

the possibility that some of the oil phase may be carried over into the implanted host.

Accordingly, there exists a definite need for gel or encapsulation materials which are not unstable under physiological conditions. There also exists a need for very mild and gentle methods for encapsulating biologics, especially for encapsulating living cells or tissues in an aqueous environment, whereby such methods allow a subsequent or simultaneous covalent crosslinking for chemical and mechanical stability without the necessity of a potentially toxic oil phase. Further, there exists a need for biocompatible encapsulation or microencapsulation materials which are mechanically and chemically stable in physiological environments. There also exists the need for such materials which provide immunoprotectivity of the encapsulated biologics. Additionally, there exists a need for biocompatible encapsulation materials which allow for the controlled release of an encapsulated biologic.

SUMMARY OF THE INVENTION

In accordance with the present invention, there are provided compositions and processes for encapsulating biologics, such as biologically active components and diagnostic markers. More specifically, the compositions of the present invention comprise a crosslinked biocompatible material having at least one ionically crosslinked component and at least one covalently crosslinked component. The crosslinked biocompatible materials are formed from mixtures having at least one ionically crosslinkable component and at least one covalently crosslinkable component.

The combination of an ionically crosslinked component and a covalently crosslinked component provides a non-cytotoxic, immunoprotective gel that can be used to entrap or encapsulate a biologic in a tightly crosslinked network, while preventing the diffusion of the ionically crosslinked component out of the crosslinked gel even in the presence of monovalent ions or ion chelators. The covalently crosslinked component further provides mechanical and chemical stability to the encapsulation material or gel. The ionically crosslinked component provides a matrix or pre-formed gel which facilitates the rapid covalent crosslinking of the covalently crosslinkable component without the necessity of an immiscible, potentially toxic oil phase required for the formation of gelled droplets or capsules. These dually crosslinked materials provide the required properties for immunoprotectivity of the encapsulated biologics (including xenotransplanted biologics) by preventing the migration of molecules through the material which are potentially harmful to the biologics. Furthermore, the biocompatible materials or compositions of the present invention provide for the controlled release of biologics, or components thereof, into the physiological environment for therapeutic purposes, such as drug delivery.

The present invention also is embodied in a crosslinkable biocompatible mixture suitable for encapsulating a biologic, such as biologically active materials or diagnostic markers, once it is properly crosslinked. The crosslinkable biocompatible mixture is comprised of an ionically crosslinkable component and a covalently crosslinkable component having at least one polymerizable functional group subject to free radical polymerization.

The present invention further relates to processes for encapsulating a biologic comprising coating the bio-

logic with a composition having a covalently crosslinked component and an ionically crosslinked component.

In yet a further aspect of the invention, a retrievable encapsulation material is provided which is comprised of a macrocapsule of the crosslinked biocompatible material of the present invention for encapsulating free cells or other microcapsules.

Other features and advantages of the present invention will become apparent from the following detailed description, taken in conjunction with the accompanying drawings and examples, which illustrate the principles of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph showing the permeability of an alginate/PEG-DA (AP) 10K crosslinked encapsulation gel to different molecular weight dextrans.

FIG. 2 is a graph comparing perfusion of canine islets in alginate/poly-L-lysine microcapsules and the AP 10K microcapsules of the present invention.

FIG. 3 is a graph comparing perfusion of canine islets in different molecular weight AP macrocapsules of the present invention.

FIG. 4 is a graph showing insulin secretion response of canine islets in alginate-polylysine microcapsules further encapsulated in AP macrocapsules.

FIG. 5 is a graph of the effects on blood glucose, urine volume and body weight of dog to rat xenotransplanted islets in AP 10K microcapsules of the present invention.

FIG. 6 is a perfusion graph of retrieved, dog to rat xenotransplanted islets in AP 10K microcapsules of the present invention.

FIG. 7 is a graph of an intravenous glucose tolerance test on rats having implanted canine islets in AP microcapsules of the present invention.

FIG. 8 is a graph showing the effects of a dog to rat xenotransplant of AP macrocapsules of the present invention containing canine islets in alginate/PLL microcapsules.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

In accordance with the present invention there is provided a crosslinkable biocompatible mixture for encapsulating biologics, such as biologically active materials or diagnostic markers. The crosslinkable biocompatible mixture is comprised of an ionically crosslinkable component and a covalently crosslinkable component. The ionically crosslinkable component is selected from a polysaccharide, a polyanion, or a polycation. The covalently crosslinkable component is selected from a polyalkylene oxide having at least one functional group capable of undergoing free radical polymerization.

The present invention also relates to crosslinked biocompatible materials having at least one ionically crosslinked component and at least one covalently crosslinked component. The crosslinked biocompatible materials are suitable for encapsulating biologically active materials, such as living cells, hormones, enzymes, tissues, drugs or pharmaceuticals, or diagnostic markers such as imaging contrast media, radio contrast media and the like.

Ionically crosslinkable polysaccharides suitable for the present invention include, but are not limited to, alginate and natural ionic polysaccharides such as chito-