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# REVIEW ON BIOCOMPATIBILITY STUDY OF POLYMER

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## ABSTRACT

Polymers are versatile materials and are used in many applications including pharmaceutical applications. Natural polymers, modified natural polymers, and synthetic polymers are used as excipients in the manufacture of cosmetics and systems for conventional and modified delivery of drugs, by altering the composition and physical properties such as molecular weight, polydispersity, crystallinity, and thermal transitions.Polymeric hydrogels are used as wound dressing material since these materials show advantages such as pain relief,exudates absorption,barrier to microorganisms, permeability, and others. Biocompatibility of polymers determined by in vitro assay of cytotoxicity in andvivo assay by using the contact test of irritability.

**KEYWORDS**: Biocompatibility, Biocompatibility testing, Surface properties for biocompatibility control, Surface modification tests.

## INTRODUCTION[1,2]

Polymers are versatile materials and are used in many applications including pharmaceutical applications. Natural polymers, modified natural polymers, and synthetic polymers are used as excipients in the manufacture of cosmetics and systems for conventional and modified delivery of drugs, by altering the composition and physical properties such as molecular weight, polydispersity, crystallinity, and thermal transitions.More recently, polymers have been developed that can modulate and deliver drugs to target areas. Biodegradable polymers,

bioadhesives, biomimetic materials, and responsive hydrogels have been included in pharmaceutical formulations.

The natural polymers have various advantages ascompare to synthetic polymers, namely biodegradability, biocompatibility,as most of them are present in the structural tissues of living organisms. Biocompatible polymers made into devices by coating to less the chance of rejection when inserted into the body. There have been significant developments in recent years in shape memory materials, tissue engineering, and coronary stents for use as biocompatible materials.Biomaterials are defined as materials that can be interfaced with biological systems in order to evaluate, treat, augment, or replace any tissue, organ, or function of the body.

Polymers are degrade by the two way, one is hydrolysis and second one idenzymatic activity and have a range of mechanical and physical properties that can be engineered to suit a particular application. Degradation characteristics depend on several parameters including their copolymer ratio, crystallinity, andmolecular structure.

## MEANING OF BIOCOMPATIBILITY: DEFINITIONS

**Defined as** any substance, except food and medications, that can be used for a length of time as part of a system that aims to treat or to replace any tissue, organ, or body function.

**Biocompatibility also defined as**

1. “ability of a biomaterial to perform its desired function with respect to a medical therapy, without eliciting any undesirable local or systemic effects in the recipient or beneficiary of that therapy, but generating the most appropriate beneficial cellular or tissue response to that specific situation, and optimizing the clinically relevant performance of that therapy.”
2. The relationship between a material and the organism so that neither produces undesirable effects.
3. Materials that can be interfaced with biological systems in order to evaluate, treat, augment, or replace any tissue, organ, or function of the body.
4. Includes that the material has to be nontoxic, non-allergenic, noncarcinogenic,and non-mutagenic,and that it does not influence the fertility of a given patient.

This term that encompasses many aspects of the material, including its physical, mechanical, and chemical properties, as well as potential cytotoxic, mutagenic, and allergenic effects, so that no significant injuries or toxic effects on the biological function of cells and individuals arise.

The utilization of polymeric materials such as hydrogels as biomaterials for wound care management has increased lately since these materials show advantages such as pain relief, exudates absorption, barrier to microorganisms, permeability to oxygen, transparency, mechanical behavior that can be adequate according to application,and general ability to deliver drugs in a controlled way.Moreover, different hydrogels have been proposed for use in bandages,burn wound dressings,adhesives, and other devices aiming to contact areas with skin lesions.[3,4,5]

## BIOCOMPATIBILITY TESTING

Tests are divided into 3 groups, corresponding to primary (level I), secondary (level II), and preclinical (level III) tests, which include analysis of the cytotoxicity and irritant potential of systemic toxicity in animals through intramuscular and subcutaneous implants, and usage tests by observation of tissue reactions after insertion of the material, for example, in human teeth.

Level I tests can be done for both in vitro and in vivo. In vitro tests assess the properties of the material directly in cultured cells that react to the effects of the experimental material. Many constituents judged initially as cytotoxic may be modified or have their use controlled by manufacturers to prevent cytotoxicity. In vivo tests are mainly based on the implantation of materials into subcutaneous or intramuscular areas in rats and rabbits to evaluate the tissue response to the implanted material after a period of observation.[6]

### *In vitro biocompatibility testing*[7,15]

It is necessary to consider aspects of biosecurity, such as other harmful effects andelimination of cytotoxicity of the material to be used.definition, the cytotoxicity of a material or device refers to the toxicological risks caused by a material or its extract in a cell culture. To perform these tests, mammalian cells, usually of mouse or human origin, obtained from a commercial supplier, are cultured in the laboratory in flasks using nutrient culture media. These cultured mammalian cells reproduce by cellular division and can be sub-cultured to produce multiple flasks of cells for use in evaluating the cytotoxicity of materials. For cytotoxicity tests in

vitro, primary cultures orpermanent cell lines are recommended. Although there are difficulties with isolation and maintenance, the primary cells are very important for biological assays because of their similarity to the original tissue.

Cytotoxicity tests are standardized method, sensitive and fast to determine the toxicity of a material. The presence in cultures of isolated cells and the absence of important physiological effect present in vivo systems, which help to protect cells within the body, produces a test with high sensitivity. Culture medium of mammalian cells is the preferred method for the extraction of substances that can be released from a material, because it is a physiological solution capable of extracting a wide range of chemical structures, not only those soluble in water.

Different types of cells are used for cytotoxicity tests such as cell lines - human and mouse queratinocytes, lymphocytes, fibroblasts, mouse odontoblast-like cells, mouse macrophages, rat submandibular salivary gland acinar cells and primary cell types - human lymphocytes, polymorphonuclear leukocytes and mixed leukocytes, mouse embryo cells, mouse macrophages and mouse blastocysts.

The various parameters and methods used in determining cytotoxicity can be grouped into the following categories of evaluation: assessment of cell damage by morphological means, measurement of cell damage; measurement of cell growth; measurement of specific aspects of cellular metabolism. There are several ways to produce results in each of these 4 categories. The investigator should be aware of the test categories and into which category a particular technique fits, so that comparisons can be made with other results on similar devices or materials at both the intra- and inter laboratory levels. Quantitative evaluation of cytotoxicity can be done using cell death, inhibition of cell growth, cellular proliferation and colony formation, cell number, amount of protein, enzyme released, vital dye release, vital dye reduction, or any other measurable parameters that can be quantified by objective means. The biochemical methods (DNA synthesis, protein synthesis, and ATP activity) demonstrated good agreement in toxicity ranking of the materials, regardless of which cell culture was used, and the cell cultures responded similarly for each method.Methods that measured the Polymerization 52 functional characteristics of cells (adhesion and phagocytosis) were highly sensitive but had low toxicity ranking agreement and reproducibility. Assays (defined as method and cell culture combinations) using cell lines were more reproducible than assays

using primary cell types. Significant differences in sensitivity were noted among the assay systems for particular material types.

***In vivo biocompatibility testing*** [16-18]

Level II tests are based on tissue assessment of animals that received implants subcutaneously and intramuscular injection of a material with potential to cause systemic toxicity by inhalation, skin irritation, among other responses. Dermal toxicity tests are important because of the large number of chemicals with which we have daily contact. When a material, product, or toxic component is identified, it can be replaced, diluted, or neutralized to reduce the level of toxicity.

Despite their high cost, controversy, and ponderous bureaucratic challenges, animal tests are critical for assessing the biological responses to a new material before it is used in humans. Many aspects of clinical biological responses cannot be modeled by in vitro tests. Animal tests offer evidence about these types of effects without putting humans at risk. Animal tests may be structured to mimic human clinical use to some degree, are commonly less expensive than human clinical trials, can be finished more quickly in many cases, and can be controlled to a greater degree. Animals may be exposed to materials or their degradation products with routes of administration or doses thatwould be unethical to consider in humans. Animal tests sometimes used to determine responses that are impossible to ethically test in humans and may be tested at many phases of life (for example, embryos or ‘children’) in a way that is not possible in humans.

Biocompatible materials cannot be genetically equivalent or influence inflammatory mediators causing systemic responses, tissue injury, teratogenic, including toxicity, or carcinogenic effects. Such materials must be free of agents that may cause allergic responses to individuals sensitive to these substances. After a material has successfully passed the tests for levels I and II, it should be tested in humans (level III test) to evaluate its performance and the favorable or unfavorable reactions that may present under normal clinical conditions.

## SURFACE PROPERTIES FOR BIOCOMPATIBILITY CONTROL

Factors that govern the biocompatibility of biomaterials are not completely understood. No single test is sufficient to characterize the material on the basis of the biocompatibility. Various types of tests are necessary to determine the degree of the biocompatibility. Therefore a range of in vitro and in vivo tests, which characterize the surface properties and

the chemical structure of the polymers that influence their biocompatibility have been developed and are routinely implanted.

Here, most important surface properties of the polymers are discussed which can be modified in order to gain the control over the degree of the biocompatibility.

**Surface morphology**

Surface morphology of biomaterials identifies the interactions occurring at the interface site of the host and biomaterial. Crystallinity is a major morphological characteristic of materials that influence host response. Moreover low dielectric constant, low refractive index, and high optical transparency along with good mechanical and thermal stability are the important properties required in bio-MEMS, blood-contact devices and cell culture substrates.

**Chemical structure and functional groups[19-22]**

Harmful response by the host, like damaged cells or irritants which cause inflammation and homogenization can be avoided by making the biomaterial attractive for endothelial cells (improved endothelialization). Similarly for various applications, proliferation and cell adhesion towards a particular host cell types are required. To making polymers surface attractive for the particular cell type, polymeric biomaterials surfaces are often functionalized through different modification techniques by trapping or dopping reactive substances on the surface. The chemical composition is therefore important to recognize the presence of externally introduced functional groups for particular applications and also to determine the presence of any toxic substance (element or compound) that may be present within the material.

**Interfacial free energy[22,23]**

For mechanicallyandbiologically stable solid (biomaterial)liquid (blood/extracellular fluid) interface a low solid–biological fluid interfacial free energy of the order 1–3 dyne cm21 is required. Although the interfacial free energy primarily depends upon the interface layer thickness, it also depend on certain variables such as temperature, friction, and pressure of the biological fluids. These variables in the biological environment are ever-changing within a specific range. This thermodynamic quantity contributes to the adsorption of blood components onto the guest biomaterial. The blood component adsorption thus can be control by interfacial free energy.

**Wettability**[24-28]

It is evident that polymeric surfaces possess quite low wettability. The wetting of a surface by a liquid is affected by the roughness of the surface. In practice it is shown that both the chemical properties (heterogeneity) and the physical properties (surface roughness, shape, and particle size) of the surface influence its wetting behavior. Wettability of the biomaterials can be optimized to limit the contact friction between the implantand thehost. Regulating the wettability influences the protein adsorption and biocontact properties. Wettability is also related to surface energy. Low surface energy polymers depict poor wettability. Good wettability is required in some biomaterials for deposition of functional groups onto the surface. Such modified polymers can be used as a substrate material used for cell cultures.

**Hydrophobicity**[29]

For biodegradable applications, biomaterials to be used should have increased hydrophobicity so that they may dissolve in water. For tissue repairing scaffolds, biodegradable biomaterials are preferred in research projects for special experiments. Such biomaterials are now employed in recent commercial applications. The differentiation and proliferation of cells can be biologically altered by control of the surface hydrophobicity and charge of culture substrates.

**Hydrophilicity**[30-32]

Protein fouling has been a major problem for biomaterials in general often making them nonbiocompatible. The aggregation of proteins results in their adsorption onto the surface of the biomaterials. Ultimately thrombus formation due to protein fouling causes not only resistance in the extracellular fluid flow but also the surface chemistry of the host alters. In membrane surfaces, increased hydrophilicity helps to suppress protein fouling.

**Cytotoxicity**

Toxic behavior investigation is neccessory in order to assess any material to be used in biomedical engineering applications. The cytotoxicity experiments determine whether the material depicts toxic behavior while in contact with the general or particular cell lines. The test is generally done in a laboratory using standard/relevant cell lines and the cells are seeded on the materials. As far as the experimental evaluation of biocompatibility is concerned, the cytotoxicity tests are widely cited as the primary assessment of biocompatibility.

## SURFACE MODIFICATION TESTS[33,34]

Surface modification to change a wide range of characteristics of surfaces is an expanding field enhancing the industries and researchers equally. Particularly for biomedical engineering applications the assorted mechanisms of host and biomaterial interaction require explicit surface characteristics in order to avoid any deleterious effects. Polymers as biomaterials in the healthcare industry is well established due to the ease in the production of versatile polymers which hold required physical and chemical properties. Because surface properties of polymers determine their biological performance during interaction with the host, biocompatibility control through surface modification is an inevitable step in the production process. Different surface and bulk properties are crucial for biomaterials in the biomedical engineering applications. It is however not possible to well define these properties during a single stage fabrication process. The common practice is to provide a special treatment following the fabrication of the biomaterials to modify surface properties to the desired level. Eventually decoupled bulk and surface properties are attained. A combination of two or more physical and/or chemical treatments can assure such modifications. In the following section a brief overview of plasma based and laser ablation based surface modification techniques used to control the degree of the biocompatibility are presented.

### 1. Plasma-enhanced chemical vapor deposition test

Plasma-enhanced chemical vapor deposition (PECVD) test is a chemical process in which gas vapors from plasma deposit on the surface of the sample being treated. Plasma deposition is quite often used in manufacturing of semiconductor devices particularly those with temperature sensitive structures. PECVD has vast applications ranging from semiconductor technology, molecular sieve membranes for gas separation and packaging barrier films. However surface modification by PECVD for biomedical engineering applications is limited to silicon based membranes and substrates, steel, and alloys. Polymer processing for biocompatibility control by PECVD is quite restricted due to non-uniformity and formation of by-products. Nevertheless a few studies demonstrated preparation of diamond-like carbon (DLC) coated films by PECVD with an improved degree of biocompatibility.

### 2. Reactive ion etching test

Reactive-ion etching (RIE) test is the main plasma etching technology used for fabrication of microstructures. The etching mechanism in RIE is a result of chemical etching which takes place due to chemical reaction between the sample (wafer or film) and gas atoms forming a

molecule to be removed from the substrate. Negligible amount of physical etching is also involved. RIE is primarily used in the semiconductor industry for the fabrication of the integrated circuits (IC). As RIE is typically used for pattern transfer, prominent applications in biomedical engineering can be found in the fabrication of membranes, microelectrode arrays (MEA), and micro electromechanical systems ( MEMS ) for biosensors and lab-on-a-chip (LOC). Such membranes minimized natural filtration system thus can be used for wide applications in biomedical engineering. Micro-patterns are introduced in poly (dimethylsiloxane) (PDMS) silicone elastomer using customized RIE technique for fabrication of elastic multielectrode array for surface stimulation of the spinal cord. However there are associated undesirable RIE effects which influence the micropatterning. Most prominent is the implantation of impurities during the chemical process of etching such as hydrogen diffusion. There is risk of pattern damage due to the presence of the energetic ions or radiation. Because of the chemical interactions loss of the doping agent which is aimed to be inserted into the sample is another major problem. Most undesirable factors can be eliminated or limited but post processing is required.

### 3. Plasma immersion ion implantation test[38-40]

Plasma immersion ion implantation test (PIII) is used to insert impurity into the substrate by extracting accelerated ions from the plasma and directing them towards the sample. PIII has been used to improve antibacterial properties of polymers. Polyvinyl chloride (PVC) which is one of the most produced plastic has been coated with triclosan and bronopol and doped with argon using plasma treatment. Improvement in antibacterial properties against S. aureus and E. coli is demonstrated by biocompatibility tests though such surface modification. Argon and oxygen immersed on surfaces of polycarbonate and polytetrafluoroethylene using PIII respectively. Oxygen enrichment result in hydrophocitiy of surface which gives higher affinity for human cell attachment. PIII used to treat polyethylene terephthalate surface by acetylene to control the degree of hemocompatibility with pronounced effect on bacteria adhesion. PIII can also be successfully employed for surface modification of the bio-implant alloys with the doping of nitrogen and phosphorus. Nevertheless in the long run, the antibacterial property introduced or enhanced by PIII is reduced significantly due to interactions in the biological world.

**4. Ultraviolet radiation surface modification test**[35-37]

UV modification test has been considered to control the degree of biocompatibility for various polymers. Heitz et al. irradiated polytetrafluoroethylene (PTFE) with UV light of a Xe2-excimer lamp at 172 nm wavelength. The polymer was treated in an ammonia atmosphere. Some samples were grafted with amino acid alanine after being treated by UV. It was observed in the study that UV irradiated PTFE foils depict higher optical absorbance, exhibit strong fluorescence and increased wettability. Consequently rat aortic smooth muscle cells (SMC), mouse fibroblasts (3T3 cells) and human umbilical vein endothelial cells adhere more to such UV irradiated polymer samples as compare to untreated samples and exhibit good proliferation. Gumpenberger from the same group performed further investigations on UV irradiated PTFE and observed formation of new chemical groups on treated polymer surfaces and demonstrated statistically higher proliferation rates and elevated adhesion on smooth muscle cells and fibroblasts. Prolonged process timings (up to 30 min UV irradiation) were used in these studies. Uchida et al. confirmed increased hydrophilicity of poly(ethylene terephthalate) (PET) film upon UV treatment. introducedmicroporosity in polyurethane (PU)-based vascular prosthesis through computer-aided excimer laser (KrF) ablation technique. This small caliber graft was expected to exhibit enhanced in vivo transmural tissue proliferation. This anticipation is further confirmed by the same group for polyurethane grafts. UV light was used to enhance the interaction between DNA molecules and the plasma polymer chains. Several other biocompatibility control studies through UV irradiation can be found elsewhere. Surface functionalization of amorphous carbon films can be used for various biomedical engineering applications. UV laser assisted micro-structuring of hydrogenated amorphous carbon thin films result in formation of carboxyl groups at the surface which leads to improved wettability of water, polar and dispersive liquids. It is quite worthy to note that rather than polymers, UV micropatterning is more suitable for control of the degree of biocompatibility of metallic alloys.

## CONCLUSION

For the biocompatibility of a material to be proved, it must be subjected to various studies ranging from in vitro assays to clinical trials and involving distinct areas such as pharmaceutics, biology, chemistry, and toxicology. The use of standardized tests allows better comparison between the results of different studies to clarify the behavior of the materials and their safety in relation to cells and tissues.Despite being a multi-billion dollar industry, control over the degree of biocompatibility is still an important research and

development challenge facing the biomaterials research and industrial communities. To overcome this challenge it is required that the processes which occur at the interface site between the biomaterial and the host do not induce any deleterious effects such as chronic inflammatory response or formation of unusual tissues. Therefore the importance of biomaterials with appropriate surface properties is evident. At the same time, specific bulk properties are essential, particularly mechanical properties for biomaterials in order to perform particular tasks in the biological world.

However there is no surface modification technique unanimously accepted to control the degree of the biocompatibility for polymers. Plasma and laser ablation techniques have been employed for surface modification of polymers however they induce alterations in bulk material due to deep penetration in to the material. To avoid such problems, extreme ultraviolet (EUV) radiation has been successfully employed for surface modifications with a few polymer types.

Only a combination of various in vitro and in vivo tests can provide an overview of the interaction of biomaterials with the host.

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