Encyclopedia of Pharmaceutical Technology

Volume 2

Editors
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ENCYCLOPEDIA OF PHARMACEUTICAL TECHNOLOGY

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VOLUME 2

BIODEGRADABLE POLYESTER POLYMERS AS DRUG CARRIERS TO CLINICAL PHARMACOKINETICS AND PHARMACODYNAMICS

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Biodegradable Polyester Polymers as Drug Carriers

Introduction

Over the past 20 years, enormous interest has been shown in the use of biodegradable polymers such as polyesters, polycyanoacrylates, and polycarbonates and proteins like albumin for the development of novel drug delivery systems with prolonged duration of action. These polymers have the property of degrading in biological fluids with progressive release of dissolved or dispersed drug. Polymer selection critically influences their rate of biodegradation, and hence products can be constructed with short or long duration of action. These polymers are particularly suitable for the design of parenteral products such as biologically active polypeptides with a short half-life. Other drug classes that have been extensively investigated include anticancer and antimalarial agents, contraceptive steroids, local anesthetics, and narcotic antagonists.

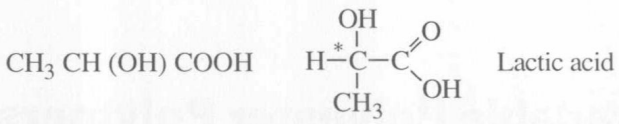
This review deals only with aliphatic polyesters such as lactide/glycolide polymers and copolymers and also polyhydroxybutyrate/polyhydroxyvalerate polymers and copolymers. This group of polymers has been the most widely investigated as drug carriers because of its broad range of biodegradability and its ease of fabrication into various dosage forms.

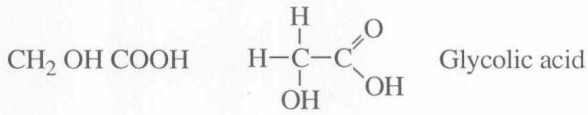
Lactide/Glycolide Polymers and Copolymers

Production

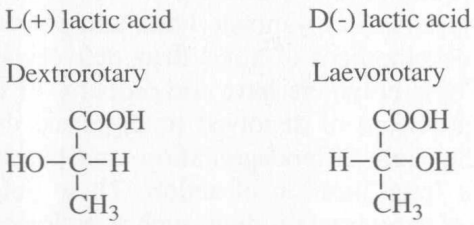
Polylactic acid (PLA), polyglycolic acid (PGA), and their copolymers are used in a variety of medical applications. Because they degrade slowly by hydrolysis to lactic acid and glycolic acid, which are body metabolites, they are biocompatible and produce little or no local and systemic toxicity on administration. These polymers are not commercially available in adequate range or with adequate characterization, and consequently most investigators interested in their use for drug delivery are obliged to synthesize them. Reproducible polymer of the appropriate type is an essential prerequisite for the design of consistent products. Unfortunately many of the reports in the literature do not give adequate detail of the precise material used, and this may well result in suboptimal products being achieved.

Lactic acid and glycolic acid are the common names used for α-hydroxypropionic acid and α-hydroxyacetic acid, respectively.

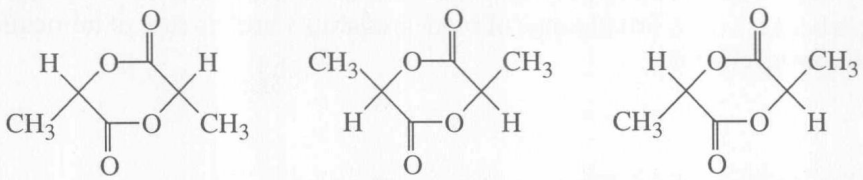




Lactic acid has an asymmetric carbon atom* that confers optimal rotatory ability on the molecule, giving it two optical isomers.

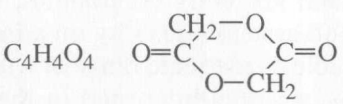


Glycolic acid, however, displays no such property. If water is removed by vacuum distillation, optically active or racemic lactic acid can form six-membered cyclic dimers, the products being optically active. The racemic DL-lactide (as shown in the following structures) consists of a mixture of (a) and (b), and there is also an optically inactive meso-lactide.



(a) (b)

Similarly, the dimer of glycolic acid is glycolide with the following general structure.



This exists in two isomeric configurations. The α-crystalline form is more stable hydrolytically than the β-form and is therefore preferred for the preparation of high-molecular-weight polymer.

Lactic acid and glycolic acid can be polymerized by simple condensation of the α-

hydroxycarboxylic acid, effected by the removal of water by boiling it off from the reaction mixture at temperatures not less than 120°C. Alternatively, below this temperature direct polymerization can be effected by the use of a heavy-metal-containing catalyst. However, these types of polymerization produce only polymers of low molecular weight ($\overline{M}_n < 10{,}000$). The preferred method for producing the higher-molecular-weight polymers required for pharmaceutical applications is the ring-opening polymerization of the cyclic dimer, lactide or glycolide, using a catalyst. Tetraphenyl tin or stannous octanoate are the preferred catalysts for biomedical applications [1]. Gilding and Reed [2] noted that polymerization does not have the classical ionic mechanism whereby all chains begin to grow at once and at a constant rate. This results in the production of polymer with a broad range of molecular weight. Copolymers can be made from a mixture of lactic and glycolic acids or more usually from their cyclic dimers. They copolymerize readily, using the reaction procedures and conditions of the parent polymer.

Polymerization of dimer is carried out in a sealed, clean, dry container under reduced pressure. The molecular weight of the polymer produced can be most effectively controlled by changing the amount of catalyst used, as decreasing concentration produces increasing molecular weight. Recrystallization of the lactide or glycolide should be carried out two or three times before polymerization. Further, when polymerization is complete, it is important that little or no residual lactide remains. This causes the formation of lactoyl-lactic acid, which catalyzes the rapid degradation of the polymer.

Characterization

Because of the importance of polymer composition and molecular weight range on permeability, biodegradability, and other physicochemical properties such as ease of compression, it is vitally important to characterize each batch of polymer produced adequately. A problem frequently encountered is difficulty in producing reproducible samples of polymer because of slight differences in the purity of starting materials and reaction conditions employed.

Gel permeation chromatography on solutions of polymers in tetrahydrofuran using a differential refractometer as detector can be used to determine weight average ($\overline{M}_a$) and number average ($\overline{M}_n$) molecular weights from which the polydispersity (M_w/M_n) can be calculated. However, lack of solubility of PGA and its high-content copolymers in tetrahydrofuran and other solvents makes it difficult to determine their molecular weight by this method. The only known solvent for PGA is hexafluoroisopropanol. This dissolves low concentrations of the polymer with great difficulty, which solutions may be characterized for molecular weight by laser light scattering determination.

Gel permeation chromatography determinations are frequently correlated with viscosity determinations using dilute solutions of PLA in chloroform and a suitable suspended level viscometer. Intrinsic viscosities [η] are often quoted for such polymers, from which values it is possible to calculate the molecular weight by using the Mark Howink equation:

$$[\eta] = KM^a$$

where M is the molecular weight (M_w or M_n) and K and a are constants for a particular system. Again this method is unsuitable for copolymers with high PGA content (> 50%) or its homopolymer because of lack of solubility in common solvents.

The molecular weight of such polymers can also be inferred from infrared spectra data, which, apart from detecting impurities, show absorbances at 2.88 μm and 4.66 μm indicating O—H and C—O—C linkages, respectively. As molecular weight increases, the number of O—H linkages remains constant but the number of C—O—C linkages increases.

Two other procedures are also widely used to characterize these polymers. Differential scanning calorimetry can be used to estimate their glass transition temperature (Tg), degree of crystallinity, and melting point. Nuclear magnetic resonance studies are useful for showing the ratio of lactic and glycolic acid monomer units in copolymers by using integral values for CHO, CH_2O, and CH_3 units. The content obtained often differs from the ratio of reactants in the starting material. The glycolide content is frequently higher, because of its greater reactivity.

Properties

The permeability, biodegradability, and mechanical properties of this range of polymers vary considerably. Poly(D-lactic acid), [D-PLA] and poly(L-lactic acid), [L-PLA] are crystalline, tough, inelastic materials of low permeability that degrade slowly by hydrolysis over several months. DL-PLA is amorphous, is more permeable, and degrades more rapidly. As the percentage of glycolide in copolymers increases, these amorphous materials become even more biodegradable. Finally, PGA polymers are crystalline and brittle and degrade most rapidly over several weeks.

In drug delivery systems, polymer permeability and biodegradability are very important, and copolymerizing is frequently necessary in order to get the desired polymer properties. Generally, the more amorphous a polymer is, the more permeable it is. Crystallinity imparts mechanical strength and brittleness to the polymer, but it tends to reduce the permeability. However, a permeable polymer that is mechanically strong is possible by increasing the length of the methylene repeat unit, as in the case of poly(ϵ-caprolactone). This reduces the Tg without changing crystallinity. Pitt and colleagues [4] found good correlation between the Tg and the permeability of these polyesters. Poly(ϵ-caprolactone) has a low Tg value (–65°C) and is very flexible and permeable, whereas DL-PLA (Tg, 57°C) and its various copolymers with PGA are in the glassy state but are relatively impermeable to drugs such as steroid hormones.

Molecular weight of the polymers and copolymers has a limited effect generally on the permeability of the polymers, but it would appear to have a significant effect on their biodegradability. Lower molecular weight polymers have shorter in vivo half-lives than higher molecular weight samples. Schindler and associates [3] showed that lactide, glycolide, and ϵ-caprolactone polymers and copolymers degrade in vitro and in vivo by a random hydrolytic chain scission process. Both in vitro and in vivo degradation followed a first-order rate. Weight loss from excised implants commenced only when a critical value of intrinsic viscosity (molecular weight) was reached, after which rapid weight loss occurred. They concluded that an auto-

accelerated random degradation process occurred throughout the bulk of the implants. Surface erosion did not significantly contribute to the overall in vivo degradation. More recently, Pitt and co-workers [5] reported an interesting biodegradation phenomenon for some cross-linked aliphatic polyesters, for example, 4-*t*-butyl-ϵ-caprolactone. Apparently in addition to the aqueous hydrolysis of ester links, an enzymatic surface erosion was also evident. The latter did not occur in uncross-linked polyesters, for example, poly(ϵ-caprolactone) and PLA. Further, the susceptibility of these polymers to enzymatic attack is believed to be related to the segmental mobility of the polymer chains, which for a low-Tg, amorphous-type polymer permits the ester group to assume the confirmation necessary to interact with the active site of the esterase.

Makino and associates [6] found that the rate of hydrolytic degradation of DL- and L-PLA was pH dependent, being slowest at pH 5.0 and increasing in either strongly acidic or strongly alkaline media. This is consistent with acid-base catalytic reactions. However, from their analysis of the degradation products, they concluded that the hydrolytic cleavage of the polymer chains of PLA proceeded in an ordered, sequential manner and not randomly, as is generally thought.

Pharmaceutical Applications

Since the reporting of PLA in a French patent in 1913, it was recognized as a useful material for the preparation of surgical implants [7], absorbable sutures [8], and various prosthetic devices [9]. Reports of histological studies indicating that PLA was nontoxic, non–tissue reactive, and biodegradable [7] probably led to the first use of this polymer as an erodible matrix for the controlled release of a drug [10,11]. These early workers were trying to develop implantable controlled-release delivery systems containing narcotic antagonists by using nonbiodegradable but biocompatible polymers such as polyethylene, but because of the need to surgically remove such implants, their attention turned toward the use of biodegradable PLA. The advantages of such a system seemed obvious: little or no tissue reaction, no need for the removal of the implant, and the possibility of improved controlled release of the drug with simultaneous biodegradation of the polymer. However, despite other reports of lack of toxicity, Ratcliffe and colleagues [12] have shown that PLA products produce an inflammatory response when injected by the intra-articular route. Likewise, Smith and Hunneyball [13] have reported that particulate products containing prednisolone in PLA elicit a cytotoxic effect on macrophages in culture.

To date, many different drugs have been incorporated in these biodegradable polymers, mainly as implants or injectable microparticles, microcapsules, microspheres, or nanoparticles, with varying degrees of success. Most of the reports in the literature use similar manufacturing procedures to incorporate different drugs in the polymer or polymers. Apart from the microencapsulation procedures used, little or no information about the effect on drug release of varying the manufacturing procedures has been given. In addition, the effects of storage conditions on product stability has yet to be publicized. Presumably, most of the polymers used to fabricate biodegradable drug-delivery devices are hydrolytically unstable to some degree. Therefore, storing the products in a moisture-free atmosphere may be necessary to minimize degradation. The laboratory of Yolles and co-workers has investigated the

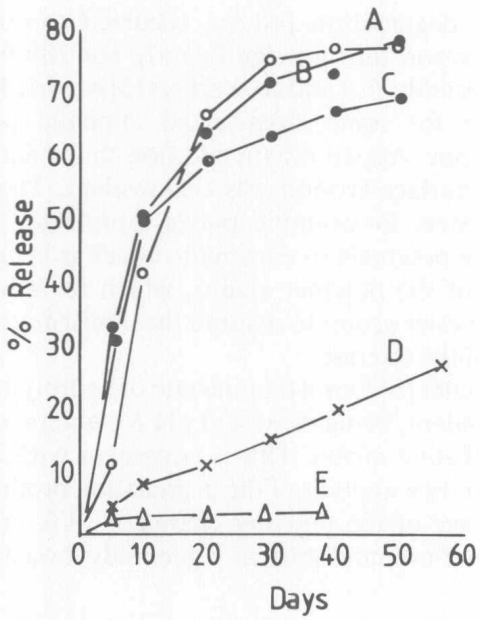


FIG. 1. Cumulative amounts of cyclazocine excreted from composites of poly(lactic acid) implanted or injected in rats (20% w/w drug loading).
A = Cyclazocine containing film of PLA, $\overline{M}_w$ 45,000
B = As in A, except PLA $\overline{M}_w$ 70,000
C = 50 : 50 A and B
D = Particles (injected)
E = Overcoated film (implanted)
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controlled release of the following drug classes: (1) steroids—progesterone, estradiol, and dexamethasone [14–17]; (2) narcotic antagonists—cyclazocine, naloxone, and naltrexone [14,16–20]; and (3) anticancer drugs—cisplatin, cyclophosphamide, and doxorubicin [14,16,17,21–23] from PLA composites.

The methods of preparation involved solvent evaporation with or without subsequent heat treatments. For example, drug-loaded films were obtained after evaporation of methylene chloride from solutions or fine suspensions of the drug and L-PLA, together with the external plasticizer tributyl citrate. The films were then melt pressed at 140 to 170°C to compact the matrix and were either used directly as implants or ground up as particles and implanted or injected. Where necessary, a cosolvent such as methanol was added to dissolve the drug [15]. Drug loadings of 20 and 35% were examined. Figure 1 shows the cumulative percentage of cyclazocine released in rats from L-PLA composites in film form (implanted) or particles (injected). Interestingly, particles (Fig. 1d) show a slower release than films of the same composition (Fig. 1b). This was attributed to an inflammatory process. The films were apparently more irritant and affected the temperature and fluids surrounding the device, causing an accelerated release rate of the drug. When particles containing 35% naltrexone were injected into monkeys, morphine-antagonistic activity of 20 days was reported by Yolles and associates [14]. In contrast, Harrigan and Downs [24] used an injectable naltrexone polylactide product of Yolles later in

monkeys (precise specifications omitted) and obtained morphine-antagonistic activity of only a few days. Furthermore, there was considerable tissue encapsulation of the injected product. Without details of the product used, it is difficult to assess the marked difference in morphine-antagonistic activity reported. However, the use of injectable particles by Yolles and co-workers was undoubtedly a useful step forward in the development of PLA as a drug carrier.

Variation in the molecular weight of the polymer had no significant effect on the release rate of cyclazocine from the implanted films (Fig. 1a, b, c). However, the lower molecular weight polymer was absorbed more quickly than the higher molecular weight polymer. Overcoating of the films with pure polymer was carried out to reduce the initial drug-release rate (Fig. 1e). This resulted in a slower and more constant release of cyclazocine in vivo for more than 1 month. For example, the time for 50% release ($t_{50\%}$) for the uncoated film was approximately 11 days, whereas the overcoated product had released only 3.6% of cyclazocine in 37 days. The coating obviously acts as a very effective barrier to the diffusing drug molecules.

Beads containing progesterone were also prepared by Yolles and associates [15] in a manner similar to microencapsulation, but unless annealed (heat treatment, 105 to 160°C), the in vivo release profile was only marginally slower than pure progesterone. Presumably the heat treatment effectively reduced the macroreticular-type structure of the polymeric matrix, leading to reduction in drug diffusivity.

Another research group interested in PLA as a drug carrier first reported its application as a steroid carrier in 1973 [25]. Films of L-PLA containing 33% D-norgestrel were prepared by evaporating off the solvent. After implantation (rats), the in vivo drug-release rate was almost constant and occurred at a rate greater than the degradation of the polymer. Subsequently, Anderson and co-workers [26] obtained apparent zero-order release of norethisterone for approximately 90 days in rats after injection of L-PLA particles containing 20% drug. Overcoating with DL-PLA reduced the initial and overall release rate of the drug from the particles.

As an extension of the above work, Wise and colleagues [1,27–29] and Schwope and colleagues [30] showed that the release of a variety of drugs such as sulfadiazine, naltrexone, and levonorgestrel could be varied by altering the shape of the implant (see Fig. 2), or by using copolymers of lactic acid and glycolic acid. The more susceptible the polymer was to degradation, the faster the drug was released.

Figure 3a and b show the urinary and fecal release of levonorgestrel from implanted solid rods (rats). After an initial unstable period, a reasonably steady state of release was obtained for a prolonged period of time. Changing the polymer from a copolymer with glycolide to a copolymer of the DL-L-PLA type with increase in drug loading to 50% gave systems that achieved a much steadier rate of release for almost 2 years.

In contrast, human studies with DL-PLA films containing D-norgestrel proved unsuitable for contraception because of the rapid release of the drug [31]. After 65 days, 99% of the drug was released in three of four subjects tested. By using a suitable polymer type, however, obtaining drug release lasting for many months should be possible.

The films used by Nilsson and colleagues [31] were sterilized by irradiation. The extremely low dose quoted (25 Gy) is presumably a misprint and more likely to be in the region of 25,000 Gy. What effect this may have had on the properties of the product was not studied. Gilding and Reed [2] showed that radiation at sterilization

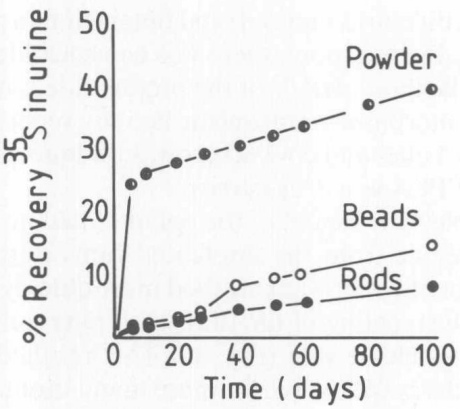

FIG. 2. The effect of shape of the implant on the in vivo (mice) release rate of sulfadiazine. Composites: poly(L(+)-lactic-co-DL-lactic acid) 50 : 50, $\overline{M}_w$ 150,000, 33% sulfadiazine. Reprinted with permission from Ref. 27.)

doses (25,000 Gy) caused a significant decrease in the molecular weight of polyglycolide sutures. Similarly, Sanders and co-workers [32] found a decrease in the intrinsic viscosity of DL-PLA-PGA microspheres with increasing radiation dose. A dose of approximately 34,000 Gy reduced the intrinsic viscosity of the copolymer from 0.097 to 0.054 $m^3\ kg^{-1}$. Curiously, Beck and associates [33] found that the rate of release of norethisterone from sterilized (gamma irradiation, 20,000 Gy) microcapsules was significantly less than that from unsterilized microcapsules. They postulated that a rise in temperature during sterilization, accompanied by scissioning of some of the polymer chains, effectively anneals the outer polymer coating. This would reduce drug diffusivity. However, the temperature rise during sterilization is unlikely to be significant, particularly if the radiation is given over a long time course.

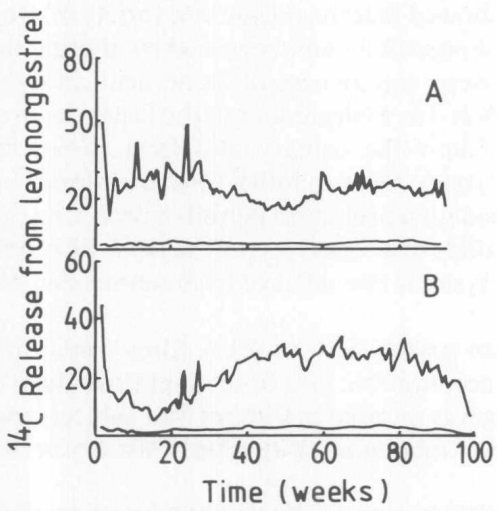

FIG. 3. Rate of urinary and fecal release (upper curve feces; lower curve urine) of ^{14}C from levonorgestrel ($\mu g\ day^{-1}$). A, Implant of poly(DL-lactide-co-L-lactide) 50 : 50, $\overline{M}_w$ 180,000, 50% w/w levonorgestrel. B, Poly(L-lactide-co-glycolide) 90 : 10, $\overline{M}_w$ 220,000 33% w/w levonorgestrel. (Reprinted with permission from Ref. 29.)

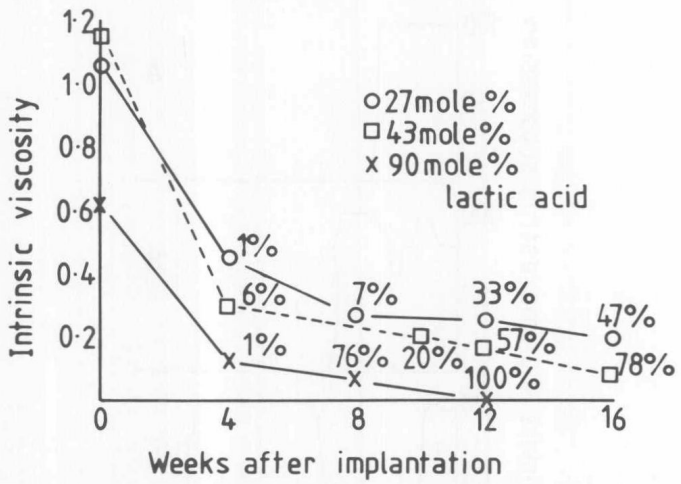

FIG. 4. In vivo degradation (rabbit) of lactide-ϵ-caprolactone copolymers in tube form (percentage weight loss indicated). (Reprinted with permission from Ref. 3.)

Copolymerization was also used by Schindler and co-workers [3] and Pitt and colleagues [4,34] to vary the lifespan of drug-delivery systems. They used copolymers of DL-lactic acid and ϵ-caprolactone. Poly(ϵ-caprolactone) has a longer biological half-life in the body than DL-PLA and could be useful for releasing steroids for up to 1 year. Wise and associates [27] found that the molecular weight of the polymer affected the release rate of the drug. This was presumably a result of an indirect effect on the biodegradation rate of the polymer. Further, the Schindler group [3] found that the molecular weight of DL-PLA or poly(ϵ-caprolactone) can decrease to about 30,000 before any appreciable weight loss is observed. Below this value, degradation accelerates, accompanied by severe weight losses. Figure 4 shows the in vivo degradation of poly(DL-lactic acid or ϵ-caprolactone) with the corresponding weight loss obtained. For most devices used, such weight loss usually occurs after the drug has been released.

Microencapsulation has also been used to incorporate a variety of drugs in PLA or its copolymers, achieving lifespans of between 2 weeks and 1 year. Microcapsules have the distinct advantage over implants in that they can be injected easily because of their small size. In addition, the methods of production used need not involve high temperatures, such as those used for annealing implants and microparticles already reviewed. Consequently, drug stability should be less affected.

In an effort to achieve higher drug loadings and more easily injected formulations, Thies [35,36] and Mason and co-workers [37] microencapsulated various narcotic antagonists, using DL-PLA and PLA-PGA. Microcapsules containing between 50 and 75% drug were prepared in size fractions less than 300 μm. The release rates of drug in vitro were faster than expected owing to microscopic defects located in the capsule walls. However, the microcapsules, when injected in vivo, had an effective antagonism of morphine analgesic effect in the rat or mouse of about 14 days for cyclazocine free base or naltrexone free base and of about 28 days for naltrexone pamoate. Details of the experimental procedure were not given, although in a later publication Thies and Bissery [38] provide details of a low-temperature phase-

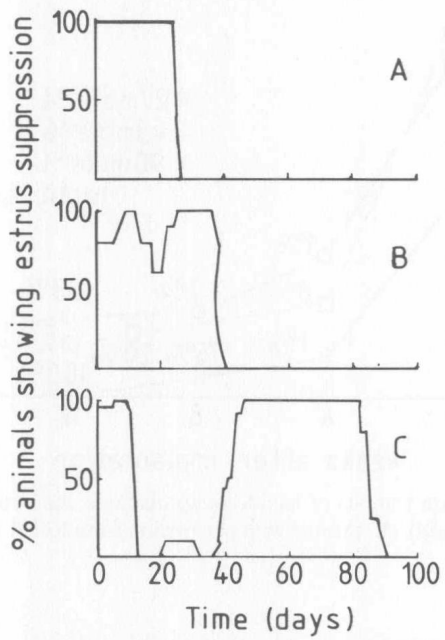

FIG. 5. Estrus suppression profiles after injection (rats) of poly(lactide-co-glycolide) microspheres containing 1% w/w nafarelin acetate. Copolymer composition. A = 50 : 50, $\eta_i = 0.38$ dLg^{-1}; B = 50 : 50, $\eta_i = 1.52$ dLg^{-1}; C = 69 : 31, $\eta_i = 0.97$ dLg^{-1}. (Reproduced with permission of the copyright owner, The American Pharmaceutical Association from Ref. 32.)

separation procedure for forming drug-loaded DL-PLA microspheres containing naltrexone pamoate were discussed. Micronized naltrexone pamoate was dispersed in a solution of the polymer, and another polymer incompatible with DL-PLA, for example, polybutadiene, was added to the system. The latter presumably competes with the former for the solvent, causing the DL-PLA molecules to aggregate and coalesce as a liquid film around the drug particles. If a solvent that is a nonsolvent for the DL-PLA is then added slowly to the system, the polymer film is desolvated and solidified. The microspheres may then be isolated and dried. It is important with this method of encapsulation that the drug is insoluble in the solvent used for the polymer. L-PLA and PLA-PGA are soluble only in selective solvents that favor solubilization of many drugs. For this reason DL-PLA, being soluble in a greater range of solvents, is a better choice for such microencapsulation procedures.

Nevertheless, DL-PLA-PGA microspheres containing nafarelin have been prepared by a phase-separation procedure [32]. Very little detail was given except that an aqueous solution of the drug nafarelin acetate was emulsified into a solution of the copolymer in methylene chloride. A nonsolvent (not specified) for the copolymer was then added to precipitate the copolymer around the aqueous droplets. The amount of nafarelin acetate present in the final hardened microspheres was approximately 1%. After injection into rats of microspheres of low molecular weight copolymer (50:50 lactide-glycolide), the estrus cycle was suppressed for 24 days, followed by an abrupt resumption of normal estrus cycle (see Fig. 5a). By increasing the molecular weight or by altering the composition of the copolymer to 69:31, the