

**Invited Paper****RADIATION PRODUCED BIOMATERIALS**

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Lodz, Poland**Abstract**

Medical advances that have prolonged the average life span have generated increased need for new materials that can be used as tissue and organ replacements, drug delivery systems and/or components of devices related to therapy and diagnosis. The first man-made plastic used as surgical implant was celluloid, applied for cranial defect repair. However, the first users applied commercial materials with no regard for their purity, biostability and post-operative interaction with the organism. Thus, these materials evoked a strong tissue reaction and were unacceptable. The first polymer which gained acceptance for man-made plastic was poly(methyl methacrylate). But the first polymer of choice, precursor of the broad class of materials known today as hydrogels, was poly(hydroxyethyl methacrylate) synthesized in the fifties by Wichterle and Lim. HEMA and its various combinations with other, both hydrophilic and hydrophobic, polymers are till now the most often used hydrogels for medical purposes. In the early fifties, the pioneers of the radiation chemistry of polymers began some experiments with radiation crosslinking, also with hydrophilic polymers. However, hydrogels were analyzed mainly from the point of view of phenomena associated with mechanism of reactions, topology of network, and relations between radiation parameters of the processes. Fundamental monographs on radiation polymer physics and chemistry written by Charlesby (1960) and Chapiro (1962) proceed from this time. The noticeable interest in application of radiation to obtain hydrogels for biomedical purposes began in the late sixties as a result of the papers and patents published by Japanese and American scientists. Among others, the team of the Takasaki Radiation Chemistry Research Establishment headed by Kaetsu as well as Hoffman and his colleagues from the Center of Bioengineering, University of Washington have created the base for spreading interest in the field of biomaterials formed by means of radiation technique. Immobilization of biologically active species in hydrogel matrices, their use as drug delivery systems and enzyme traps as well as modification of material surfaces to improve their biocompatibility and ability to bond antigens and antibodies have been the main subject of their investigations. The rising interest in the field of application of radiation to bioengineering was also recognized by the International Atomic Energy, which has initiated the international programs relating to those studies. In this lectures some directions of investigations on the formation of hydrogels and their applications to biomedical purposes have been specified. Also, some examples of commercialized products being produced by means of radiation technique have been presented.

BIOMATERIALS AND BIOCOMPATIBILITY

Biomaterials is defined as any substance (other than a drug) or combination of substances, synthetic or natural origin, which can be used for any period of time, as a whole or as a part of a system which treats, augments, or replaces any tissue, organ, or function of the body. *Device* was defined by the 1976 amendment to the Food, Drug, and Cosmetic Act to mean: „an instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article, including any component, part, or accessory, which is... intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, in man or other animals,... and which does not achieve any of its principal intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its principal intended purposes”

Virtually every individual will have contact with biomaterials at some time during his or her life. This contact may occur in several ways:

- permanent implantation, e.g., heart valves, total joint replacement, dental restoration, intraocular lenses;
- long-term application, e.g., fracture fixation devices, contact lenses, removable dental prostheses, hemodialysis systems;
- transient application, e.g., needles for vaccination or phlebotomy, wound healing dressings, cardiopulmonary bypass and cardiac assist systems.

In evaluating safety and effectiveness of biomaterials, the material cannot be divorced from the device. Effectiveness must be considered in relation to the specific device and the indications for its use.

There are three general situations in which biomaterials are used: to sustain life or limb viability; to restore or improve function; to restore or improve contour.

Most cardiovascular and neurosurgical implants are in the first category, e.g., cardiac valves, vascular grafts, pacemakers, and hydrocephalus shunts. These implants have allowed major advances in treatment, and, although significant improvements still can be made, they are generally effective.

The second category includes biomaterials intended to restore function, such as joint replacement, fracture fixation devices, and dental implants. The success rates vary significantly in this category, ranging from excellent results in total hip replacement to lesser success rates in other joints. The biomaterials used in these devices have been improved through an increased understanding of the relevant properties, and are a key to further progress.

Facial reconstruction and breast augmentation and reconstruction are procedures representative of the third category (restore or improve contour). Even though these types of devices are not employed in life-threatening situations, they play an important role in restoring and preserving psychological and social well-being. If used properly, they have a high degree of effectiveness.

In order to consider the safety of biomaterials, a balance of risk to benefit must be recognized. Biomaterials in devices used to maintain life can carry some degree of risk in terms of time to failure and still be considered relatively safe. On the other hand, devices used to restore function or contour must have a higher degree of safety to justify their use. Overall, currently used biomaterials have been found to be safe, causing little difficulty with local tissue reaction or systemic toxicity.

While functional aspects of the performance of materials in the human body can be predicted with some reliability, forecasting the biological performance of implants is difficult. There is limited fundamental information on the subtle variations of the host response to the different classes, types and forms of materials, anatomic places, and duration of contact. Each

biomaterials considered for potential clinical application has unique chemical, physical, and mechanical properties. In addition, the surface and bulk properties may differ, yielding variations in host response and material response. Evaluating biological performance also depends on the unique biological characteristics of the anatomic site of implantation. All these factors suggest that the failure of material in a particular application may not preclude it from consideration in a different setting. Conversely, the success of a material in a given application does not guarantee its universal acceptance. In fact, the mechanism of failure in one application may provide the key to success in another application.

Design of replacement tissues or medical devices must include analysis of desired functions of a biomaterial and its localization into an organism, physiology of tissue and body fluids which will be in direct contact with man-made species, choice of constituent materials and technology to achieve product, fabrications of prototype and examination of its chemical, physical and mechanical properties, analysis of biocompatibility, end-use functioning of prototype in cell culture and in animal models, regulatory review and human testing. Such sequence of events force very closely collaboration between specialists from various domains of science. Any materials to be intended for contact with living organisms have to fulfil some specific requirements, which can be divided into four groups (Williams, 1992):

- (1) Non-toxicity; materials must not be pyrogenic and carcinogenic, must not evoke hemolysis, antigenic reactions and chronic inflammation;
- (2) Functionality; biomaterials should replace temporally or for life span the defective organs and tissues, heal wounds and targeted organs, correct and assist the malfunctioning system of the organism;
- (3) Sterilizability; they should be easy to sterilize by heat (autoclave) or ionizing radiation (the sterilization with toxic gases like formaldehyde or ethylene oxide because of some problems with residuals causing inflammation as well as environmental poisoning is expected to be limited).
- (4) Biocompatibility; the meanings of this term sometimes cause confusion - other properties of biomaterials are decisive in the case of vascular grafts and with respect to dressings or drug delivery systems. Nevertheless, there are some common requirements to be fulfilled. The biomaterials should adhere well to bones, teeth, soft tissues and undergo cell covering and, in general, evoke and minimal stress in the organism of the recipient. Minimal stress can be understood as non-causing of damage of host cells and tissues nor their hyperplasia or loss. In the long-term no calcification or encapsulation should occur. Also biomaterials, especially devoted to contact with blood, should not cause thrombus formation, complement activation and protein deposition.

With the estimation of thrombogenicity one should be very careful, because materials satisfying all the above mentioned requirements *in vitro* can be unacceptable *in vivo*. Using the chronic arterio-venous (AV) shunt systems for animal experiments *in vivo* Sefton (1993) indicated that low platelets deposition, which is observed *in vitro* can not be taken as evidence of blood compatibility. With PVA surface, both heparinized or not, he observed a dramatic drop in platelet count, indicate of platelet consumption and activation problems. He proposed a new definition of thrombogenicity, which consists of a thrombin production rate constant less than 10^{-4} cm/s, partially deposition and spreading of platelet on a surface, and low platelet consumption (or activation). Although blood compatibility is only a part of the general meaning of biocompatibility, Sefton's experiments and conclusions force a revision in the conventional point of view.

HYDROGEL BIOMATERIALS

Polymers seem to be today the largest group of materials used for biomedical purposes. They are used separately or/and in combination with other materials, especially of natural origin. The latter includes human tissues and cells as well as those taken from animals. The main areas of today's applications of hydrogel materials include:

Topical applications as wound dressings

The hydrogel materials are used in direct contact with living tissues. They prevent contamination of a wound by microorganisms from outside, inhibit the loss of body fluids, deliver oxygen to the wound, and generally accelerate healing processes. A commercially successful example of such a dressing is the hydrogel dressing known under the trade name HDR or AQUA-GEL and marketed mainly in the Central Europe. It is manufactured by means of radiation technology in the form of a thin swollen slide of hydrogel (Rosiak, 1991). It was announced that Nichban Co. Ltd of Japan begins commercial production of hydrogel dressings on the base of poly(vinyl alcohol) due to radiation-chemical technology developed at the Takasaki Radiation Chemistry Research Establishment (Yoshii et al., 1995; Makuuchi, 1977).

Hydrogels can also be utilized as sprays, emulsions, ointments and creams, with or without the addition of active compounds. All the above types of wound dressings and covers can act also as slow-release drug depots, or drugs can be administered through the hydrogels *in situ*.

Drug delivery systems

Such materials in the form of hydrogel matrices enable sustained and or controlled release of embedded medicines to body fluids after their implantation, injection or other introduction into the organism. Generally speaking there are two different concepts of such systems. The first one consists of releasing of small drug molecules as a result of hydrogel swelling. The second one consists of a gradual erosion of polymer matrix containing drug. In this case the diffusion of medicine into the surroundings is controlled by the rate of biodegradation. Sometimes, hydrogels are used as membrane encapsulating drugs, which allow the control of the rate of release of medicine by changing the degree of crosslinking and chemical composition of the hydrogel. Special cases of drug deposits are called "intelligent" or signal-responsive hydrogel. Small changes of the environment, e.g. pH, temperature, ion concentration, osmotic pressure, electric or magnetic field can cause huge changes of hydrogel properties and in this same way influence the rate of drug release. An example of the application of hydrogel technology is prostaglandin delivery system for the ripening of the cervix in women at full term in labour. The product constructed with poly(ethylene oxide) and prostaglandin E₂ has been granted a product license in the U.K. and Ireland and is marketed under the trade name Propress by Roussel (Graham, 1990). Another hydrogel system, with similar functions was developed in Poland using radiation technology and successfully passed clinical tests (Rosiak and Olejniczak, 1993).

Transdermal systems

Hydrogels are applied as the reservoir for biologically active species. The properties of skin and its interaction with the solutes as well as properties of the membrane usually placed between skin and drug container are the main factors controlling the delivery of a medicine. The first devices were developed for astronauts who become sick in space. The little patch containing scopolamine and designed to be placed behind the ear was commercialized under trade name Transderm-Scop. A number of other transdermal systems containing various

therapeutic agents are now available on the market, including glycerol trinitrate, clondine, estradiol/progesterone etc. An example of such systems are the devices for glaucoma patients, in which hydrogel strips or sacs containing pilocarpine are placed in the fornix of eye-lid. Such systems have been introduced in the market under the trade name Ocusert by Alza Corporation, U.S.A. Similar devices in form of thin foil fabricated using radiation technology have been also clinically tested (Czechowicz-Janicka *et al.*, 1992).

Dental applications

There are some two- and multicomponent denture base materials, containing HEMA or other hydrophilic polymers in form of a monomer or prepolymer of the jaw they are polymerized and/or crosslinked. In many cases these reactions are initiated by UV light delivered through a light guide. Some trials were undertaken to fabricate by radiation crosslinking the hydrogel dental material composed of poly(vinyl alcohol) and gelatin (Dybek *et al.*, 1992).

Injectable polymers

Injections of collagen have been used to fill and repair cosmetic defects by plastic surgeons. The drawback of this treatment consist in relatively fast collagen resorbition. Some hybrid types of materials were proposed, e.g. collagen and poly(vinyl alcohol) or specially crosslinked collagen (Guisti *et al.*, 1993). The latter belongs to the group of polymers which undergo crosslinking under action of ionizing radiation. Other promising application include the fabrication of microgels encapsulating the therapeutic species or being attached to them. After injection they can be sieved by part of the circulatory system. In addition, if such microparticles were equipped with antibodies, they might act as "magic bullets" targeting a receptor on the particular cell to be treated. The radiation technique allows to obtain microparticles of different shape and size (Kaetsu, 1985).

Implants

Poly(vinyl alcohol), the first hydrogel widely used for implantation, is still a subject of intensive investigations, especially by radiation chemists. For example, a new PVA material withstanding the autoclaving temperature for a few hours has been developed lately (Yoshii *et al.*, 1992). The hydrogels have been used as postenucleation balls, breast implants, for repair of cranial defects, noses and chins, cleft palates, as films for ear drum replacement, columels for tympanoplasty and for other special purposes. It seems that the use of hydrogels as cartilage replacement, tendon sheaths and aortic grafts will be soon commercialized.

Radiation grafting and/or similar methods, e.g. plasma treatments, give the opportunity to modify the surface properties of implants made from various materials toward better and permanent biocompatibility (Hoffman, 1990).

Ophthalmic applications

The market of contact lenses is completely dominated by products on the base of polyHEMA. There is also a great number of various hydrogel compositions, which contain as copolymers such compounds as poly(vinyl pyrrolidone), poly(vinyl alcohol), poly(methacrylic acid), chitosan, etc. Copolymerization is mainly used to improve polyHEMA'S mechanical properties and increase its oxygen permeability. Some contact lenses produced by radiation technology have been marketed in China (Carenza, 1992).

An intraocular lens (JOL) currently used in the treatment of cataracts is generally made of poly(methyl methacrylate). Despite the great number of implantations performed, in about 10% of cases the implanted JOL have had to be removed. Hydrogel intraocular lenses made of poly(vinyl alcohol) have been successfully clinically tested and seem to be the next generation of such implants; contrary to the former, they can be sterilized by ionizing radiation (Gen, 1989). Also the use of hydrogels as corneal implants, artificial vitreous humor, postenucleation implants and rods for retinal detachment surgery have been clinically tested with very good results.

Stimuli-responsive systems

Various polymer gels have been found to undergo reversible swelling changes in response to small changes in solvent composition, pH, temperature, intensity of light as well as magnetic and electric fields. The applications of such hydrogels in devices as actuators, artificial muscles, controlled molecular separators have been suggested (De Rossi *et al.*, 1991). There are many papers devoted to radiation and conventional synthesis of such systems, although their practical commercialization has not yet been achieved. The polymers used in these investigations include N-substitute polyacrylamide derivatives, polyacrylic and methacrylic acid derivatives, poly(vinyl alcohol) and their combinations. Especially often used are poly(N-isopropylacrylamide) and poly(vinyl methyl ether). Their aqueous solutions show thermoresponsible characteristics. Both polymers exhibit phase separation at lower critical solution temperature (LCST), which is equal to 32 and 38°C, respectively. The hydrogels swell below and shrink above those temperatures.

Hydrogel hybrid-type organs

Such devices designed for implantation consist of living cells surrounded by suitable membranes. The living metabolic cells, e.g. Langerhans islets, hyapatocytes, hepatoma (Hep G2) etc. placed in appropriate capsules secrete specific compounds in response to the changes in body fluids. The system works as a self-controlling bioreactor. From an engineering point of view, the point of the matter is the choice of suitable materials and preparation procedures to fabricate the membrane. It should satisfy the following requirements:

- it must be permeable to water, oxygen, nutrients as well as specific secretions of living cells;
- it must be impermeable to components of the immune system;
- it should be completely "invisible" for its environment to avoid deposition of proteins and biodegradation.

There are two methods used for obtaining such systems: microencapsulation and preparation of some special larger containers. The first consisted of the entrapment of a few cells inside of macrocapsules, which can be injected into the organism. The second consisted of construction of a massive container, whose walls are semi-permeable membranes. Such devices containing a great number of cells able to substitute damaged organs, can be implanted into the peritoneal cavity of a recipient. There is some information about a successful clinical application of devices prepared from poly(vinyl alcohol) as implanted artificial pancreas (Inoue *et al.*, 1992). The appropriate connection of some functions of living cells and the properties of man-made plastics will result, in the near future, in fabrication of hydrogel, hybrid-type artificial organs.

HYDROGEL DRESSINGS

Hydrogel dressings were originally invented as wound burn dressings (Rosiak *et al.*, 1989). Since their commercialization, first on the domestic, market under the trade name HDR and AQUA-GEL, they have also been used for medical treatment of other types of wounds and

illnesses. During laboratory studies on the properties of various hydrogels obtained by means of radiation technology, the inventors attention was mainly drawn to those close to the so-called "ideal" burn dressing. Although there is no general consensus, such a dressing should obviously fulfill the following requirements: absorb effectively the body fluids and prevent their loss, act as an efficient barrier against bacteria, adhere well to the wound but stronger to healthy skin, exhibit high elasticity but also some mechanical strength, show good transparency, enable the oxygen to penetrate through the volume of dressing to the wound surface, enable to control drug dosage, offer good handling (i.e. easy placement and replacement) without pain. In addition they should be sterile, easy to store, relatively cheap and generally accelerate healing. Such a set of sometimes opposite properties is almost impossible to achieve, so some equilibrium must be adjusted between them. However the commercial success of AQUA-GEL and much clinical evidence of their almost "miraculous" action in hopeless cases seems to confirm their excellent medical properties. Details about the medical properties can be found in the KIK-GEL Company *Pamphlet of QUA-GEL Dressings* (1993).

The hydrogel dressings are typical hydrogels governed by all the relations described in this article. They are composed of poly(vinyl pyrrolidone), poly(ethylene glycol), agar and water. In the end-use form they represent transparent sheets of thickness of a few millimeters, containing over 90% of water.

The first stage of technology consists in the preparation of aqueous solution of dressings components. After dissolving and mixing them at elevated temperature a homogeneous solution is formed. Then the moulds, which can also be used as final packages, are filled with the liquid components of the dressing. After solidification of the solution it is cut into pieces of desired size and packed in the proper final boxes, non permeable for air and microorganisms. In the final step of the production these semi-products are treated with ionizing radiation. The dose of 25 kGy is sufficient to sterilize the material and insures the formation of a permanent three-dimensional network consisting of polymer chains joined together by covalent bonds. Upon irradiation these semi-products turn into sterile hydrogel dressings. Due to radiation processing the product is fully sterile and durability of this property depends mainly on the quality of packing material. In spite of high content of water it retains the capacity for its further absorption (over 50% of its won weight). It ensures access of oxygen to the wound being healed and, if desirable, permeation of drugs. It sticks to healthy skin surrounding the wound but not to the new forming dermis. It protects the wound from contamination. Usually, 8 - 10 dressings allow for complete recovery. Besides healing burn wounds, AQUA-GEL are applied for the treatment of bedsores, thropic ulceration, in plastic surgery and to other skin damages, in which a humid medium is favorable. In addition, the production cost is very low, especially if an electron accelerator is used for irradiation.

This radiation technology presents some advantages in comparison with other chemical processes. There are no side-products such as wastes, sewage, fumes, and all chemicals used to manufacture the dressings are safe for humans (human-friendly). There is no need to maintain special sterile rooms, but the final product is fully sterile according to the GMP for radiation processes.

Due to the advantages of technology and the excellent properties of hydrogel dressings investigations on similar hydrogel products are currently being undertaken in other countries, e.g. Indonesia, China, Italy, Japan, Brazil, Malaysia, Iran.

HYDROGEL DEVICE FOR INDUCTION OF LABOUR

In the case of serious prolongation of pregnancy over natural time limit, or in the case when life of women and infant is in emergency, it is necessary to accelerate the beginning of labour. In such cases therapeutic induction of labour must be undertaken. The essential problem may be

unripened uterine cervix. Local induction of prostaglandins ($E_2, F_{2\alpha}$) is usually applied for acceleration of ripening. However, the known methods of introducing prostaglandin often cause negative side effects.

New therapeutic system for local release of prostaglandins have been elaborated by author's group (Rosiak and Olejniczak, 1993). It is based on hydrogel devices obtained by irradiation of N-vinylpyrrolidone. This device has the shape of thin rod of 8 mm diameter and 35 mm long, equipped with round head on the one side and surgical thread on the other side. The method of obtaining the therapeutical system is a three-stage procedure. It consists of: radiation polymerization and crosslinking of VP, incorporation of prostaglandin into hydrogel matrix and radiation sterilization of product. The polymerization is carried out in a special form which enables to obtain the desired shape of devices. Placing the surgical silk thread in the monomer prior to irradiation makes it possible to obtain the rod with strongly fixed thread. Incorporation of prostaglandin into the devices is carried out by placing this rod in appropriate solution of hormone. The swelled rod is dried and then packed into foil bags. The sterilization is carried out in cobalt source with the dose of 25 kGy.

After placing by physician the rod into vicinity of the uterine cervix, hydrogel absorbs the body fluids and begins to swell. The hormone gradually diffuses into surrounding environment. The local action of this device, besides prostaglandin release, is based also on the mechanical (expanding) action on the uterine cervix, because in course of swelling the dimensions of insert increases. In several hundred cases of labour being induced by means of these devices it has been found that these therapeutic systems are highly useful and safe for women in childbirth. The system may also be applied for abortion of dead fetuses.

CONCLUSIONS

Biomaterials have made an important contribution to modern health care. Their field of application, already much more extensive than generally appreciated by the public, is likely to expand even further as chronic, debilitating disease becomes a dominant concern in an aging population.

The implantation of biomaterials can result in some complications, but in most cases it is difficult to discern whether the problems are related to background disease, faulty implantation techniques, improper device design, or inadequate material properties. It is important that the source of such problems be identified, since failure related to implanted devices can threaten the life of the patient.

Continuing attention must be paid to the conditions under which biomaterials are prepared, evaluated, and implanted. Follow-up clinical studies constitute the best approach to the assessment of long-term safety and reliability. Device retrieval programs must be encouraged, together with the evaluation of materials that have been exposed to the body environment for prolonged periods.

The biomaterials field is in transition from cottage industry to an integrated research and product development effort. There is a distinct problem of technology transfer, with clinical application often considerably ahead of fundamental science. There is no uniform set of principles in biomaterials research. Rather, each participating discipline has been bringing its own precepts to bear on it an empirical fashion. In the future, an interdisciplinary approach should be taken to answer critical questions related to material compatibility with living tissues. One approach will be to bring together the various participants in the process of developing biomaterials (government, industry, academia, and the medical profession) in periodic scientific gatherings.

The growth potential of biomaterials is now recognized by observers of the biomedical industry. The UK-based Clinica Reports estimates that the world market for advanced biomaterial-based products will grow by 13,6% a year to reach a value of \$15.2 billion by the end of the century (Enany A. A., 1996). The main areas of future growth include:

- the controlled release of drugs;
- artificial skin, cartilage and other body parts;
- orthopaedic and wound care activities; and
- the cardiovascular and incontinence sectors.

Some segments of the biomaterial product market may grow faster than others. A study release last year by Frost&Sullivan projects a whopping 24% compound growth rate of absorbable and erodable biomaterial products, from \$466 million in 1994 to \$2.1 billion in 2001. This is sub-segment of the biomaterial products market that includes collagen, hyaluronic acid, gelatin products, and polymers such as polylactic acid.

Although the US market for biomaterials is dominated by big firms, such as DuPont or Depuy, many small firms have made inroads into the research-intensive, advanced materials segment of this market. A recent survey conducted by CorpTech of 17 of these firms found that 41% plan to expand their work force during 1997 by an average of 10,8%.

Human-friendly hydrogel systems, due to the rising trend to prolong life span and improve results of medical care, seem to be one of the most expected and required products. The unique advantages of radiation technology can be successfully utilized for the preparation of new commercial products, with designed functions which satisfy expectations of patients and physicians. Implants, drug delivery systems, artificial organs, and bioengineering generally are the domains in which radiation formed polymer materials begin to play an increasingly significant role. Despite a great number of investigations on radiation processes which allow clarification of some mechanisms of reactions and elaboration of some general rules governing those phenomena, there are still some doubts and need of further studies. Both fundamental and applied. Despite many patents devoted to radiation bioengineering there are continuing needs for new products and more sophisticated biomaterials. The use of ionizing radiation in the production of human-friendly products seems to be the most promising way to broaden the range of commercial applications of radiation technology.

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