PHARMACEUTICAL COMPOSITIONS USING SEMI-SOLID DELIVERY VEHICLE

RELATED APPLICATIONS

This application is a continuation of U.S. application Ser. No. 10/409,408, filed Apr. 7, 2003, now U.S. Pat. No. 6,790,458, which is a divisional of U.S. application Ser. No. 09/854,180, filed May 11, 2001, now U.S. Pat. No. 6,613,355; which claims the priority under 35 USC 119(e) of U.S. Provisional Application No. 60/325,790, filed May 11, 2000.

FIELD

This invention relates to semi-solid delivery vehicles comprising a polyorthoester and an excipient, and to controlled release pharmaceutical compositions comprising the delivery vehicle and an active agent. The pharmaceutical compositions may be in the form of a topical, syringable, or injectable formulation for local controlled delivery of the active agent.

BACKGROUND

A large of class of active agents such as antibiotics, antiseptics, corticosteroids, anti-neoplastics, and local anesthetics may be administered to the skin or mucous membrane by topical application, or by injection. The active agent may act locally or systemically. Topical delivery may be accomplished through the use of compositions such as ointments, creams, emulsions, solutions, suspensions and the like. Injections for delivery of the active agents include solutions, suspensions and emulsions. All of these preparations have been extensively used for delivery of active agents for years. However, these preparations suffer the disadvantage that they are short-acting and therefore they often have to be administered several times in a day to maintain a therapeutically effective dose level in the blood stream at the sites where the activity/treatment is required.

In recent years, a great deal of progress has been made to develop dosage forms which, after their administration, provide a long-term therapeutic response. These products may be achieved by microencapsulation, such as liposomes, microcapsules, microspheres, microparticles and the like. For this type of dosage forms, the active agents are typically entrapped or encapsulated in microcapsules, liposomes or microparticles which are then introduced into the body via injection or in the form of an implant. The release rate of the active agent from this type of dosage forms is controlled which eliminates the need for frequent dosing. However their manufacture is cumbersome which often results in high costs. In addition, they, in many cases, have low reproducibility and consequently lack of reliability in their release patterns. Furthermore, if an organic solvent is used in the manufacturing process, there could be organic solvent residues in the compositions which may be highly toxic. The use of an organic solvent is also undesirable for environmental and fire hazard reasons.

Interest in synthetic biodegradable polymers for the delivery of therapeutic agents began in the early 1970's with the work of Yolles et al., *Polymer News,* 1, 9–15 (1970) using poly(lactic acid). Since that time, numerous other polymers have been prepared and investigated as bioerodible matrices for the controlled release of active agents. U.S. Pat. Nos. 4,079,038, 4,093,709, 4,131,648, 4,138,344, 4,180,646, 4,304,767, 4,946,931, and 5,968,543 disclose various types of biodegradable or bioerodible polymers which may be used for controlled delivery of active agents. Many of these polymers may appear in the form of a semi-solid. However the semi-solid polymer materials are often too sticky. As a result, the active agents frequently cannot be easily and reliably released from the semi-solid polymer materials.

SUMMARY

A first objective of the present invention is to provide a semi-solid delivery vehicle which comprises a polyorthoester and an excipient. The excipient is readily miscible with the polyorthoester and the resulting semi-solid delivery vehicle has a smooth and flowable texture. The polyorthoesters suitable for the invention are represented by formula I and formula II below.

Another objective of the present invention is to provide a controlled release semi-solid pharmaceutical composition for local controlled delivery of an active agent. The composition comprises an active agent and the semi-solid delivery vehicle.

A further objective of the present invention is to provide a semi-solid syringable or injectable composition for the controlled delivery of locally acting active agents, in particular local anesthetics.

The polyorthoester can be homogeneously mixed with the excipient at room temperature without the use of a solvent. The resulting semi-solid delivery vehicle and controlled-release pharmaceutical compositions have a useful texture and viscosity, and the release rate of the active agent from the compositions can also be conveniently and reliably adjusted to accommodate the desired therapeutic effect.

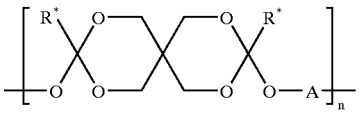
Thus, in a first aspect, this invention is a controlled-release semi-solid pharmaceutical composition comprising:

an active agent; and

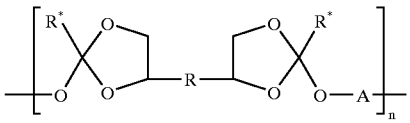
a semi-solid delivery vehicle, comprising:

a polyorthoester of formula I or formula II

(I)



(II)

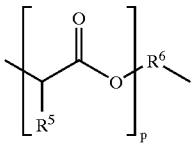


where:

R is a bond, $—(CH_2)_a—$, or $—(CH_2)_b—O—(CH_2)_c—$; where a is an integer of 1 to 10, and b and c are independently integers of 1 to 5;

R* is a C_{1-4} alkyl;

n is an integer of at least 5; and

A is R^1, R^2, R^3, or R^4, where

R^1 is: