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Controlled Delivery Systems for Quinacrine for Female Sterilization

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The transcervical instillation of quinacrine hydrochloride into the fallopian tubes to effect permanent sterilization, as practiced by Zipper and associates, was found to have two limitations: (1) reflux of quinacrine from the uterine cavity to the vagina⁶ and (2) leakage of the drug through the ostial opening of the fallopian tubes into the peritoneal cavity.³ To overcome these problems, investigators sought a system to deliver, at a controlled rate, only the minimum amount of drug needed to induce occlusion of the fallopian tubes.

The quinacrine hydrochloride pellets developed by the International Fertility Research Program were the first attempt to sustain the delivery of quinacrine. The dissolution of the pellets within the uterine cavity reduced the reflux of the drug from the uterus and also reduced the risk of rapid intravascular absorption. As a result, this system decreased both the side-effects and the pregnancy rate associated with the use of quinacrine as an occluding agent. Release of quinacrine from the pellets was sustained for only a few minutes, however, and longer delivery times were desired.

A fibrous polymer delivery system appeared to offer an advantage over other systems in delivering quinacrine to the uterus, because the soft, flexible fibers could be attached to the tips of T- or Y-shaped IUDs and could deliver quinacrine directly to the fallopian tube openings when the IUD was placed in the uterus.

Previous studies showed that a fairly large initial dose of quinacrine was needed for effective occlusion and that a first-order delivery system was desirable in which a relatively large dose of drug is released initially, followed by a gradual decline in amount with time.^{1,4} Fibrous polymer delivery systems displaying first-order release kinetics are normally obtained with monolithic fibers, and the drug is dissolved or dispersed within the polymer matrix.⁵

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With these considerations in mind, we undertook the studies of fibrous delivery systems, described in the following sections, with the hope of effectively delivering quinacrine to the fallopian tubes at a controlled rate to produce tubal occlusion.

MATERIALS AND METHODS

PREPARATION OF DELIVERY SYSTEMS

Fibers are normally produced by wet-, dry-, or melt-spinning processes. Because melt spinning is the most convenient and the least expensive process, it was used to produce all the fibers in this study. Quinacrine dihydrochloride (Sigma Chemical Company, St. Louis, MO) and quinacrine, prepared as the free base by precipitation of the salt from aqueous solutions with sodium hydroxide, were incorporated into nonbiodegradable polymers (polyethylene and polypropylene) and biodegradable polymers (poly[DL-lactide] and polycaprolactone). These drug/polymer mixtures were then extruded into monolithic fibers with a laboratory melt rheometer.

Coaxial fibers, in which a drug/polymer core was surrounded by a drug-free rate-controlling polymeric sheath material, were prepared by drawing the highly loaded monolithic fibers through a syringe needle that contained solutions of the sheath material in an appropriate solvent. The solvent was evaporated, and the procedure was repeated several times to obtain the desired sheath thicknesses.

Large monolithic rods (>3 mm in diameter), containing high levels of quinacrine dihydrochloride in polycaprolactone, were prepared on a melt rheometer by the same procedure that was used to prepare the smaller fibers. The monolithic rods were then coated with a drug-free sheath of polymer, as described for the fibers, to give coaxial rods.

DETERMINATIONS OF *INVITRO* RELEASE RATES

The *in vitro* release rates of the quinacrine-loaded fibers were initially determined with a receiving fluid (27.5% by weight ethanol and 72.5% by weight water), to provide infinite-sink conditions for both the salt and the relatively water-insoluble free base. Later, *in vitro* release studies were conducted with the 27.5% aqueous ethanol, distilled water, and acidified saline solution. Aliquots of the receiving fluid were removed periodically and analyzed for quinacrine or quinacrine hydrochloride by ultraviolet (UV) spectroscopy. Appropriate Beer's law plots of absorbance versus drug concentrations were prepared to quantify the mass of drug released from the fiber samples.

DETERMINATION OF *IN VIVO* RELEASE RATES

The first *in vivo* release studies were conducted by implanting 1-cm sections of the best candidate monolithic fibers in the uteri of sexually mature female Charles River rats and recovering the sections after specified periods of exposure. The individual fiber sections were secured to a 7-0 silk suture that was attached to a glass bead and then implanted in rats (under general anes-

thesia) by puncturing the uterine horn with a 19-gauge needle and inserting the quinacrine-loaded fiber into the uterus by way of the puncture hole. The bead remained free in the peritoneal cavity and prevented the fiber from being expelled from the uterus. Three rats were sacrificed at 2-hour intervals for the first 12 hours after treatment. Additional animals were sacrificed at 1, 2, 4, 8, and 16 days. The fibers were retrieved, cut into small fragments, and extracted with acidified saline solution. The quantity of residual drug extracted from the fibers was determined by UV spectroscopy. In addition, a blood sample from each of the sacrificed rats was assayed by spectrofluorometry for concentration of quinacrine to establish the clearance rate of the drug.²

A second series of *in vivo* tests was conducted in *Cebus* monkeys by Antonini in São Paulo, Brazil. Polycaprolactone coaxial fibers loaded with quinacrine were inserted into the uteri of ten *Cebus* monkeys, and two monkeys each were sacrificed at 1, 2, 3, 4, and 5 weeks following treatment. The medicated fibers were removed and analyzed for residual quinacrine dihydrochloride.

RESULTS AND DISCUSSION OF FIBER STUDIES

MONOLITHIC FIBERS

Monolithic fibers were prepared with levels up to 50% by weight of quinacrine and quinacrine hydrochloride in polyethylene and polycaprolactone, with the other polymers giving much lower loadings. In general, fibers containing quinacrine as the free base were of good quality and uniformity; those spun with the dihydrochloride were uniform but of poor quality, owing to the heterogeneous polymer mixture created by the nonmelting of the salt. The fibers containing the free base could be drawn and oriented to give mechanical properties approaching those of normal textile yarns; however, the dihydrochloride fibers were fragile and no drawing or mechanical properties could be obtained. The results of the spinning trials showed that quinacrine as the free base gave better fibers than the salt and that polycaprolactone was the best matrix polymer.

The fraction of the total drug released from the various polymers, when plotted versus time in hours, showed that the rate of release from the monolithic fibers was first order, as expected, and dependent on the polymer matrix, the quinacrine composition, and the loading. Polycaprolactone and polyethylene gave the fastest release rates, with release from polypropylene being very slow. In the first two polymers at the 50% loading, quinacrine dihydrochloride was released at a faster rate than the free base, although this effect was reversed at low loadings.

These results indicate that at the high loadings of quinacrine, dissolution of the quinacrine from the polymer matrix is the rate-controlling step. Because the salt is more water soluble, and is dispersed throughout the fiber as discrete particles, it dissolves faster and creates pores for the penetration of water into the fiber, where the water dissolves more salt. At the lower drug loadings, diffusion of the drug through the polymer membrane is the rate-controlling step and quinacrine as the free base is more permeable than the

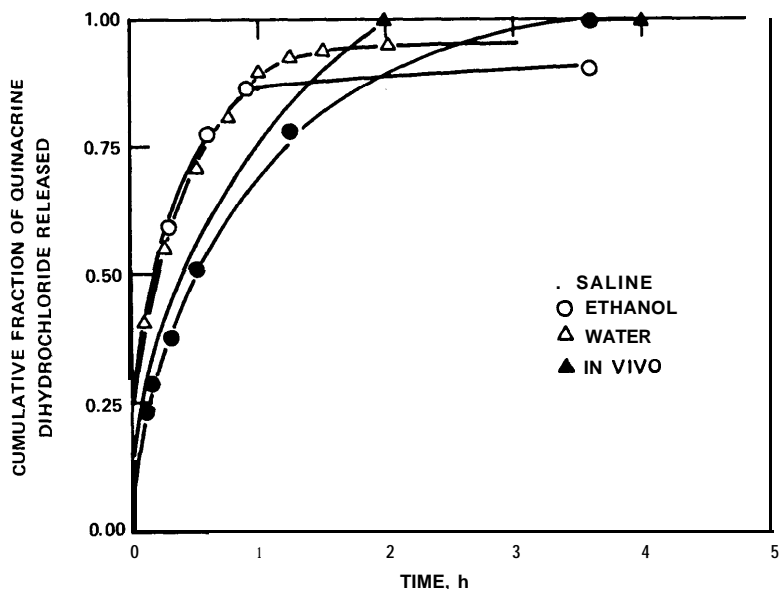


FIG. 14-1. Correlation of *in vitro* and *in vivo* release rates of quinacrine dihydrochloride.

dihydrochloride salt. No major differences in the release rates of either form of quinacrine were observed in the three receiving fluids evaluated.

Because the polycaprolactone monolithic fibers had the best mechanical properties and release rates, samples of these fibers containing quinacrine or quinacrine dihydrochloride (50% by weight) were inserted into the uteri of rats, as described earlier. The cumulative fraction of drug released from each fiber was plotted versus time in hours. These release profiles, given in Figures 14-1 and 14-2, show a good correlation between *in vitro* and *in vivo* release rates for the salt. The data for the *in vivo* release of the free base were scattered, owing to several factors, including fiber nonuniformity, location within the uterus, and incomplete recovery of fiber samples; however, comparison with the *in vitro* release rates showed the same trend. These results confirmed that the *in vitro* model was a suitable system for predicting release rates of quinacrine-loaded fibers.

The amount of quinacrine absorbed into the body was also determined, and Figures 14-3 and 14-4 show the correlation of *in vivo* release with drug levels in the blood of the rats. Although the concentration of quinacrine in the blood was quite low, the levels correlated with the maximum release of quinacrine and its salt.

COAXIAL FIBERS

The release data for the highly loaded monolithic fibers indicated that the delivery of quinacrine and its salt from these systems was too rapid. To in-

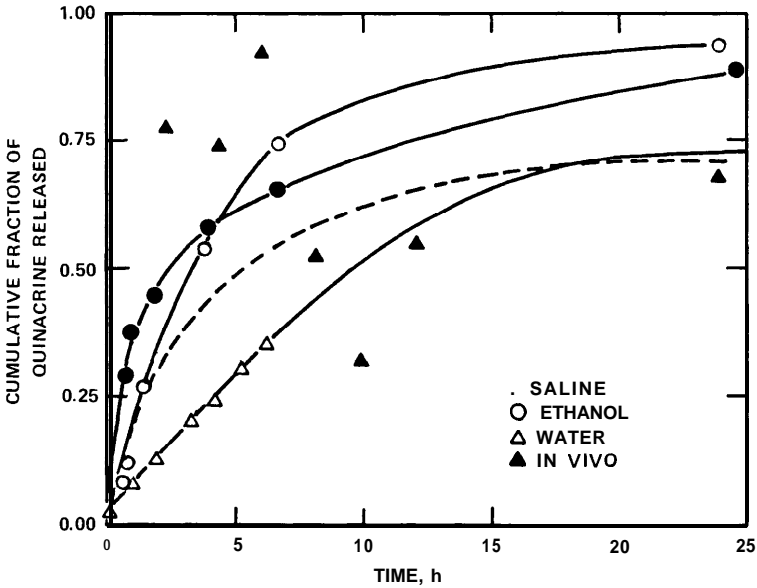


FIG. 14-2. Correlation of *in vitro* and *in vivo* release rates of quinacrine.

crease the duration of drug release of the fibers, quinacrine-loaded coaxial (sheath-core) fibers were prepared with an Estane 5'7 14 or a polycaprolactone sheath and a core matrix of quinacrine or quinacrine dihydrochloride (50% by weight) and polycaprolactone (50% by weight).

The *in vitro* release of samples of these fibers sealed on each end was determined in acidified saline solution. With both fibrous systems, the free

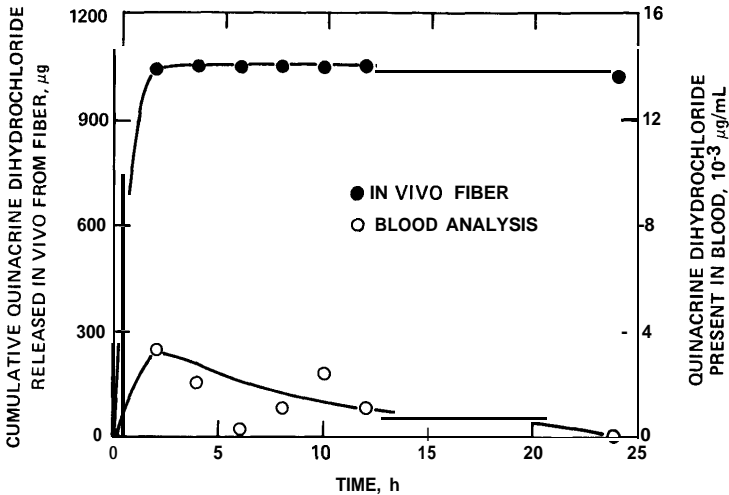


FIG. 14-3. Correlation of *in vivo* release with quinacrine dihydrochloride blood levels.

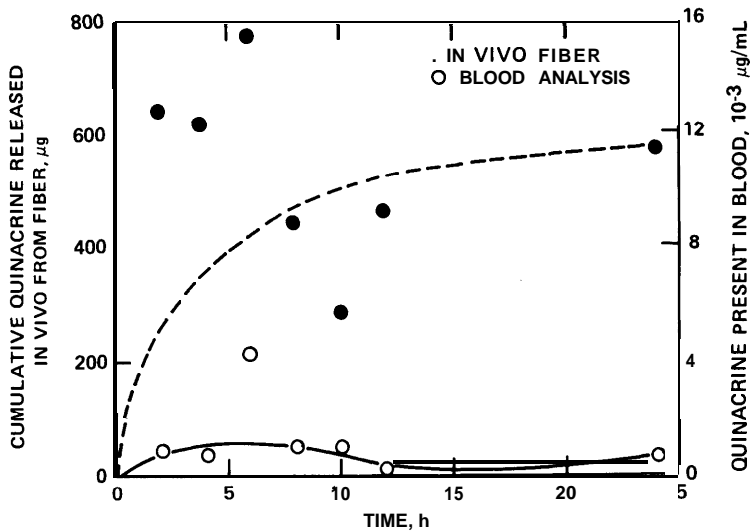


FIG. 14-4. Correlation of *in vivo* release with quinacrine blood levels.

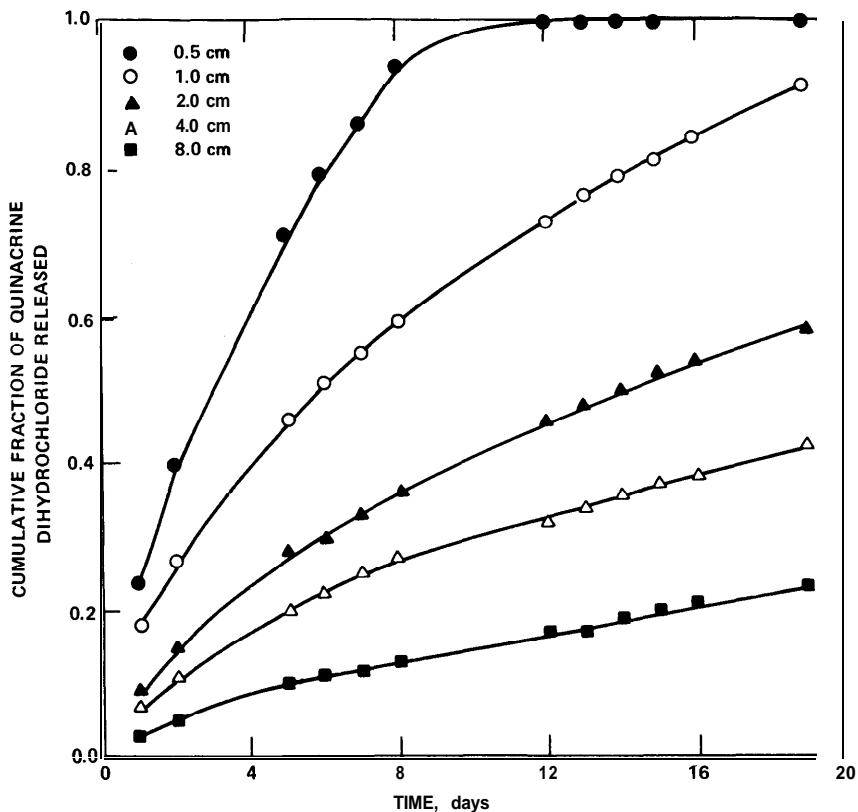


FIG. 14-5. Cumulative *in vitro* release of quinacrine dihydrochloride from various lengths of unsealed coaxial fibers with polycaprolactone sheath.

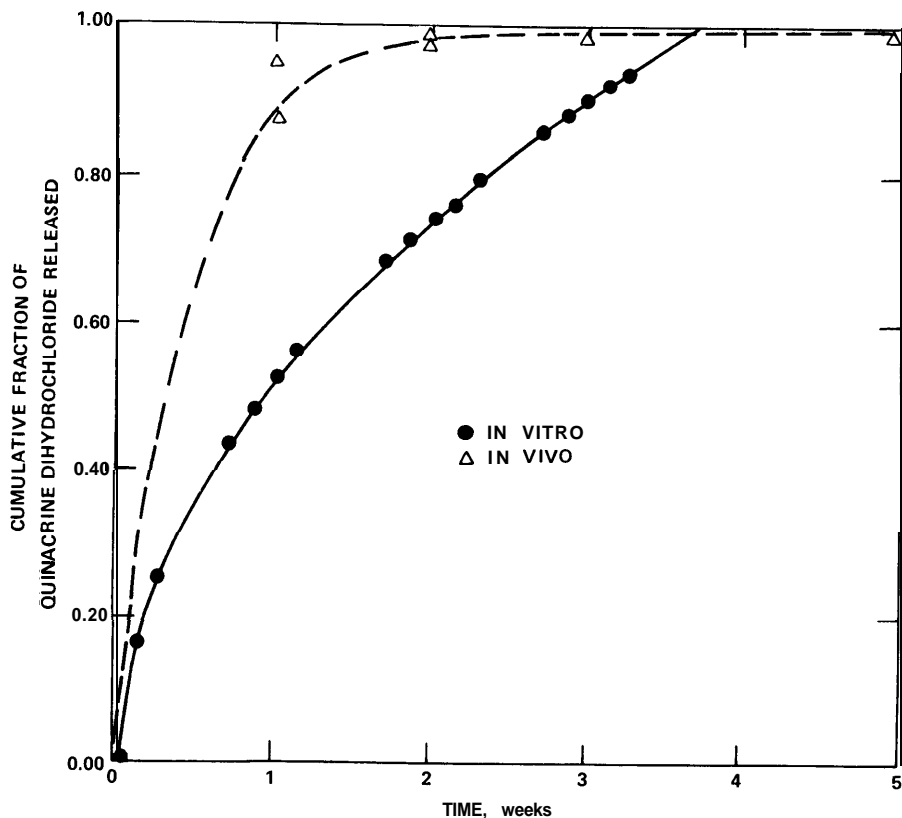


FIG. 14-6. Correlation of *in vitro* and *in vivo* release rates of quinacrine dihydrochloride from coaxial fibers.

base gave the expected decrease in initial burst, but the fiber loaded with the salt gave almost no release at all. These results also indicated that a simple cutting of the coaxial fibers to various lengths should give a controlled delivery of quinacrine dihydrochloride at a rate dependent on the fiber length, because fibers of the same size, when cut to different lengths, have different ratios of unsealed to sealed surfaces. As the salt dissolves from only the unsealed portions, the release rates should correspond. In Figure 14-5, the cumulative fraction of drug released as a function of time for various lengths of unsealed polycaprolactone coaxial fibers shows that the rate and duration of release are indeed dependent on the length of the fiber.

Because of these *in vitro* results, small sections (1 cm in length) of the polycaprolactone coaxial fibers unsealed at the ends were placed in the uteri of *Cebus* monkeys. Although the fibers had a high expulsion rate from the uterus, samples retrieved after the monkeys had been sacrificed were analyzed for residual quinacrine and the rate of *in vivo* release was compared with that determined *in vitro*. The close correlation between the two, with the *in vivo* release being somewhat faster than that predicted by the *in vitro* data, is shown in Figure 14-6.

COAXIAL RODS

Because of the high expulsion rate of the quinacrine fibers in primates and the low quantities of drug available, it was necessary to change the shape of the fibrous quinacrine system for further evaluations in pigs. In these new studies, a 7-day delivery system with an increased dosage was desired. Therefore, the diameter of the coaxial quinacrine fibers was increased to the size of rods.

The coaxial rods were cut to various lengths, and the release rates were determined in saline solution. These data, and calculations based on the required amount of quinacrine dihydrochloride to be delivered, indicated that the 5-mm length of coaxial rod was the most promising. However, the duration of release from a rod this length was greater than the desired 7 days. To limit the duration of release, two approaches were tried.

The first approach was to drill a hole lengthwise through the core of each 5-mm rod. The hole would create more uncoated surface area and increase the release rate with corresponding decrease in time of release. Although the larger holes gave faster release rates, the duration was only decreased to 11 days.

The second approach was to increase the drug loading of the core of the coaxial rod. The increased drug content would produce a more porous matrix as the quinacrine salt was dissolving and would increase the rate of dissolution of salt from within the coaxial rod. *In vitro* release data on the 65% loaded rod showed a decrease in release of quinacrine to about 9 days.

A combination of the two approaches gave the desired delivery system. The optimum coaxial rod was 3.7 mm in diameter and 5.0 mm in length, with a center hole diameter of 0.6 mm. The rod contained a core of 65% quinacrine dihydrochloride in polycaprolactone, and the sheath was a drug-free layer of polycaprolactone. The *in vitro* release of this system, as given in Figure 14-7, shows an approximately zero-order release of quinacrine dihydrochloride for about 7 days.

Ten devices for controlled delivery of quinacrine dihydrochloride were prepared for use in fallopian-tube occlusion studies with pigs. Each device contained five of the optimum quinacrine coaxial rods, held together with a polypropylene monofilament suture running through the hole of each rod. Ten additional devices, each containing three of the optimum rods, were prepared in the same manner. Each device was sealed in plastic bags and sterilized with ethylene oxide, which had been shown to have no effect on release rates. The devices were then implanted in pigs near the uterotubal junction by Zaneveld (see Chapter 13). The rods were recovered at prescribed times and analyzed for residual quinacrine. These analyses showed that essentially all of the quinacrine had been released within 7 days, as predicted by the *in vitro* release data.

CONCLUSION

The results from this study show that modified monolithic delivery systems can be prepared from quinacrine or quinacrine dihydrochloride with poly-

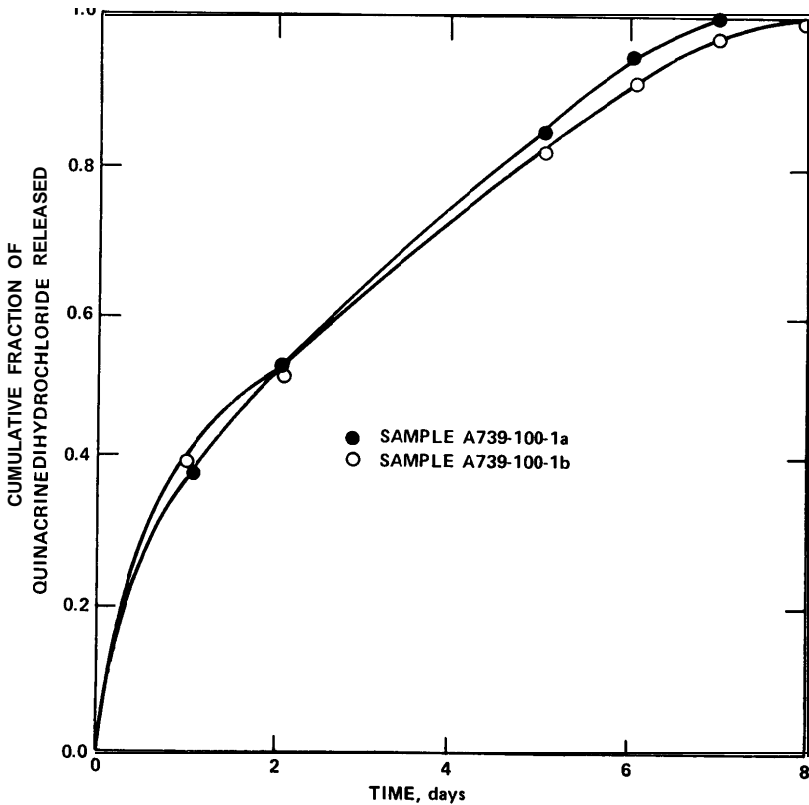


FIG. 14-7. *In vitro* release of quinacrine dihydrochloride from 7-day pellets with polycaprolactone sheath, 65:35 quinacrine dihydrochloride/polycaprolactone core.

caprolactone, a totally biodegradable polymer. These systems, in the form of coaxial fibers or rods, can be designed to give almost zero-order release of quinacrine dihydrochloride for various times, ranging from several days to several weeks. Although the fibers are limited in the quantity of drug they deliver, owing to size and flexibility, both systems provide an effective method of delivering quinacrine at a controlled rate to the fallopian tubes.

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