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Review Article

BIOMEDICAL POLYMERS – CLASSIFICATION, APPLICATIONS AND STRATEGIES FOR IMPROVEMENT

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Abstract

Biomedical polymers are one of the most important biomaterials for research and clinical applications. They are an exceptional group of materials designed to work harmoniously inside the human body and constitute a very important part of artificial organ generation and replacement, intended to fit the body. Biomedical polymers have opened a new dimension in the field of research and technology. The utilization of biomedical polymers as biomaterials has influenced the progress of modern medicines. This study highlights the importance of Biomedical Polymers in the field of medical sciences. The demand and need for biomedical polymers are growing largely and also it supports the diverse research system. This study aims to provide in-depth about them and to find solutions for the associated problems.

Keywords: Chemistry; fate; *PEGylation*; Polymer drug conjugates; Biocompatibility.

Introduction

Biomedical polymers are a specific group of substances that are designed to work within our body in various forms, for example- implants, artificial organs, and various other devices [1]. The human body is composed of various types of cells, tissues, and body fluids that can exist in a wide range of pH, temperature, and physiological conditions, therefore biomedical polymers must be manufactured, keeping in mind, their stability and safety inside the human body. Biomedical Polymers are one of the most important biomaterials for research and clinical applications. It is convenient to alter their chemical, physical, and biological properties for targeted delivery [2]. Due to this versatile nature, they are seen to replace a wide variety of substances such as ceramics or metals in the industry. The demand and need for biomedical polymers are growing largely and also it supports the diverse research system. The main growth in the field of biomedical polymers has been seen in the last few decades mainly in chemical and physical sciences (including biomedical engineering in multidisciplinary stages). Biomedical polymers are also known as biodegradable polymers and they are mainly divided into two classes' i.e. natural and synthetic polymer. Exploring the areas of biomedical polymers has become the need of time. Because of their biocompatibility and chemically tunable properties, biomedical polymers have become excellent materials for biomedical applications [3].

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Classification of Biomedical Polymers

Biomedical polymers can be of several types, and their classification can be done in several ways [4].

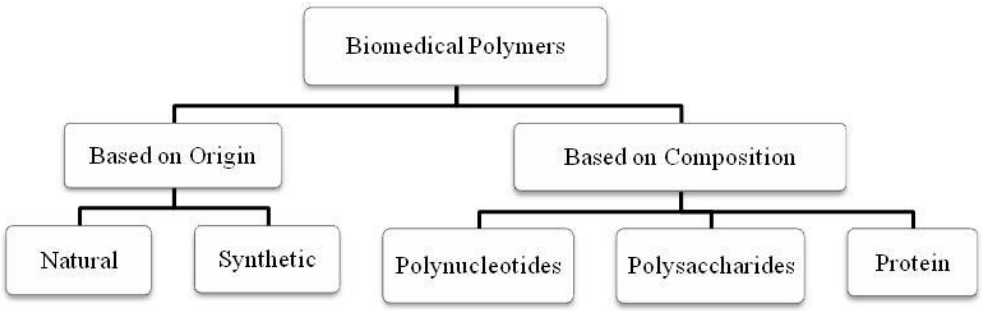

Fig. 1: Classification based on the origin of biomedical polymers

Based on origin, they can be of two different types:

1. Natural Biomedical Polymers: NBPs are the polymers that occur naturally. They are isolated from natural substances and purified for use in the biomedical sector, which includes drug delivery to targeted sites, application on wounds, and also in tissue engineering [5]. They are used safely for biological and medical applications. Examples of some natural polymers are cellulose, chitosan, hyaluronic acid, sulfates of chondroitin, gelatin, collagen, proteins, and DNA [6]. The properties of natural biopolymers cannot be controlled in their native form and hence modification is usually required. However, it is seen that modification is often difficult, and on extensive modifications, they come under a completely separate category known as semi-synthetic polymers. Production on a large scale can be difficult [7].
2. Synthetic Biopolymers: SBPs are synthesized chemically. They are designed specifically for particular usage such as in implants, tissue engineering, prosthetics, bimolecular delivery, and wound dressing [8]. Examples of SBPs are PEG (Polyethylene glycol), PLGA (copolymer of Polylactic acid and Polyglycolic acid) [9], PET (Polyethylene terephthalate), etc.

Classification based on the composition of biomedical polymers*:* Based on composition, biomedical polymers can be classified into the following types.

1. Polynucleotide: Polynucleotides are polymer chains of high molecular mass. They are composed of nitrogenous bases, a pentose sugar, and a phosphate moiety [10]. DNA studies can be performed by observing the polynucleotide sequences, especially the single-stranded molecules. They are bound through covalent bonds and are a combination of various nucleotide monomers. Ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) are the natural polymers that are found in our bodies [11].
2. Polysaccharide: Polysaccharide biomedical polymers are macromolecules that are derived from renewable sources, and are highly efficient. They have a variety of functions; they act as

cross-linkers, thickeners, and adsorptive materials. They are also used as fluid additives, agents for plugging, and correctors of fluid properties affecting their performance and expense [12]. They play a very important role in the petroleum industry, especially in their recovery cases. Their performance is a function of their physicochemical characteristics and the environment. They are prepared under highly controlled conditions. Their market is found to reach 10 billion USD by the year 2021. Some examples include Cellulose, Chitin, etc.

3. Protein: Proteins are fabricated to be used as a versatile biomedical polymer for drug delivery. They occur naturally, plus they have many advantages - mucus-adhesiveness, less toxicity, biodegradable and biocompatible. The end products can be readily eliminated from the body. There are also some challenges regarding commercial utilities. Immune and inflammatory responses are triggered due to the presence of cross-linkers in proteins. Some examples include haemoglobin, gelatin, enzymes, etc.

Sources of Biopolymers

i. Collagen**:** Collagen consists of three intertwined protein chains which form a helical structure [13]. It is a natural protein found in animals and fish. It is a non-toxic substance. Collagen can be processed into various forms such as porous sponges, gels, sheets, etc. Tissues from skin and tendons, which are rich in fibrous collagen, are used to generate collagen which is used in drug delivery processes.

ii. Alginate**:** Alginate is an anionic polysaccharide derived from seaweed. It is non-toxic, biodegradable, and can be easily processed in water. When in its extracted form, it can absorb water of about 200-300 times its weight in water [14]. It can be combined with different other polymers for its usage in drug delivery systems. For example, alginate combined with chitosan, chitosan calcium alginate microsphere, etc.

iii. Chitosan: Chitosan is a natural polymer that is derived from chitin, which is found in the shells of crustaceans such as crabs, shrimp, lobster, etc. [15]. Chitin is also found in microorganisms such as yeast and fungi. The n-deacetylation product of chitin is called Chitosan. Chitosan is soluble in most organic acidic solutions (pH <6.5). Chitosan can be used in a different modified manner to be used in drug delivery devices such as inhalable powder, transdermal patches, etc.

iv. Gelatin: Gelatin is derived from collagen obtained from various animal and fish products. It is a translucent, brittle, colourless food substance [16]. It has its usage in pharmaceuticals, cosmetic manufacturing, and gelling agents in food. Gelatin is the product of partial hydrolysis of collagen obtained from bones, connective tissue, organs, and intestines of some domesticated animals. It is used in various modified forms in drug delivery systems-agar-modified gelatin, DNA-loaded gelatin nanoparticles, cat-ionized gelatin, etc.

v. Carrageenan: Carrageenan is a sulfated polysaccharide obtained from red edible seaweeds. These polymers consistof chains of (1–3)-linked-D-galactose and (1 → 4)-linked α-d-galactose units which are substituted and modified. These are highly flexible molecules and form helical structures when highly concentrated. Carrageenans when modified and combined with bean gum, chitosan, and gallant gum can be used in drug delivery applications.

Table 1: Comparison of Natural and synthetic polymers

NATURAL POLYMERS	SYNTHETIC POLYMERS
Natural polymers are obtained from natural sources like living animals.	Synthetic polymers are prepared by complex chemical processes.
They are biodegradable.	Synthetic biomedical polymers are not always biodegradable.
Usually non-toxic and non-inflammatory.	Some of them might possess toxicity as they are prepared synthetically.
Natural polymers have a low degree of porosity.	Synthetic polymer can be prepared by desirable methods to produce a wide degree of porosity
Very readily available.	Not readily available, to be prepared in laboratories.
Low cost of manufacture	Relatively higher cost of manufacture
Example – Collagen, Cellulose, Alginates, Dextrin, etc.	Example – Polyethylene, Poly (methyl methacrylate), Polypropylene, Polytetrafluoroethylene, etc.

Ideal Properties of Biomedical Polymers: For a biomedical polymer to be efficient, it should contain the following major properties [17].

1. Biomedical polymers should have flexibility and they should be versatile.
2. They should have low molecular weights.
3. They must be fairly resistant to the biochemical processes which take place inside the body of an organism.
4. They should be easy to manufacture.
5. They should have the ability to be moulded into different desirable shapes.
6. They must be available in a composition of a wide variety.
7. They must be recyclable.
8. They should possess minimum levels of toxicity to the organism or the environment.
9. Biocompatibility and biodegradability.
10. They should be stable at the physiological pH of the organism.

Chemistry of Biomedical Polymers

Biomedical polymers are exceptional groups of substances designed to work harmoniously inside the human body. They constitute a very important part of artificial organ generation and replacement which are intended to fit the body [1]. They contain carbon atoms, that is, they are organic. They have backbones which are in π-conjugation. They have distinct photophysical and photoelectric properties. There are many biomedical polymers with diverse chemical structures, quickly evolving in the

specific biomedical field. In inclusion, the functionalized side chains grant their water-solubility, biological response, and biocompatibility. Some basic structures of biomedical polymers include

1. Sugar-Based Polymers***:*** These are nanoparticles; used widely in cancer therapy and imaging. They've been recognized as biocompatible and durable as they are effective for endocytosis by the membrane of cancer cells designed for different sugar internalization programs. For example, lactose.
2. Starch Based Polymers***:*** It is composed of glucose and obtained from tissues of plants. They have replaced petrochemical-derived plastics. They can also be used as biocomposites (derived from wastes in agriculture); with the help of plasticizers. Examples: Maize starch, potato starch, etc.
3. Cellulose-Based Polymers***:*** In solid dispersions, they exhibit a wide range of physicochemical characteristics and hence are used as stabilizers. There is a large scope for exploring their physical and chemical properties for future use [18]. Its various advantages are drug solubility, inhibition of crystallization, and improvement in the properties. Examples: Cellulose Succinate, Carboxymethyl cellulose derivatives, cellulose phthalate derivatives, etc.
4. Synthetic Materials: They are petroleum-based products, synthesized in laboratories and industries by scientists and a few engineers. Polyethylene is a widely used synthetic material, whereas ethylene is a monomer. Its linear polymer is named HDPE (High-density polyethylene). They might also be known as 'plastics'. Examples are nylon, Teflon, etc. [19].

Applications of Biopolymer in Different Fields

1. Food Industry: Biopolymers are a part of structures specialized with specific qualities. They are currently used in the food industry and are processed widely due to their ability to react with other food components and enhance their physicochemical properties and stability properties [16]. Monosaccharides of distinct or identical residues are employed to make polysaccharides [20]. Genetic engineering is used to sophisticated materials and enhances preservatives for producing different materials of different food quality management and packaging. Much advancement has taken place which is targeted at tackling the shortage of global food for an increasing population. Biomedical science has benefited from the advances in biopolymer research and recent studies also show that new products prepared from biopolymers have a relevant influence on the food industry and research [21].
2. As Packaging Material: Food is an important element in a human's life. As there is growth in the production of food, there are increased challenges in the storage of food and its safety. Therefore, it is improved to preserve food by using suitable packaging materials. Packaging materials play a vital role in giving longer life to the food and improving quality during shipment, warehousing, and marketing [22]. Transformation and developments in packaging in food is very important in the food industry. Various packaging materials like plastics, paper, glass, and metals are used in food packaging. Packaging materials that are used commonly are non-biodegradable plastics but these are also harmful to the environment and human health. Therefore, the food industry is researching the environment-friendly replacement of non-biodegradable plastics with biodegradable plastics. However, no systematic literature is available on the subject, so there is a need to summarize the available information systematically. Polymer packaging materials with special reference to biodegradable plastics have been discussed in detail. Different type of biodegradable plastics with their functionality and applications in food packaging has been summarized. It has been shown that it’s better to use biodegradable plastics for food packaging as compared to other

packaging materials. Increasing research in the use of biodegradable polymers in food packaging and effort has been taken to protect the environment [23]. It requires a deep understanding and there may be a lot of challenges coming up for commercialization, which are to be tackled. Packaging plays a very important role in the food industry. Good packaging can make sure that food and beverages are free from contamination or tampering which helps in retaining their desired quality throughout their shelf life. Biopolymer-based packaging film, made from sustainable raw materials maintaining simplified end-of-life disposal, is one alternative packaging method that can reduce mass dependency on fossil fuel resources for packaging [24].

3. In Pharmaceutical Field: There are many applications of biomedical polymers in the pharmaceutical field. One of the major uses is in the Drug Delivery System [21]. Biomedical Polymers are used in the Drug Delivery Systems which help to carry and deliver the drug throughout the body or to the target organ are known as Drug Delivery System. Biomedical Polymers play an important role in this system, examples of some Drug Delivery Systems (DDS) are

I. Matrix Delivery

In a matrix or monolithic delivery system the drug is either molecular dissolved or dispersed inside a matrix. Compared to a reservoir system, a matrix system is not enveloped within a rate-limiting membrane [24]. As such the release rate of the drug from the matrix system is normally not constant and decreases in time [23]. In literature, various types of matrix systems are described. In principle, they can be categorized as follows.

- Diffusion-based designs (homogenous matrix, porous matrix)
- Dissolution-based designs
- Erosion-based designs (bulk erosion or surface erosion)
- Combination of diffusion/dissolution based designs

Diffusion-based matrix system

In a diffusion-based design, the release of a drug is mainly influenced by the diffusion properties of the drug in the matrix. In contrast to a dissolution-based matrix system, the matrix itself is inert and does not dissolve nor degrade in the dissolution medium. This means that the dimensions of the matrix do not change during the release of the drug.

Fick’s laws of diffusion describe the diffusion process of molecules in a matrix and were derived by Adolf Fick in 1855 [25]. For steady-state conditions, the diffusion process is described by Fick's first law of diffusion which states that the drug in solution passing a unit area is proportional to the concentration difference over this unit area [26]. In Fick’s second law, two types of matrix systems are generally mentioned, i.e., homogenous and porous matrix systems.

Homogeneous matrix: In a homogeneous matrix system, the drug is either dissolved or dispersed in a homogeneous matrix, mostly a polymer. Once the matrix system is immersed in a dissolution medium the drug, present at the surface of the matrix, will dissolve in the dissolution medium. This will result in a concentration difference and the drug will diffuse from the inner layers to the outer layers of the matrix [27]. As a result, a depletion zone will be formed at the boundary of the matrix which increases in time. Because the drug has to diffuse over a longer distance the release rate will also decrease in time. The release of a drug from a planar matrix system under sink conditions was described by Higuchi in 1961. The

square root of time shows that the release rate is inversely proportional to the square root of time. If the release rate is plotted versus the square root of time a straight line is obtained.

Porous matrix system: A porous matrix system is a variation of a homogenous matrix system. In this case, the drug is dissolved in a porous polymer. Once the matrix system is immersed in a dissolution medium the pores will be filled with dissolution medium and the drug will dissolve into the filled pores of the matrix [27]. Besides the solubility and diffusion coefficient of the drug in the release medium the shape and volume of the pores in the matrix are of importance. It should be noted that the Higuchi equations are only valid for matrices that are inert to the dissolution medium. If the matrix swells, dissolves, or if the diffusivity changes in times the Higuchi equations are not accurate anymore. To predict the release from these systems Korsemeyer and Peppas (1983) derived a simple relationship also known as the Power Law.

Dissolution-based matrix system: In contrast to a diffusion-based design the release rate of the drug from a dissolution-based design is mainly determined by the slow dissolution of the matrix in a dissolution medium. Once the matrix system is immersed in dissolution medium the matrix will slowly dissolve thereby releasing the drug [28]. This means that the dimensions of a dissolution-based matrix design will alter over time. In the case of spherical or cylindrical based matrix designs the drug release rate will also decrease in time. The basic equation for the dissolution of a matrix was described by Noyes and Whitney [29]. They state that the dissolution rate at which a planar matrix dissolves is proportional to the difference in saturation solubility and the concentration in the dissolution medium. This basic equation was later modified by Nernst and Brunner. Because the release of the drug is proportional to the Surface area of the matrix system the geometry of the matrix system is of influence. For a spherical dissolution-based matrix system the release of drug can be described by the Hixson & Crowell equation [28]. This equation is also known as the cube root law and describes the release from systems where there is a change in surface area and diameter of particles. When the cube root of the amount of drug released is plotted versus time a straight line is obtained. Erosion-based matrix system: In an erosion-based matrix system, the drug is mainly released when the matrix in which the drug is dissolved or dispersed erodes either by bulk erosion or by surface erosion. The release mechanisms based on polymer erosion are complex and it has been difficult to describe the release process in simple equations [30]. As in the case of diffusion-controlled matrix systems, the release of a drug from an erosion-based matrix system also depends on the geometry of the delivery system. Since surface erosion is easier to control than bulk erosion, surface erosion is preferred in drug delivery. The following mathematical expression has been described by Hoffenberg to predict the drug release from simple surface-eroding geometries.

II. Reservoir System

A reservoir system is a type of system that is a drug reservoir surrounded by a non-degradable biopolymer [31]. There are many possible planar configurations for example, we have:

A. Reservoir between 2 membranes - Ocusert
B. Reservoir above a polymer membrane - Skinpath
C. Reservoir between cylindrical configurations – Norplant.

Rate Of 1st-Order Kinetics: The rate of reaction is directly proportional to the drug remaining which is in the implant [32].

Ex –Bulk eroding polymer devices

Order of Kinetics
Rate of release=constant

III. As Polymer Drug Conjugates

Around 60 years ago, drugs were conjugated to natural and synthetic macromolecules; this marked the initiation of Polymer drug conjugates. In the early 50s, Jatzkewitz tried conjugation by using a dipeptide (GL) spacer for the attachment of a drug (mescaline) to PVP (polyvinylpyrrolidone). In the 60s and 70s, a group under Ushakov synthesized several hydrophilic polymer-drug conjugates, which mainly focused on the conjugates of polyvinylpyrrolidone and numerous antibiotics [17]. Drug conjugation to immunoglobulin was pioneered by Mathé et al., which paved a new way for targeted delivery. Many other discoveries were considered remarkable, one of which constituted lysosomal cells, stating the various enzymes present inside it. This discovery was made by DeDuve and it was considered a relevant phenomenon for designing polymer drug conjugates. Ringsdorf finally depicted a clear idea regarding the use of polymer-drug conjugates as targeted drug carriers. Studies on the biocompatibility of cross linked and soluble hydrophilic polymers in the laboratory paved the way for its application as hydro gels clinically and also helped in the selection of N-(2-Hydroxypropyl) methacrylamide polymers (HPMA) and copolymers as drug carrier [32]. Studies on the enzyme-catalyzed cleft of oligopeptides in HPMA hybrid copolymers aggregated for choosing oligopeptide GFLG spacer as drug attachment or release site. Some of the important key points which can be included under PDC (Polymer Drug Conjugates) are:

a. Protein modification with hydrophilic polymers: The concept of protein modifications with hydrophilic polymers started in the late seventies. Conjugation of semitelechelic (ST) polyethene glycol (PEG) with therapeutic proteins by Davis and coworkers resulted in proteolysis resistance, antigenicity reduction, and intravascular t1/2 prolongation [33]. Modification of liposome, nanoparticles, and lysosomes with other polymers like ST is widely used these days. One of the most important examples is PEG (Polyethylene glycol) conjugation, also known as PEGylation. A biochemical process of attaching bioactive molecules with polyethylene glycol through a covalent bond is called PEGylation [34]. It has several properties to antibodies, peptides, non-peptides, and vesicles used in the genetic modification of cells. This process changes the physical and chemical properties of bioactive molecules, for example, hydrophilicity or hydrophobicity, conformation, bindings, etc., and improves the pharmacokinetic, pharmacodynamic, and immunological behavior of the drug. In the case of PEGylated derivatives, coalescence, and degradation slow down. It also improves the solubility of the drug and decreases immunogenicity and toxicity. Polyethylene glycol is a majorly user polymer in drug delivery systems and is a water-soluble biologically inert, synthetic polymer consisting of ethylene glycol in a repeating manner. It is a polymer of choice and is biocompatible. PEG (Polyethylene glycol) is one of the most widely used polymers; PEG-conjugated proteins and liposomes are approved by the Food and Drug Administration. The degree of PEG architecture (branched or linear), PEG molecular weight and PEG substitution play a role in determining the changes in protein property [35]. Several proteins modified and conjugated with PEG have been approved by the FDA for use in clinical studies; some of these proteins are adenosine deaminase, interferon α2a, asparaginase, interferon α2b, granulocyte colony-stimulating factor (G-CSF), uricase and anti-TNFα Fab.

   Mechanism of Conjugation: PEG polymer is synthesized by anionic polymerization of ethylene oxide carried out by a nucleophilic attack of s methoxide ion on the epoxide ring. Frank F. Davis in the late 1970s was the one who brought up PEGylation. He together with his colleagues linked methoxy leg to bovine serum albumin15 covalently. The studies showed

that when a protein is attached to PEG improves the overall properties and stability of the protein [36]. It was indeed a major contribution to the field of drug delivery. The applications of PEGylation can be taken into account by peptides, enzymes; antibody fragments nucleotides and small organic molecules.

Why Conjugation is important? PEGylation has certain purposes such as improving drug solubility, reducing the frequency of drug dosage without diminishing the efficacy with reduce toxicity, increasing drug stability, avoiding proteolytic degradation extending circulatory life, and minimal loss of biological activity [37]. Pegs work in three ways, by reducing kidney filtration, the hydrophilicity of peg leads to increased solubility, and accessibility for proteolytic enzymes and antibodies is decreased.

Methods to improve conjugation: Molar mass is a major factor that brings about biocompatibility, stealth behavior, and the ability of peg to modulate the pharmacokinetic profiles of other molecules [38]. Having a molar mass of 400 Da to 50kDa can be used in different biomedical applications. PEG with molar mass 1-5 kDa is used in conjugation with antibodies and nanoparticles while peg of molar mass 20-50 kDa is used in conjugation with low molecular weight drugs or products that are highly unstable such as oligonucleotides and siRNA. PEGs with a molar mass of 3-5 kDa have been approved as laxative by FDA.

b. Overcoming Multidrug Resistance

One of the major causes of failure of cancer therapy can be traced back to the phenomenon of acquired resistance of malignant tumors towards therapeutics [39]. The transporters of the membrane from the ABC (ATP binding cassette) help in the transportation of protein families (for example Polyglycoprotein and multi-drug resistance proteins) and in reducing the intracellular concentration of drug elucidation of PGP function and other ATP-driven pumps (which are used in efflux) as, as well as the mechanisms involved in multi-drug resistance, has been seen to provide a major role in the understanding of MDR (multi-drug resistance) of the tumors of the human body. Nanomedicine exclusion (including polymer-drug conjugates) from the cytoplasm of the cells by intracellular trafficking in the organelles (membrane limited) leads to less efficient efflux pumps [40]. Sub cellular trafficking through the endocytic pathway to the perinuclear region from the plasma membrane leads to the change of distribution of drugs through gradient difference inside the cells.

Selection Criteria

For Polymer

Some of the basic criteria for the selection of biomedical polymers for the Drug Delivery System are [41].

1. The cost of the polymer should be less than the cost of the active constituents.
2. The polymers should be inert chemically and physically with the drug [37].
3. Its compressibility index should be below 15%.
4. Its release rate should be less than 80 % in 8 hours.
5. It should not be photodegradable.
6. It should not undergo oxidative degradation.
7. It should have good absorption-enhancing and bio adhesive properties.

For Drug

Some of the basic criteria for the selection of drugs for the Drug Delivery System are [19].

1. The molecular weight of the drug should be more than 1000 Da.
2. The solubility of the drug in the polymer matrix should be greater than 0.1ug/ml.
3. The drugs that are absorbed passively through GIT are an ideal feature for sustained-release tablets.
4. The drugs should have a low half-life.
5. The drug should be affected by enzymes and pH.
6. Drugs should be selected with high permeability, as matrix tablets are not permeation rate limiting but release rate limiting.

Biocompatibility of Biomedical Polymers:

Biocompatibility is the science that detects or determines the extent of adverse physiological reactions which might include inflammation, immune responses, levels of toxicity and a few more, in the material place inside the body that is the biopolymer [33]. The fewer adverse drug reactions more bio-compatible is material. Biodegradability might come across as a similar term to bio compatibility but there are differences in both the terms. Biodegradability is the ability of materials to break down into smaller units by physiological forces and their either adsorbed (metabolized) or excreted by the body. Biocompatibility occurs as a result of normal physiological processes which are designed by nature to act as host defenses in this field [40]. The key to using bio-polymers is that the body should not get mad that is they can tolerate and coexist along with the physiological organs and in the physiological PH of the body, hence it should be biomimetic. All the materials or the polymers which will interact with the host will be a matter of concern and hands the extent of interaction of the biopolymers with the host issues is extremely important. Some key interactions that are kept in mind before developing such biopolymers are encapsulation, leukocyte adhesion or activation, scar tissue formation, blood material interaction, protein absorption, coagulation, platelet adhesion, complement activation and finally inflammation and infection.

How can Biomedical Polymers be assessed? There are various methods to assess the biocompatibility of biopolymers, and the following are some of the most important ones.

1. In vivo tissue reactions in this type of assessment, the histological evaluation that is tissue-based evaluation followed by implantation is performed. Further, time point studies are also undertaken which determine the extent of the reactions to which the interaction takes place.
2. Cytotoxicity measurement morphological cell culture assays and biochemical cell function assays are the two most important parts. Morphological cell culture assays include direct contact and elution or extract dilution. Whereas, biochemical cell function assays include the enzymatic activity following polymer exposure [42].
3. Compatibility of blood with the polymers: These studies of coagulation are undertaken, and hemolytic measurements along with the experiments are conducted in Vivo to evaluate the toxicity of the systems are also performed [43].
   Methods For Improving Biocompatibility: As we know biocompatibility is one of the most important factors in the development of bio biopolymers, and improving its features has become the land parcel of today's research programs. If you waste by which biocompatibility of a biopolymer can be improved are as follows.
   1. Addition of Biomimetic Substances: the use of substances like polythene glycol and hyaluronic acid, surface modifications can be improved [44].

2. By protein absorption: Lower protein exception will imply low blood interactions. Making the surfaces more hydrophilic and less cationic might be some ways to decrease the protein adsorption and hence improve by compatibility of the materials.
3. By the use of anti-inflammatory agents: using substances that have concurrent or direct delivery of anti-inflammatory agents at the implantation sites might be helpful.
4. Alternative routes: using some alternative routes that is by changing the route of administration of the implants in the body might also help in decreasing the chances of systemic toxicity.

Combination Methods to Satisfy Biocompatibility Needs: Some combination methods can also be utilized to improve the biocompatibility of the materials; some of them are as follows.

1. Copolymerization: The chemical and the mechanical properties of the materials are adjusted and this varies the polymer composition, type of polymer and also the ratio of substitution [45]. This might be helpful in both synthetic and natural polymers. In particular modifications with the hydrophobic and the hydrophilic areas of the polymers which have special characteristics like degradability and mucus-adhesiveness are used.
2. Blending: Biopolymers are a mixture or blend of a wide variety of compositions that are useful in drug delivery and tissue engineering systems. Blending can change surface properties, drug release ratio and also the quantitative and the quantitative characteristics of the hydro gels [46].
3. Networking: Networking is used in tissue engineering and three-dimensional polymer environments; specifically useful in the control of microstructures porosities and surface properties of the biomedical polymers [47].

Fate of Biomedical Polymers in the Human Body

Long-chain organic molecules make up biopolymers. They are mainly synthetic and produced by joining small chemical building blocks. Each polymer has unique characteristics that affect how it is employed in the production process. Depending on their chemical makeup and processing behavior, polymers can either be or. Thermo sets cannot be remolded, although thermoplastics can. When heated, thermoplastics melt, but thermo sets do not melt but instead break down into gases. Thermo sets are therefore not suited for use in extrusion procedures because, when heated, their molecular chains begin to disintegrate [48]. The science of creating polymers is known as polymer chemistry. It can be used in a variety of production processes. Plastics, rubbers, and adhesives are made using manufacturing procedures that utilize polymer chemistry [49]. It can also be used as drying agents for paint and coatings spray propellants, and fabric fire retardants, among other things. As previously mentioned, polymers are made up of long chains of atoms that are joined together, and the variations among them depend on how these chains are arranged [50]. For example, some polymers are soluble in water or oil, while others are insoluble, elastic, or brittle depending on the material they are made from.

Polymers play a significant part in manufacturing processes like pharmaceuticals, packaging, textile manufacture, adhesives, ceramics and metals, and printing thanks to the aforementioned properties. The use of polymer products is expanding every day in sectors like electronics, personal care, and filtration, so this is only the tip of the iceberg. The use of polymer materials has expanded significantly over the past few years as 3D printing has opened up new avenues for product design. For those who may not be interested in conventional manufacturing procedures, this has increased their possibilities. It provides an enormous opportunity for product designers to develop novel and

intriguing goods today. Prototypes are not the only use for the application; massive production runs are also an option [51]. The process of "binder jetting," which entails spraying layers of plastic binder onto a platform full of powdered materials, is one technique to employ 3D printers to create larger goods [52]. Once the binder dries, it turns into solid plastic and, layer by layer, creates the desired object. Warm air bonds adjacent layers together once each layer has finished printing to produce a solid printed product [53]. It is simple to understand why synthetic polymers have grown so popular when you take into account the variety of applications and how swiftly science is producing more of them [54].

Metabolism of Biomedical Polymers

Toxicity studies of biopolymers in pediatric, adult, and elderly populations have been conducted to evaluate their safety and potential adverse effects [55]. The toxicity of biopolymers can depend on several factors, including the source, purity, molecular weight, and chemical structure of the polymer. In general, biopolymers are safe and well-tolerated in pediatric and adult populations [56]. However, studies have shown that certain biopolymers may have adverse effects in some individuals, particularly those who are allergic to the source material or have pre-existing medical conditions [57].

For example, Chitosan, a biopolymer derived from chitin, has been studied for its potential use in weight loss and as a wound dressing. While Chitosan has generally been found to be safe, some studies have reported adverse effects, including gastrointestinal disturbances and allergic reactions. Similarly, studies have shown that some individuals may be allergic to collagen, a biopolymer commonly used in cosmetic and medical procedures [58]. Adverse reactions to collagen can range from mild itching and redness to severe anaphylaxis. In elderly populations, biopolymers may have different effects due to changes in the body's metabolism and immune system. For example, studies have shown that elderly individuals may have a reduced ability to clear certain biopolymers from the body, leading to prolonged exposure and potentially adverse effects.

Problems Associated with Biomedical Polymers and Their Suggested Solutions

There have been various challenges in the development and use of Biomedical Polymers [59]. Some of these are mentioned below.

i. Toxicity and Safety Issues: The safety of polymers of biological origin and medical devices has been a matter of controversy since its inception [60]. Infections caused by the device, are associated with bacteria mostly and also, the dangers of using polymers like PVC biomaterials have caused disquiet in the medical field. The use of technique like ethylene oxide sterilization is associated with various toxicological reactions [61]. According to a survey made in the United States of America, it was seen that around 1 million people had developed infections due to biomedical devices. Around 2.5 million orthopedic implants have been used in humans since 2001 per year among which around 4% were found to be infected. The cost of treating these infections was believed to exceed more than three billion annually. This margin is most likely to grow because more patients are receiving biomedical implants [62].

   Suggested Solution:
   One of the ways by which these device-associated infections can be prevented, is by developing microbial surfaces or materials that are novel; with the help of introducing

antibiotics or substances like biocides [63]. However, they are also connected with the risk of high toxicity associated with the cytoplasm which is more commonly known as cytotoxicity and antibiotic resistance. This has raised concerns because of their threat to human life and environmental safety. There is also an alternative method by which biomaterials can become resistant to bacterial attachment i.e. by constructing anti-fouling coatings [64]. Although they have good biocompatibility, these coatings are not able to kill the bacteria adhered to the surface. Infections can be effectively lowered by these methods.

ii. Hydrolytic Degradation: The Polymers which undergo hydrolytic degradation are known as hydrolytically degradable polymers. This happens because they contain bonds in their backbone which are cleavable in the presence of water and they can be broken down without any external influences [65]. When the bonds are broken down, two parts of the compound are formed; one part receives the -OH group while the other receives a hydrogen atom. The functional groups that are most susceptible to the hydrolytic degradation reaction are anhydrides, esters, carbonates, acetals, urethanes and phosphate groups. Degradation rates can depend on a variety of factors like monomer solubility, water diffusion, geometry of the device and size [66].

Table 2: Information on the Infections caused by the implants or devices over a lifetime and the site at which these implantations work [48].

Device	Implantation Sites	Infection Percentage (%) (Over Lifetime)
Central venous Catheter	Percutaneous	2-10
Temporary pacemaker	Percutaneous	4
Peritoneal dialysis Catheter	Percutaneous	3-5
Dental Implants	Percutaneous	5-10
Voice Prosthesis	Percutaneous	25 (monthly)
Short indwelling Catheter	Percutaneous	3
Suture	Percutaneous	1-5
Fixation Pin	Percutaneous	5
UT Catheter	Urinary Tract	33 (weekly)
Cardiac pacemaker	Subcutaneous	1–7
Penile prosthesis	Subcutaneous	2–5
Mammary prosthesis	Soft tissue	1–7
Abdominal wall patch	Soft tissue	1–16
Intraocular lens	Eye	0.1
Contact lens	Eye	0.1–0.5

Prosthetic heart valve	Circulatory system	1–3
Vascular graft	Circulatory system	1.5
Prosthetic hip	Bone	2–4
Prosthetic knee	Bone	3–4
Tibia nail	Bone	1–7

Erosion is a major hindrance; especially surface and bulk erosion or both. In surface erosion, the polymer degradation rate is much greater than the water diffusion rate into the material bulk [67]. This leads to the formation of a device that degrades almost completely at the surface. On the other hand, in bulk erosion, the water diffusion rate is much greater than the polymer degradation rate and hence this leads to a device in which degradation occurs throughout the material bulk. An investigation was conducted which showed that the degradation rates could vary from 12 folds from hydrolytically unstable polymers (polyphosphazenes) to hydrolytically stable polymers (polyamides).

Suggested Solution

Properties of material and their processing influence polymer degradation behavior; this includes monomer structure, phase microstructure, molecular weight, crystalline and processing of the material [68]. Porosity helps in the removal of byproducts and hence can slow down the rate of degradation.

Table 3: Some important biomedical polymers along with their applications and degradation rate constants are given below [48].

Polymer	Applications	Degradation Rate Constant (S-1)	Advantages	Disadvantages
Polyphosphazenes	Tissue Engineering	4.5×10^{-2} -1.4×10^{-7}	Synthetic Flexibility Controllable Mechanical Properties	Complex Synthesis
Polyanhydrides	Tissue Engineering	1.9×10^{-3} – 9.4×10^{-9}	Monomer Flexibility Controllable Degradation Rates	Low Molecular Weights Week Mechanical Properties
Polyacetals	Drug Delivery	6.4×10^{-5}	Mild pH Degradation Products pH-Sensitive Degradation	Low Molecular Weights Complex Synthesis
Poly (ortho esters)	Drug Delivery	4.8×10^{-5}	Controllable Degradation Rates pH-Sensitive	Weak Mechanical Properties Complex Synthesis

Polyphosphoesters	Drug Delivery	1.4 × 10−6	Degradation Biomolecule Compatibility Highly Biocompatible Degradation Products	Complex Synthesis
Polycaprolactone	Tissue Engineering	3.5 × 10−8	Highly Processable Many Commercial Vendors Available	Limited Degradation
Polyurethanes	Tissue Engineering	8.3 × 10−9	Mechanically Strong Handle Physical Stresses Well	Limited Degradation Require Copolymerization with Other Polymers
Polylactide	Tissue Engineering	6.6 × 10−9	Highly Processable Many Commercial Vendors Available	Limited Degradation Highly Acidic Degradation Products
Polycarbonates	Fixators	4.1 × 10−10	Chemistry-Dependent Mechanical Properties Surface Eroding	Limited Degradation Require Copolymerization with Other Polymers
Polyamides	Drug Delivery	2.6 × 10−13	Conjugatable Side Group Highly Biocompatible Degradation Products	Very Limited Degradation Charge Induced Toxicity

Conclusion

As a result of their biocompatibility, biodegradability, and flexibility to be tailored to particular drug delivery requirements, biopolymers have improved the efficacy of drugs, and the risk of adverse effects has decreased. For their potential as drug delivery systems, several biopolymers, including Chitosan, alginate, and hyaluronic acid, has undergone substantial research. For instance, Chitosan has been demonstrated to improve drug stability, prolong drug release, and promote drug absorption. Hyaluronic acid has been utilized to enhance drug delivery to the eye, whereas alginate has been used to encapsulate medications and target them to particular areas in the body. Moreover, biopolymers can be utilized to develop drug delivery systems that respond to external stimuli, such as pH, temperature, or enzymes, to cause the release of the medication. This strategy may increase drug effectiveness while minimizing adverse effects. Overall, biopolymers have demonstrated significant promise as

drug delivery systems and further study is anticipated to result in the creation of novel, biopolymer-based drug delivery systems that can enhance patient outcomes and lower medical expenses.

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Conflict of Interest
The authors declare no conflicting interests.

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