molecular weight decrease, coupled with annealing, is associated with a considerable increase in crystallinity (Fig. 6), which, in turn, reduces polymer permeability. The significance of this finding was evaluated by determining the initial release rates of norgestrel from capsules with different crystallinities corresponding to increasing degrees of polymer hydrolysis. The release rate from capsules pretreated to increase the crystallinity to 51% was essentially the same as that observed with unannealed virgin capsules, 45% crystallinity, over 60 days (Fig. 10). This equality demonstrated that, despite a superficial correlation, the initial rapid decrease in release rate shown in Fig. 6 was not a manifestation of the crystallinity change but of drug dissolution. However, when the crystallinity was increased to 55%, the release rate was both lower and essentially constant (12–15 μg/day) for 60 days. Evidently, this increased crystallinity reduced the polymer permeability sufficiently so that drug diffusion, not dissolution, became the rate-determining process.

When the polymer crystallinity was increased to 59%, the release rate was even lower (6–7 μg/day). These release rate reductions with increasing crystallinity explain the longer term changes in release rates *in vitro* and *in vivo*. For example, after 220 days *in vitro*, the crystallinity of poly(ε-caprolactone) capsules increased from 45 to 58%. The norgestrel release rate after the same time had declined to 6–7 μg/day, which is the rate associated with a crystallinity of 58% (Fig. 10).

In conclusion, the rate and constancy of steroid release from poly(ε-caprolactone) capsules can be a function of both the steroid dissolution rate and the polymer crystallinity. The influence of steroid dissolution rates may be eliminated by appropriate choice of capsule dimensions. Methods of controlling the polymer crystallinity will be discussed in a later publication.

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