CONTROLLED RELEASE OF BIOLOGICALLY ACTIVE AGENTS

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The development of injectable systems for sustained delivery of drugs at a controlled rate has been the object of various publications. In 1946, a patent [1] was issued claiming pellets consisting of dispersions of a desiccated hormone in waxy media as a new system for a slow and prolonged release of active materials. Substitution of the waxy media as matrices by silicones for fertility control was reported by other investigators [2, 3, 4, 5]. A recent innovation is the use of biodegradable polymers such as polylactic acid (PLA), which will also assure a complete delivery of the drug [6].

Several papers have been published dealing with factors influencing the release of a drug from waxy granular matrices [7] and from methylacrylate-methylmethacrylate copolymers [8]. In addition, various investigators have presented mathematical approaches to describe the migration of a drug through solid polymer matrices of various shapes [5, 9, 10, 11].

Composites of drugs and polymeric matrices are at present under intense investigation as fertility control agents [3, 4, 5, 12], narcotic antagonists [6, 13, 14], anticancer agents [15], weight-gaining agents for beef cattle [16] and for the treatment of glaucoma [17] and ulcers [18].

The system for sustained delivery of drugs investigated by this laboratory comprises incorporating a drug in a polymeric
matrix, shaping the composite into a convenient form such as films, pellets or chips, and then implanting the structure into the body tissue of animals by surgery or hypodermic injection. The drug diffuses continuously from the interior of the polymeric composite to the outer surface, where it is mechanically swept away by body fluids surrounding the structure. The mechanism of migration through the polymer is that of diffusion and the thermodynamic driving force is the concentration gradient [9, 10].

Previous papers [6, 19] from this laboratory have dealt with the influence of the following factors on the release of cyclazocine (2-cyclopropylmethyl-2'-hydroxy-5, 9-dimethyl-6, 7-benzomorphan; Structure I, Fig. 1): (a) nature of the polymer, polyethylene and polylactic acid, (b) molecular weight of the polymer and (c) form of the composites, films and particles.

We report in this paper the results of recent investigations concerning (1) release rates of two new narcotic antagonists, naloxone (17-allyl-4, 5-a-epoxy-3, 14-dihydroxymorphinan-6-one, II,