Preparation of New Biomedical Materials and their Application in Clinics

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SUMMARY: Biomaterials - tissues interaction is important to study in biomaterials science. The information is indispensable to make medical devises and artificial organs and to predict their performance. It is also very useful to consider a hypothesis to design new biomaterials. New materials have brought big progress in the society as we know. There are few biomaterials specially designed to use in biomedical fields. The most important effort must be preparation of biocompatible materials, that must be essential to develop new type high performance devices and artificial organs. Preparation of new dental biomaterials used in bonding of prostheses to dentinal tissues that require fundamental change in modern dentistry and a new methacrylate, MPC, to develop promising several kinds of biomaterials with unusually excellent biocompatibility and functions are going to present. Topics in tissue engineering are also discussed.

Introduction

Biomedical materials are very important today in polymer science and technology. Many polymers have widely been used in medical fields directly and/or indirectly. Unfortunately, they are mainly conventional products, not specially prepared for biomedical application. The most important factor in biomaterials is biocompatibility. It has several meanings. Before discussing biocompatibility, non-toxicity to our body must be guaranteed. Some believe non-toxicity is same as biocompatibility. The preparation of biocompatible biomaterials is a key step. In artificial kidney devices, blood shunts are required to transfer blood into a hemodialyzer for purification. Infection or clotting at the interface between skin or blood vessels and shunts has fostered the use of fistulas into which needle insertion is made. Artificial heart must be connected with arteries and veins. Interfaces between artificial materials and tissue or blood have always been troublesome. They are clotting, infection and rejection, etc. Unfortunately we have not had reliable ideas for solving these problems.

Application of biomaterials

There must be described many biomaterials used in disposable and implantable medical devices. Moreover, each of them possesses their own unique problems to be resolved.

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Fig. 1 represents where biomaterials are used as artificial organs to support defects of our body. Several medical devises are widely used for medical treatments as shown in Table 1. Most of their raw materials are conventional commercialized polymers. They are plasticized polyvinyl chloride, polypropylene, polyester, cellulose, polysulfone, polyurethanes, etc.

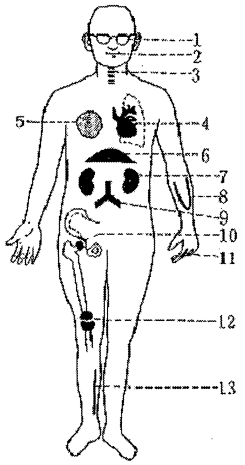

Fig. 1: Biomaterials used in artificial organs

No.	Artificial organs	Biomaterial
1	glasses contact lens intraocular lens	CR-39,MR-6,PMMA PMMA, PHEMA, MPC polymer PMMA
2	resin teeth, denture filling material	PMMA methacrylates & fillers
3	esophageal prosthesis	polyethylene/natural rubber
4	artificial heart valve substitute pacemaker membrane oxygenator	segmented polyurethanes carbon coated titanium, gluteraldehyde-preseved polyurethane porous polypropylene, silicone (extracorporal)
5	mammary prosthesis	silicone
6	liver assist device	coated charcoal, porous polymer-beads
7	hemodialyzer	cellulose, cellulose acetate, EVAL, PMMA, polysulfone
8	shunt	silicone/PTFE
9	vascular graft	polyester (knit), PTFE
10	artificial hip joint	metal alloys/UHMWPE
11	artificial finger joint	silicone
12	artificial knee joint	metal alloys/UHMWPE
13	bone substitute	hydroxyapatite, alumina, titanium alloy

Table 1. Products of biomedical devises in Japan (1996)

Device	Product (pieces x 10^4)	Biomaterial
disposable needle	279 198	stainless steel
disposable syringe	207 428	polypropylene (PP)
disposable catheter and circuit		
digestive, respiratory, ureteral	8 296	plasticized PVC
vessel	7 765	plasticized PVC, silicone polyurethane
catheter for hemodialysis	3 787	PTFE
blood taking set	66 270	silicone, plasticized PVC
blood bag	753	plasticized PVC
blood infusion set	1 059	plasticized PVC
transfusion solution set	60 602	plasticized PVC
extracoporeal circuit	4 242	plasticized PVC
hollow fiber hemodialyzer	4 435	cellulose, cellulose acetate, polysulfone, PMMA, EVAL
artificial joint	12.2 (import 90 %)	polycarbonate (housing) metal
	3.3 (import 5 %)	ceramics
intraocular lens	75	PMMA
membrane oxygenator	15	porous PP, silicone

They must be sterilized either by heat, steam, chemicals or irradiation with UV light or γ-ray. Before making medical devices commercially available, the approval must be taken from the regulatory agency, the FDA , the Ministry of Public Welfare, etc., and

they have to be produced following approved processes exactly.

There are two major classes of tissue, hard and soft, in the body. When ideal biocompatible materials is implanted, the molecules of the implant and those of the host tissues may mix homogeneously at the interface as in a blend polymer. This kind of biocompatible polymer has been sought for a long time. The hard tissues could divide into two, one is tooth that does not regenerate and the other is bone. Connection of biomaterials with tooth could be possible by developing good adhesives, as the tissue could not fill the space. Fortunately, in the case of bone, the space could be filled by newly formed bone when the materials do not give adverse effect on the regeneration. Connection of polymers to soft tissues is very difficult and we have to challenge to provide good resolution. Such biomaterials that could encourage tissue- or cell-growth and accept their invasion into them could be a candidate. Examination of soft tissue compatible materials is particularly difficult because of differences in mechanical properties between implants and the tissues. It is very hard to distinguish the lack of compatibility from mechanical failure at the interface when the implant ends in failure. Stress concentration problems at implant interface would be severe in cases of soft tissue biocompatibility. We have been working hard to prepare good blood compatible materials to support artificial heart programs. Unfortunately, they became available without development of new blood compatible materials. These explanations could be illustrated as Fig. 2.

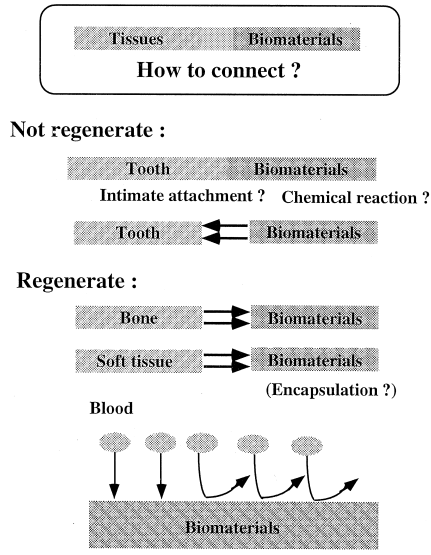

Fig. 2 : How to connect tissues and biomaterials

Dental polymers[1)]

Dental hard tissues do not regenerate. When they get defect, we have to use biomaterials to restore the function and esthetics. So it has been believed that dental biomaterials

could support development of dental treatments for long time. And dentists try to replace natural tissues with artificial materials. But enamel is much more superior to any artificial materials. They should have considered properties and function of enamel itself more carefully. Once burs remove enamel for a dental treatment, dentin and pulp are exposed to several stimuli. And it is very difficult for them to survive longer that could be modern dental treatments. It resulted in promoting loss of tissues but they believed they treated tooth to recover the defects.

It was hypothesized that when adhesive technology could be introduced, they could improve dental treatments and better clinical results could be expected. This was not bad idea but introduction of conventional adhesive technology in dentistry was not successful. We had to think about the bonding substrate being a natural tissue, not artificial surfaces. The important point was how to get adhesion to dental hard tissues, kind of living tissues. Connection of biomaterials with natural tissues is essential in biomaterials field but there is not reliable bonding mechanism available even today except bonding to tooth substrates. Nakabayashi found in 1982 that hybridization of dental hard tissues could unite dentin with polymers (see Fig. 2).

Bonding to dentin is taken place when the tissue surface has improved to have good affinity with artificial materials such as acrylic polymers. Then we could bond acrylic polymers to the modified dentin surface. Generally, soft tissues do not accept low molecular weight man-made compounds and must be irritated by their impregnation. But, dental hard tissues are not so active and could permit monomer impregnation. Then, we could polymerize the monomer in situ and the hybridized dentin, a molecular mixture of dentinal substances including collagen fibrils and polymer chains, could be prepared. New methacrylates, which could promote monomer diffusion into dentin, were synthesized as shown in Fig. 3. They have both hydrophilic and hydrophobic group in the molecule. It means they have good affinity with dentinal hard tissues as the

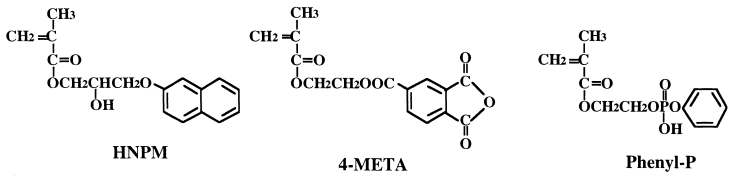

Fig. 3 : Hydrophobic and hydrophilic methacrylates for bonding agents to tooth substrates

tissue accepts their impregnation. We could say they are biocompatible methacrylates.

Dentin is mainly composed of hydroxyapatite that is demineralized by acids and collagen fibrils that are degraded by sodium hypochlorite. Acrylic polymers are stable against both acids and sodium hypochlorite in the same condition. Then, we could differentiate three of them even when they are mixed at molecular level in the hybridized dentin by comparison of morphological changes of polished, demineralized and then proteolytic-degraded surfaces with SEM examination after soaking samples in 6 mol/L HCl for 30 sec and then in 1 % NaOCl for 10, 30 and/or 60 min. The good hybridized dentin could resist well against both acidic and proteolytic attack. The chemical reactions must be akin to those of caries formation. This means the hybridized dentin could protect dentinal caries that has been impossible before in dentistry.

Usually dentin requires epoxy resin embedding before ultra-thin cross-sectioning. It reinforces the substrate. Epoxy embedding is a kind of hybridization of dentin with the epoxy resin. When we could prepare ultra-thin cross-section directly from the hybridized dentin with acrylic polymers (adhesive resins), we could conclude the hybridization was carried out well. It also suggests that the bonded dentin specimens could well resist shear stress loaded by cutting instrument. The hydroxyapatite crystallites in the hybridized dentin (H in Fig. 4) could resist against HCl demineralization. This suggests that hybridized dentin is an impermeable membrane created in the subsurface of dentin that could protect pulp from invasion of several stimuli. We have not had such excellent biomaterials before.

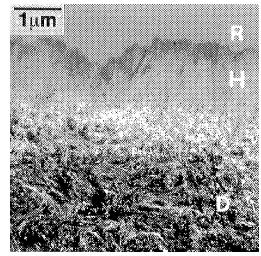

Fig. 4 : TEM picture of a resin-dentin bond created *in vivo*. The hybrid layer (H) appears to be well infiltrated with 4-META/MMA-TBB resin (R). d: Mineralized dentin.

Development of MPC surfaces for biomedical application[2)]

Improvement of blood compatibility has been top interest for long time but we do not have reliable materials even today. Hydrophilic surfaces covered with hydrophilic moieties like polyethylene glycol, heparinized surfaces and poly (styrene-block-HEMA) were promising surface. It was hypothesized that polymers having good affinity with phospholipids could adsorb them on the surface and might show new interesting properties as biomaterials. Phosphorylcholine is a major phospholipid in many cells and tissues. And 2-methacryloyloxyethyl phosphorylcholine (MPC, Fig. 5) was prepared. It was found that MPC copolymers have several functions good for biomaterials, such as long term blood compatibility (Fig. 6)[3)], inhibition of proteins adsorption and increasing their stability, good permeability for mass transport, transparent hydrogel and good to keep surface moist, etc. MPC can copolymerize with many conventional monomers and it is easy to prepare desired biomaterials with multi-characteristics. Modification of fabricated devises is also possible (Fig. 6). The most interesting points were that copolymers accumulate the phospholipid on the surface and the accumulated could construct biomembrane-like surface, which possesses same melting point as the liposome. It is a kind of biomimetic membrane surface (Fig. 7).

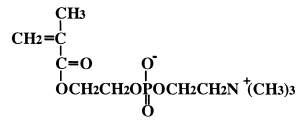

Fig. 5 : MPC

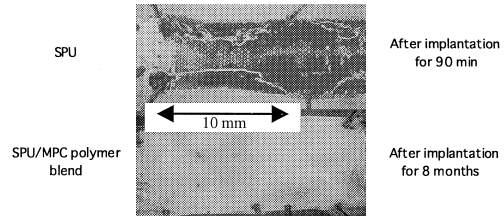

Fig.6 : Optical microscopic picture of small diameter blood vessels.

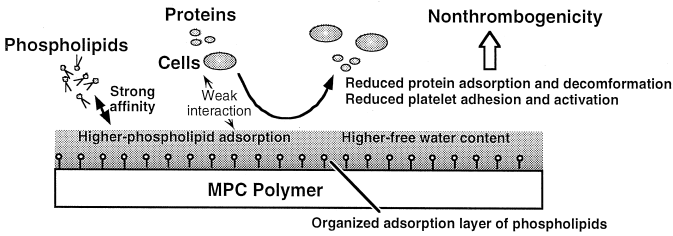

Fig.7 : Illustration of biomimetic membrane on MPC polymer surface

MPC is useful in contact lenses and their care, hemodialysis and oxygenator membranes effective even absence of anticoagulants, long lasting glucose monitoring biosensors (Fig. 8) , surface coatings for several catheters and devises, prevention of protein accumulation, lubrication, carriers for drug delivery systems and increasing stability of enzymes, etc.

Biomaterials and non-invasive surgery

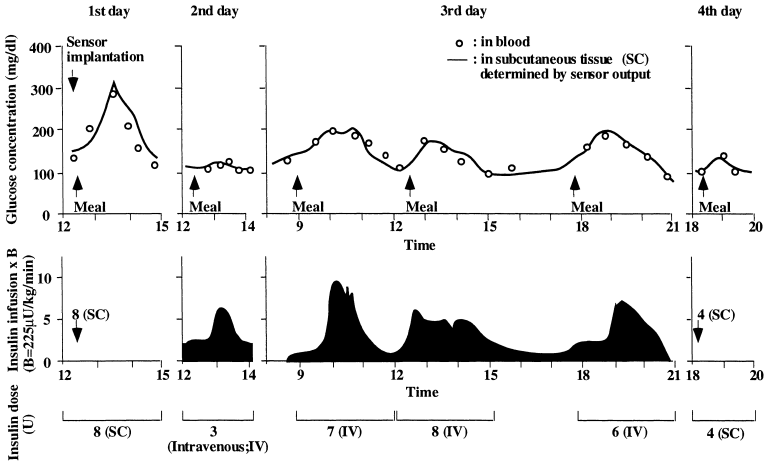

Fig. 8 : Continuous monitoring of subcutaneous tissue glucose concentrations and blood glucose regulation in an insulin requiring NIDDM patient with a ferrocene-mediated needle-type glucose sensor covered with MPC polymer membrane.

Recently, less-invasive surgery is required in many cases and biomaterials could contribute on the developments. It could improve patient quality of life very much. Using several new functional catheters such as balloon catheters could develop new surgical technology.

Biomaterials and tissue engineering

Tissue engineering technology is very important for biomaterials field to develop bioartificial organs. Preparation of tissue reconstruction would be possible by combining gene-technology. An artificial skin could be prepared by this technology

using the patient skin elements. Small diameter vascular grafts are fabricated also. It has been difficult to prepare the graft out of biomaterials as thrombosis occludes easily the small open space where blood flows before neointima could cover the surface. Hybridization of small vascular graft with endothelial cells, which secrete heparin, is promising way (Fig. 9)[4].

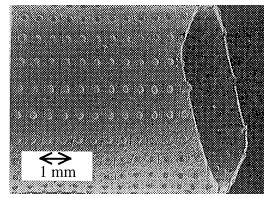

Fig. 9 : Gelatin coated polyurethane substrate with pores to prepare small diameter vascular graft by tissue engineering.

Another important targets must be artificial organs that require solutes transport mechanism. Typical examples are hepatic and pancreatic assist devices. In these cases, a combination of suitable biomaterials with tissues or cells such as hepatic or islet cells could afford good resolution. We could call them bioartificial organs (devices) or hybrid artificial organs. Oxygen, carbon dioxide, nutrients and cell products must be transported through the biomaterials. We have to make research how to prepare three-dimensional matrix out of biomaterials that make tissues or cells cultivation possible. Vascularization between cells and biomaterials are encouraged for their transportation. Their immunologic interactions with patients are also considered. In this sense, we have to develop new multifunctional and high performance biomaterials before tissue engineering possible.

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