

BIOCOMPATIBLE COATING FOR SOLID SURFACES

This application is a continuation of application Ser. No. 920,567, filed Oct. 17, 1986, now abandoned.

FIELD OF INVENTION

This invention relates to the field of biochemistry and particularly to the enhancement of the biocompatibility of various surfaces.

BACKGROUND OF THE INVENTION

The implantation of such biomaterial articles as substitute blood vessels, synthetic and intraocular lenses, electrodes, catheters and the like in and onto the body is a rapidly developing area of medicine. A primary impediment to the long-term use of such biomaterial implantables as synthetic vascular grafts has been the lack of satisfactory graft surfaces. The uncoated surfaces of synthetic blood vessels made from plastics, for example, often stimulate rapid thrombogenic action. Various plasma proteins play a role in initiating platelet and fibrin deposition on plastic surfaces. These actions lead to vascular constriction to hinder blood flow, and the inflammatory reaction that follows can lead to the loss of function of the synthetic implantable.

A "biomaterial" may be defined as a material that is substantially insoluble in body fluids and that is designed and constructed to be placed in or onto the body or to contact fluid of the body. Vascular grafts and contact lenses are examples of biomaterials.

Ideally, a biomaterial will have the following characteristics:

1. It will not induce undesirable reactions in the body such as blood clotting, tissue death, tumor formation, allergic reaction, foreign body reaction (rejection) or inflammatory reaction.
2. It will have the physical properties such as strength, elasticity, permeability and flexibility required to function as intended.
3. It can be purified, fabricated and sterilized easily.
4. It will substantially maintain its physical properties and function during the time that it remains implanted in or in contact with the body, whether it be an hour or a lifetime.

As used herein, the solid surface of a biomaterial is characterized as "biocompatible" if it is capable of functioning or existing in contact with biological fluid and/or tissue of a living organism with a net beneficial effect on the living organism. Long term biocompatibility is desired for the purpose of reducing disturbance of the host organism.

A number of approaches have been suggested to improve the biocompatibility of implantable items. One approach has been to modify the surface of a biomaterial to prevent undesirable protein adhesion by providing the biomaterial with a low polarity surface, a negatively charged surface or a surface coated with biological materials such as enzymes, endothelial cells and proteins. Solid surfaces have been coated with biochemical materials such as heparin, albumin and streptokinase to enhance thromboresistance. Albumin in particular has been physically adsorbed onto and electrostatically and covalently bound to polymer surfaces.

Munro, et. al, U.S. Pat. No. 4,530,974 discloses a method of adsorbing albumin to a water-insoluble polymer such as polyurethane by covalently binding to the

surface a nonionic hydrophobic aliphatic chain to which albumin will selectively bind.

Nimni et al, U.S. Pat. No. 4,378,224 teaches a method of coating animal tissues, used to make prosthetic devices, through the formation of a three dimensional cross-linked matrix primarily composed of a calcification inhibitor.

An example of an adverse reaction that is caused by the presence of a biomaterial is the deposition of protein on contact lenses. Often contact lens wearers develop an intolerance to their contact lenses with time and this intolerance may be linked to irritation and allergic responses to biochemicals (proteins, lipids, mucopolysaccharides, and others) which deposit onto the lenses while they are worn. Current cleansing and disinfection procedures remove some of these deposits, but these procedures often leave holes and crevices in the lenses which add to the eye irritation of the wearer and serve as foci for further biochemical deposition.

Guire, U.S. Pat. No. 3,959,078, describes the use of reagents to covalently bind an enzyme to aminoethyl cellulose or alkylamine glass. See, also: Guire, *Stepwise Thermophotochemical Cross-linking for Enzyme Stabilization and Immobilization*; Enzyme Engineering 3:63-70 (1978) and Guire, *Photochemical Immobilization of Enzymes and Other Biochemicals*, Methods in Enzymology XLIV:280-288 (1976). These references describe a process of covalently binding an enzyme to substrates such as chemical derivatives of controlled-pore glass, cellulose, agarose and polyacrylamides by thermochemically coupling a linking reagent to the solid surface and photochemically coupling the enzyme to the linking reagent to provide a surface useful in the performance of in vitro diagnostic assays.

SUMMARY OF THE INVENTION

The invention relates to biomaterials that are provided with desired biocompatible surfaces. A method for modifying the solid surface of a biomaterial employs molecules of a biocompatible agent and a chemical-linking moiety possessing a photochemically reactive group capable, upon activation, of covalently bonding to the solid surface and possessing a different reactive group that is capable, upon activation, of covalently bonding to separate molecules of the biocompatible agent. One of the groups is unresponsive to activation by a stimulus to which the other group is responsive. The method comprises applying stimulus to sequentially activate the groups to covalently bind the different reactive group of the linking moiety to the molecules of the biocompatible agent and to photochemically covalently bind the linking moiety to the solid surface with a sufficient population density to enable the molecules of the biocompatible agent to effectively shield the solid surface and to provide a biocompatible effective surface.

A biocompatible "effective" surface is thus formed of a plurality of separate molecules of a biocompatible agent covalently linked, through a linking moiety, to the solid surface of a biomaterial to provide that surface with substantially the same biocompatible characteristics as are possessed by the biocompatible agent. The effective surface formed by the molecules of the biocompatible agent need not cover the entire surface of a biomaterial. It may cover the surface in spots. For example, spots along the surface of vascular grafts may be covered by a cell attachment factor such as fibronectin. The biocompatible effective surface formed at those