Pharmaceutical Research, Vol. 13, No. 12, 1996

Review

Biocompatibility Issues of Implantable Drug Delivery Systems

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Received August 21, 1996; accepted September 21, 1996

KEY WORDS: biomaterials; biocompatibility; implantable drug delivery systems; implantable glucose sensors; hydrogels.

INTRODUCTION

Research in controlled drug delivery during the last three decades has been focused mainly on control of drug release rate for maintaining the pharmacologically effective drug levels in blood for extended periods of time. Controlled release technology has now advanced to such a level that zero-order delivery of drugs for up to several years can be achieved easily. As a result, many controlled release dosage forms, mainly for oral and transdermal delivery, have been a commercial success. To be truly useful for long-term treatment of diseases, however, controlled release devices may have to be implanted into the body. It is time to consider the biocompatibility issues unique to these systems.

Appreciation for the importance of biocompatibility in determining the therapeutic usefulness of biomedical products has been growing steadily since the passage of the Medical Device Amendments of 1976, which were designed to assure the safety and efficacy of devices. When artificial materials are implanted inside the body for long-term ranging from month to years, concerns are raised on the potential undesirable body responses to the implanted materials. Serious adverse effects have been identified with some implantable biomaterials, such as silicone gel-filled breast implants (1), Norplant® contraceptive implants (2), and Teflon-coated temporomandibular joint implants (3). Pharmaceutical scientists involved in the long-term implantable drug delivery systems may benefit from an understanding in biomaterials and biocompatibility relevant to controlled drug delivery systems. This article briefly describes the definitions of biomaterials and biocompatibility, examples of importance of biocompatibility, and implantable biomaterials.

BIOMATERIALS AND BIOCOMPATIBILITY

Biomaterials are basically any non-viable materials which become a part of the body either temporarily or permanently to restore, augment, or replace the natural functions of the living tissues or organs in the body (4). Biomaterials have been used in prosthetic, diagnostic, and therapeutic applications. Many controlled drug delivery systems, especially implantable systems, are also biomaterials. Recently, a variety of drugs have been incorporated into implantable biomaterials to improve the functions of the biomaterials. For example, antibiotics or growth hormone was incorporated into implantable biomaterials for delivery at the implant interface to prevent deep-wound sepsis or to improve wound healing and tissue repair (5).

When biomaterials are placed inside the body, they are expected to perform with a desirable host response in a specific application without any side effects, such as toxic, carcinogenic, immunogenic, and inflammatory responses. Biocompatibility is the appropriate biological performance, either local or systemic, of a given implant in a specific application (6). Appropriate host response varies depending on the type of materials implanted and their intended use (7). Thus, the desirable host response may be total inertness and no interaction with tissues surrounding the implanted materials or positive interaction resulting in active participation of the cells surrounding the materials. Biocompatibility is a dynamic two-way process that involves the time-dependent effects of the host on the material and the material on the host (8). No clear, absolute definition of biocompatibility exists yet mainly due to the fact that the biomaterials area is still evolving. Simply put, however, the performance of a biomaterial, if biocompatible, should not be affected by the host and the host should not be negatively affected by the implanted biomaterials.

Blood Compatibility

When a biomaterial is exposed to blood, certain blood proteins adsorb rapidly and the protein adsorption, depending on the type of adsorbed proteins, is followed by platelet adhesion. The activation of adherent platelets lead to the formation of thrombi on the surface. Almost all biomaterials, including polymers, ceramics, and metals, are known to cause surface-induced thrombosis. The proposed sequence of the surface-induced thrombosis is shown in Figure 1 (9). The sequence shown in Figure 1 is repeated, although the repetition is not regular and predictable. The formation of thrombi on the surface

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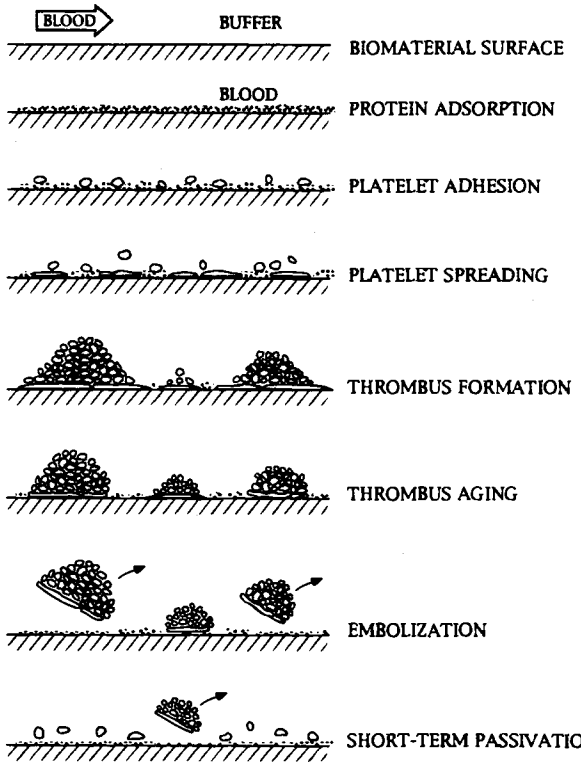

Fig. 1. Proposed sequence of thromboembolization occurring on biomaterials exposed to flowing blood (From reference 9).

causes many undesirable, sometimes detrimental, effects. Embolization of the thrombi may result in blockage of cerebral blood supply, and thus stroke. Thrombus formation on blood-contacting drug delivery devices will also affect the drug release profiles. The most desirable host response to blood-contacting biomaterials would be no thrombus formation at all, which is known to be quite difficult to achieve. The most widely used approach to improve blood compatibility is to modify the biomaterial surface. It is generally accepted that modification of biomaterials surfaces with poly(ethylene oxide), heparin, albumin, or other hydrophilic polymer chains prevents or minimizes the protein adsorption and/or platelet adhesion (10). These hydrophilic macromolecules prevent protein adsorption and cell adhesion by the steric repulsion mechanism which has been well established in colloidal chemistry. Figure 2 describes the steric repulsion of adsorbing proteins by the surface grafted linear polymer chains and globular proteins. The hydrophilic, flexible molecules on the surface can be regarded as entropic "springs" (11). When the molecules grafted on the surface are compressed by the adsorbing proteins and platelets, the repulsive energy arises due to the increased osmotic pressure and elastic forces of the compressed molecules.

Surface modification for the preparation of blood-compatible biomaterials would be highly beneficial for the delivery of various drugs from the blood-contacting devices. For example, restenosis remains the principal limitation in the treatment of coronary artery diseases by coronary angioplasty despite the use of stents (12). To minimize the adverse effect of coronary angioplasty, stent surfaces have been coated with polyurethane layers for the controlled intravascular delivery of forskolin pos-

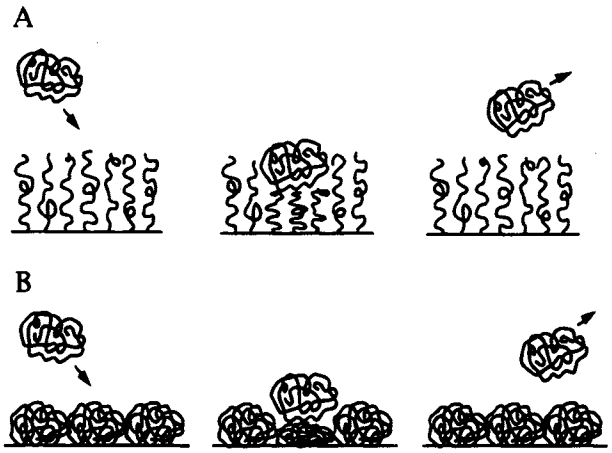

Fig. 2. Schematic description of steric repulsion exerted by the surface-grafted linear polymers such as poly(ethylene oxide) (A) and globular proteins such as albumin (B).

sessing vasodilating and antiplatelet function (13). Stents may also release antisense oligonucleotides or genes that selectively prevent muscle cell proliferation. Delivery of these agents from the stent to the cells in the vicinity of the implanted stent would not be effective if the surface-induced thrombosis cannot be prevented or minimized.

Tissue Compatibility

The tissue damage created by the implantation procedure usually results in inflammation, which is the local, nonspecific reaction of vascularized tissue to injury (14). Reddening, swelling, pain, and fever are the classical signs of early events of inflammation indicating battle against infection. These signs are accompanied with a series of defensive reactions by neutrophils (or polymorphonuclear leukocytes), eosinophils, macrophages, and foreign body giant cells. The primary role of these cells appear to be phagocytosis for the removal of dead tissue and other small particulates resulting from implantation (7). Macrophages initiate the repair of damaged tissue by forming the scaffold for repair, which is called granulation tissue. The granulation tissue starts to surround the implant and foreign body giant cells (which comprised of fused macrophages) attach to the surface of implant. If the implant is not phagocytosed by the cells, the body tends to completely isolate the foreign implant by forming a sheath-like fibrous membrane capsule (i.e., scar tissue) around the implants (15). The formation of capsules around implanted biomaterials (i.e., encapsulation) is mediated by fibroblasts originating in perovascular connective tissue (16). The fibrous encapsulation process is schematically shown in Figure 3. Encapsulation of materials may affect the functions of the materials in many different ways. Even this brief discussion on thrombus formation and encapsulation makes it clear that the success in the applications of implantable drug delivery systems relies heavily on the biocompatibility of materials used in the systems.

IMPLANTABLE DRUG DELIVERY SYSTEMS AND OTHER DEVICES

In this section, we will consider a few examples (silicone rubber implants and artificial pancreas) to point out the impor-

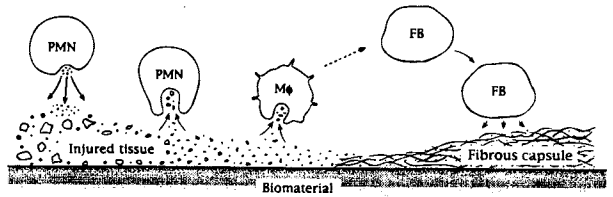

Fig. 3. Description of fibrous capsule formation around the implanted biomaterial. Activated polymorphonuclear leukocytes (PMN) release enzymes to remove dead cells, and macrophages (Mϕ) participate in the phagocytosis of foreign and cellular debris. Mϕ also stimulate fibroblasts (FB) to secrete collagen and other extracellular matrix components to form a fibrous capsule around the implanted biomaterial (From reference 16).

tance of biocompatibility in clinical applications of biomaterials for controlled drug delivery. A serious safety issue has been raised for an implantable silicone rubber drug delivery system, and implantable artificial pancreas provide the ultimate challenge in controlled drug delivery.

Silicone Rubber Implants

Silicone rubber implants are usually made by crosslinking of copolymers of dimethylsiloxane and methylvinylsiloxane (17). Silicone rubber has been used as biomaterials since early 1950s and regarded as one of the most biocompatible materials (18). Two recent, most widely publicized incidents dealing with biocompatibility problems, however, were related to silicone rubber products: silicone gel-filled breast implants and Norplant® implants. Both of them are made of crosslinked silicone rubber. Although the silicone gel-filled breast implant is not drug delivery devices per se, it presents a good example of the importance of biocompatibility. Norplant®, developed by the Population Council and Wyeth-Ayerst Laboratories, is contraceptive device which can be implanted under the arm by a simple surgical operation. It is made of six silicone rubber tubes with size of a match stick (2.4 mm in diameter and 34 mm in length and each containing 36 mg levonorgestrel). The six silicone rubber tubes release progestin at a constant rate for up to 6 years (19). As mentioned above, the typical tissue reaction around the nondegradable implants is the formation of a thin fibrous capsule similar to scar tissue. Such fibrous capsule membranes were formed around silicone gel breast implants (20) as well as around Norplant implants (21). Contraction of the fibrous capsule around the breast implants often causes pain and deformity of the implants. The fibrous capsule around Norplant implants makes it difficult to remove the devices from the implanted sites. In some cases silicone rubber tubes were not found in the implant site at all (22). While the problem with fibrous capsule formation may not occur with all the patients, it is an important issue in the development of nondegradable, implantable devices.

Implantable Artificial Pancreas

Development of implantable, self-regulating insulin delivery systems is one of the ultimate challenges in the controlled drug delivery area. Self-regulated insulin delivery systems (i.e., artificial pancreas) requires glucose sensing ability and the ability to modulate the release of insulin in one device. The key to the development of artificial pancreas is the development of glucose sensors for continuous glucose monitoring. Since the glucose concentration in the subcutaneous tissue is known to be essentially identical to the plasma glucose concentration under stationary conditions (23,24), the glucose sensor can be placed under the skin. Subcutaneously implantable needle-type glucose sensor has been suggested and developed for short-term applications ranging from a day to a week (25,26). One of the problems of using such systems clinically, however, is that biocompatibility of those systems is rather poor (27). The possibility of infection at the implant sites is always present (28). More importantly, the sensor immediately starts losing the sensitivity upon implantation by protein adsorption and cell adhesion to the sensor surface (29,30). This leads to the problem of the validity of glucose calibration. Understanding which proteins adsorb to the sensor surface and how they interfere with sensor function is critical in developing reliable, predictable implantable glucose sensors. One approach of developing reliable implantable sensors is to modify the surface in such a way to prevent protein adsorption in general. As shown in Fig. 2, grafting of PEO and other hydrophilic polymers to the sensor surface is expected to prevent protein adsorption, and thus maintain the stable sensitivity. These problems are something that can be overcome, but the answers are at least several years away before the technology can be applied to clinical practice. Along with the glucose sensing problem, one needs to solve the problems associated with the stability of insulin in the self-regulating delivery systems. It is not uncommon to see the aggregation of insulin molecules in the reservoir leading to blockage of the delivery portal from the implanted insulin delivery devices (31,32), and such an episode may require premature removal of the whole device.

In another approach of making hybrid artificial pancreas, pancreatic cells were encapsulated in polymeric microspheres to prevent immune rejection before implanting in the body. Various microencapsulation chemistries have been used for the encapsulation of islet cells, but the most widely used system is the sodium alginate system. Intraperitoneal injection of alginate-encapsulated islets into humans by a minimally invasive surgical procedure resulted in effective maintenance of glycemic control for more than a year (33,34). While the clinical study on such approaches has been successful, the issue of biocompatibility of such a dosage form for lifelong application has not been resolved completely (35). The membrane surfaces, upon implantation, may cause inflammatory response, which is detrimental to the survival of the encapsulated islet cells, and fibroblast proliferation. Many attempts, including the surface modification of the membranes with PEO, have been tried to make the membranes more biocompatible (36). Full resolution of the biocompatibility issue may be prerequisite for the successful development of clinically useful hybrid artificial pancreas. Recently, composite grafting of allogeneic islets with syngeneic myoblasts expressing Fas ligand, which is the signal that maintains immunoprivileged sites, protected the islet graft from immune rejection and maintained normoglycemia for more than 80 days in mice with streptozotocin-induced diabetes (37). Eventually it will be possible to combine all these approaches to develop truly biocompatible artificial pancreas.

Challenges and Opportunities

For successful long-term applications of implantable materials, one has to consider prevention or minimization of surface-

induced thrombosis and/or fibrous encapsulation (or isolation) of implants by the body. While the surface modification of biomaterials with PEO, heparin, albumin, and other hydrophilic polymers appears to be promising, further systematic studies on the long-term effects of surface modification of biomaterials are necessary for the development of truly biocompatible materials.

For most subcutaneously implanted biomaterials, the formation of fibrous capsules around the implants may be of great concern. There is no clear evidence that it is possible to prevent capsule formation either by regulating cell functions or any other means (16). Thus, an alternative approach could be to consider the capsule formed around the implant as a part of the implant. Recently, Wood et al. isolated the fibrous tissue from rats for characterization of the drug permeability through the tissue (38). It was found that the rank ordering of permeabilities through the fibrous tissue membranes of estrone, 3-0-methylglucose, and dextran (6.0×10^{-5} cm/s, 1.9×10^{-5} cm/s, and 5.6×10^{-6} cm/s, respectively) was consistent with expectations based on the molecular weights and partitioning behaviour of the model compounds. This type of study is highly important in considering the fibrous capsule membranes in the control of drug delivery or in the calibration of the analyte concentrations in the presence of capsules (16). In cases where the clinical usefulness of implantable devices is compromised by the inflammatory reaction, a small quantity of anti-inflammatory agent such as dexamethasone can be released from the devices (39).

As a stepping stone to the development of a fully functional artificial pancreas, one may consider the development of glucose sensors that can be implanted under the skin for continuous glucose monitoring or glucose monitoring at patience convenience without pricking the finger. Figure 4 shows a few possibilities of noninvasive glucose sensing. Subcutaneously implanted glucose sensor may be isolated from the body by fibrous capsule, but as long as the diffusion of glucose through the fibrous tissue membrane is characterized, the fibrous capsule may be used to secure and stabilize the glucose sensor (Fig. 4-I). In glucose sensing, one of the most promising approaches is the lifetime-based fluorescence resonance energy transfer between fluorescent probe-labeled dextran and concanavalin A (Con-A) as shown in Fig. 4-II.A (40,41). The problem of this approach, however, is that the instrument is prohibitively expensive. Alternatively, optical density changes at the visible wavelength can be used for glucose sensing (Fig. 4-II.B), since sol-gel phase-reversible hydrogels can be made to respond to changes in glucose concentration between less than 1 mg/ml to higher than 4 mg/ml (42–44). Measuring the optical intensity may be easy to implement in a controlled laboratory environment, but it may not be practical in clinical applications since the intensity is affected by various factors. The problem of variable optical intensity may be overcome by using either multiple sensors responding to a gradient of glucose levels or a number of control sensors with certain optical density.

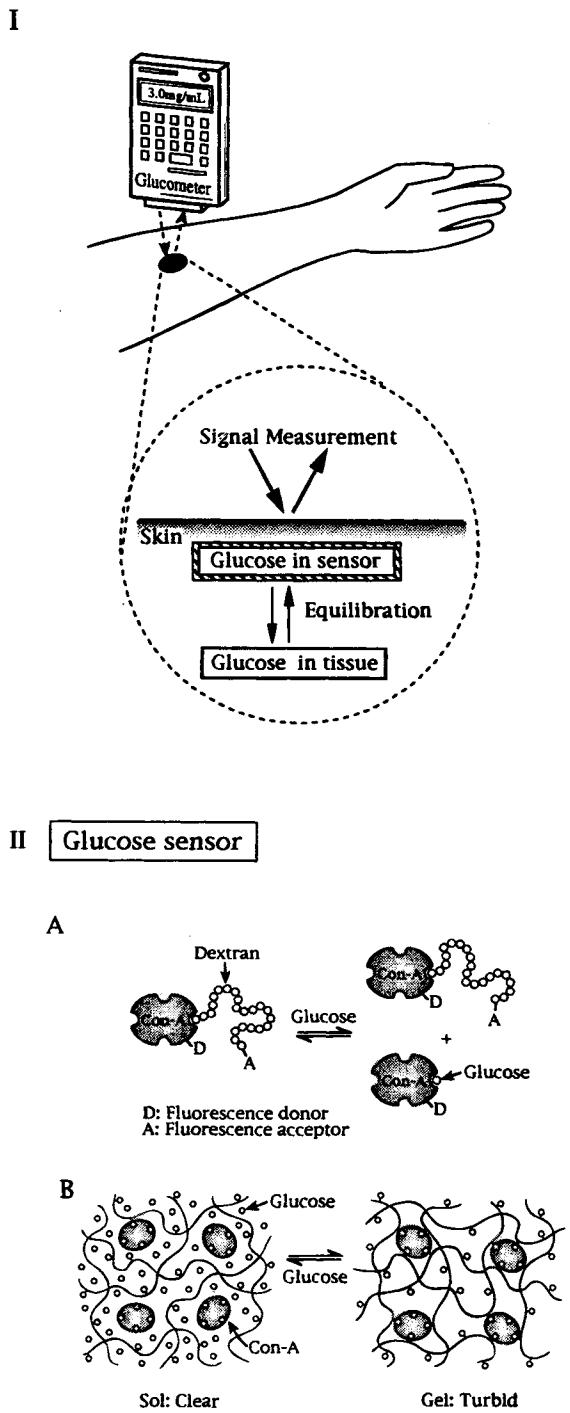

Fig. 4. Non-invasive detection of in vivo glucose levels using an implanted glucose sensor (I). The glucose sensor may generate signal for detection either by lifetime-based fluorescence resonance energy transfer between dextran and Con-A (II-A) or by simple optical density changes of glucose-sensitive phase-reversible hydrogels (II-B).

IMPLANTABLE BIOCOMPATIBLE MATERIALS

Only a handful of biomaterials have been developed as materials intended to be used specifically inside the human body. The majority of biomaterials were developed for industrial applications in mind, and some materials happened to be found useful as biomaterials. As mentioned above, in the absence of clear criteria to evaluate the biocompatibility, many materials were claimed to be biocompatible without proper testing. Silicone rubber is a case in point. For sometime, silicone rubber was believed to be totally biocompatible. Clearly it is necessary to reevaluate the biocompatibility of the existing biomaterials, do more research on improving the biocompatibility of current biomaterials and develop a new generation of biomaterials.

Efforts have been made to develop new biomaterials from scratch. Many polymers, such as polyanhydrides (45), poly(ortho esters) (46), pseudopoly(amino acids) (47), crosslinked polypeptide matrices (48), protein polymers (49), polyphosphates (50), were synthesized as implantable biomaterials from the beginning. For this reason, all the toxicity and other biocompatibility problems were considered during development, and as a result, they tend to have much improved biocompatibility. One of the main advantages of these biomaterials is that they are degradable and the degradation products are the same as naturally occurring products in the body or non-toxic at all. Some polymers such as protein polymers are currently made by using microorganisms and such polymers are expected to be more biocompatible. Undoubtedly, the most biocompatible materials are those found in the body. If we can understand how the biological materials are synthesized, they can be simulated by synthetic systems. The study of biological structures, their functions, and their synthetic pathways is known as biomimetics. The knowledge obtained from biomimetics will allow us to fabricate biocompatible materials from components found in nature rather than from synthetic components (51). This will be a quantum leap from our current practice of fabricating biomaterials.

One of the physical forms of biomaterials known to be biocompatible is hydrogel. Hydrogel is a three dimensional network of hydrophilic polymers crosslinked by chemical or physical interactions. Hydrogels have several properties that make them biocompatible as listed in Table I. Hydrogels swell in water by the same reason that an analogous linear polymer dissolves in water to form an ordinary polymer solution. Due to the hydrophilic nature, polymer chains at the surface of moderately crosslinked hydrogels are highly mobile, and this property is believed to simulate some hydrodynamic properties of cell surfaces and contribute to the prevention of protein adsorption and cell adhesion (52,53). The hydrophilic nature of the hydrogel surface also results in a very low interfacial tension with surrounding biological fluids and tissue, which minimizes the driving force for protein adsorption and cell adhesion. It, in turn, leads to a very low adverse interaction of the gel surface with the aqueous biological environment (54). Although hydrogels can sustain reversible deformations without rupture to a certain extent, they are generally weak after swelling. The increase in crosslinking density would result in hydrogels with higher mechanical strength, but other useful properties will be affected. Thus, hydrogels are usually grafted on the surface of solid biomaterials with good mechanical properties by covalent bonding. The soft, elastic and pliable property of hydrogels is known to minimize the mechanical and frictional irritation to surrounding tissues and thus reduce reactive proliferation of the fibrous tissue (55,56). Because of better biocompatible properties than other rigid biomaterials, various natural and synthetic hydrogels have been used to prepare implantable drug delivery systems, especially hybrid artificial pancreas (57,58). It is certainly challenging but possible to make composite of hydrogels and other form of biomaterials to combine the desirable properties of both materials.

Table I. General Properties of Hydrogels

1. Swelling in water
2. High chain mobility at hydrogel surfaces
3. Low interfacial tension
4. Elasticity
5. Low friction surface (Slipperiness)

SUMMARY

One of the main problems in the development of long-term implantable drug delivery systems is the lack of biocompatibility of most implantable materials. The issue of biocompatibility is huge and can be solved only by the concerted multi-disciplinary efforts. In the absence of truly biocompatible materials, the long-term implantable drug delivery and other biomedical devices will sooner or later face the biocompatibility problems, which may lead to the termination of the otherwise useful products. Advances in drug delivery technology for implantable drug delivery devices have to be accompanied by the advances in biocompatibility of the materials used in those devices.

ACKNOWLEDGMENTS

This study was supported in part by National Institute of Health through grant HL 39081.

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