SYNOPSIS

Most studies of the sustained release of drugs from subdermally implanted polymer devices have centered on the use of silicone rubber. However, the use of this polymer has serious limitations because of its non-biodegradability. The depleted capsule has to be surgically removed if one is to eliminate potential problems associated with non-degradable foreign substances remaining in the body for an indefinite length of time. The development of polymer systems which combine the release properties of silicone rubber with biodegradability will represent a significant advance in the technique of controlled release of contraceptives. The polymer system selected for our investigations were polyesters comprising homo and copolymers of glycolide, dilactide, ε-caprolactone, and ε-decalactone. These polymers were found to undergo random hydrolytic degradation under in vitro and in vivo conditions. The polymers were characterized by their rates of biodegradation and their release parameters for contraceptive steroids. Long time release rates of steroids from monolithic and reservoir devices were determined. Especially poly(ε-caprolactone) was found to come close to meeting the requirements of a biodegradable reservoir device for controlled drug delivery, with a useful lifespan approaching one year. Copolymers of ε-caprolactone and racemic dilactide are more permeable than poly(ε-caprolactone) and are of value for biodegradable devices with shorter than one year lifespan.
INTRODUCTION

Until recent times the routes of drug administration have remained essentially unchanged, consisting almost exclusively of either oral or parenteral administration. The necessity for new techniques becomes apparent with the development of drugs with increased potency. Increased potency with minimal persistence or side-effects is usually a consequence of rapid metabolism which means effectiveness only within a narrow limit of time and concentration. Repeated application of a drug in individual doses generates strongly fluctuating drug levels in the body with the possibility of overdose or underdose.

Provided the drug is continuously delivered at a constant rate by a controlled-release device and its removal follows first order kinetics then a stationary drug level will be established given by the ratio of both rate constants. The stationary level can be kept extremely low if the delivery device is placed close to the target organ.

A controlled-release delivery system is a combination of a biologically active agent (drug) with an excipient, commonly a polymeric material which can play either an active or a passive role in the delivery process. In the first case the drug is released from the polymeric matrix by changes in the chemical or physical properties of the latter. Such changes can involve, among others, biodegradation of the polymer (surface erosion), progressive swelling with subsequent drug diffusion from the swollen region, and hydrolysis of drug-polymer bonds.

The polymer will play a passive role if it acts solely as a barrier which controls the rate of drug delivery by diffusion. Indeed, changes in the properties of the polymer are undesirable in this case since thereby the parameters governing the diffusion process will change. Purely diffusion controlled delivery systems generally belong to either one of two types, monolithic devices or reservoir devices.

In monolithic devices the drug is uniformly mixed with the polymeric matrix and is present either in dissolved or dispersed form. For a dissolved drug