



BIODEGRADABLE POLYMERS FOR ADVANCED DRUG DELIVERY: APPLICATIONS, CHALLENGES AND FUTURE PERSPECTIVES

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ABSTRACT :

Biodegradable polymers in pharmaceutical and biomedical technologies are a new generation of materials that offer many advantages. This characteristic feature of polymers is their ability to degrade into harmless products that can be removed or absorbed by the body. Unlike nondegradable polymers, biodegradable polymers are widely used in drug delivery systems because they allow the implementation of various forms of controlled drug release.

The article presents the concepts and characteristics of polymers, the history of their development, and areas of application. The article answers the questions of how and why polymers were created, what properties and advantages they have, and which industries use them. This review covers natural and synthetic polymers, including polylactic acid, poly(lactico-glycolic acid), polycaprolactone, polyhydroxyalkanoates, chitosan, sodium alginate, gelatin, cellulose derivatives, and related compounds. They are used in the controlled and targeted delivery of drugs, including nanoparticle and microparticle forms, hydrogels, biodegradable implants, pharmaceutical coatings, mucoadhesive and transmucosal drug delivery systems, 3D-printed drug delivery systems, tissue engineering, and wound healing. The article also addresses the challenges and prospects of biodegradable polymers, including polymer modification strategies, smart nanocarriers, and targeted and triggered drug delivery. Moreover, the factors affecting the biodegradation of polymers are discussed, including the chemical structure of the material, its molecular weight, and other properties: crystallinity, morphology, hydrophobicity, and more. Factors such as processing, sterilization, storage, and environmental conditions are also important aspects of biodegradable polymers. Moreover, the authors explore the issues of cost, inconsistent drug release, variable drug loading, inadequate storage, and scalability. The future of biodegradable polymers depends on several key factors, including research into new materials, smart polymers, and nanotechnology, standardization of biodegradation tests, and optimization of processes and technologies for degrading polymers, reducing microplastics, and sustainable production and recycling of materials

Key word: Biodegradable polymers; Natural polymers; controlled drug release; pharmaceutical applications; Nanoparticles

Introduction:

Biodegradation refers to the process by which organic substances existing in the environment are decomposed, mineralized, and incorporated into biogeochemical cycles such as the carbon, nitrogen, and Sulphur cycles[1]. Biodegradable polymers have found extensive use in biomedical applications due to their biocompatibility and biodegradability. Such polymers are mostly used in applications that require temporary presence in the body such as suture threads, scaffolds for tissue engineering, and drug delivery[2]. They must be strong enough for a particular period before they are broken down into simpler forms and eliminated from the body. The reason why biodegradable polymers are preferred in drug delivery is because one does not have to remove them from the body after use[3]. Despite this wide variety of biodegradable polymers, not many of them are appropriate for use in pharmaceutical production. The reason why they are not used is because they must present biodegradability and high biocompatibility. The polymers should also be processable, easily sterilizable, and have good storage properties[4] to add to their pharmaceutical applicability. The main advantage of polymers that can be degraded is that they can be degraded to form simple end products that are easily excreted from the body through regular physiological products that must be tolerated within the body and should not cause adverse effects[5]. These by-products and the overall biodegradation process must undergo a lot of evaluation because various factors can influence the process itself. A list of the most important factors influencing biodegradation is given below; and this list highlights the most important factors that could influence biodegradable polymer-based drug delivery systems.

History

Very early work on biodegradable polymers necessarily preceded the arrival of synthetic polymers that require petrochemicals as feedstocks. This early work focused on natural polymers or their derivatives. One of the earliest biomedical applications of a biodegradable polymer was the catgut suture,

which was in use at least as early as AD 100. The first catgut sutures were made of sheep intestines, but modern catgut is made from purified collagen from the small intestines of cows, sheep, or goats[6].

In the 1830's, cellulose was modified into gun cotton (cellulose nitrate) and later converted to cellulose acetates, which are probably the first biodegradable (semi-synthetic) polymers. Early research on biopolymer polyhydroxyalkanoate (PHA) was performed, leading to its commercial production in the 1950s by ICI (UK) using *Alcaligenes latus* bacteria to produce polyhydroxybutyrate (PHB)[7].

Research efforts by W.R. Grace & Co. (USA) proved fruitless. Besides, when oil exports from the OPEC nations were suspended to finance the national budget in 1973, attempts by Imperial Chemical Industries (ICI UK) to produce polyhydroxybutyrate (PHB) using *Alcaligenes latus* also failed. The specific PHA is short-chain-length PHA (scl-PHA), and the research continues to this day. Similarly, research efforts on PHA led to the development of polylactic acid (PLA). Studies on the polymerization of lactic acid and its derivatives started in the 1930's at DuPont. In the 1970's, a copolymer of PLA and polyglycolic acid was commercialized as Vicryl resorbable suture[8].

The concept of synthetic biodegradable plastics and polymers emerged in the 1980's. In 1992, an international meeting was convened where representatives of biodegradable polymer manufacturers attempted to establish a common definition, standard, and testing regimen for biodegradable polymers. Noteworthy, ASTM (American Society for Testing of Materials) and ISO (International Standards Organization) were formed to promote and standardize biodegradable polymers.[citation needed] Various clothing and grocery store chains have advocated for the use of biodegradable bags in the late 2010's. Industrial scale production of biodegradable polymers commenced in the late 1990's[9].

Biodegradable Polymers in Drug Delivery

One of the key advantages of biodegradable polymers is their ability to prolong the drug's activity through their capacity for continuous release of the active substance at the site of action. This effect is especially advantageous in the treatment of chronic diseases, where the frequent administration[10] of the drug is associated with poor adherence to the treatment regimen and systemic toxicity. Moreover, biodegradable micelles and nanoparticles allow for masking the molecule to enhance its solubility and bioavailability and protect it from enzymatic degradation[11].

In addition to the mentioned above synthetic polymers, biodegradable natural polymers, including alginate, gelatin, and dextran, are used as effective and safe materials for drug delivery due to their biocompatibility and low immunogenicity. Such polymers are used in a wide range of drug formulations, including various nanoparticles, hydrogels, and injectable depots allowing for prolonged and targeted release of the drug.

Moreover, the development of novel pH-, temperature-, or enzymatically sensitive biodegradable polymers has further expanded the application potential of biodegradable polymers for stimuli-triggered drug delivery[12]. It can be anticipated that the mentioned polymers will be instrumental in the development of customized and personalized treatment options allowing for minimizing systemic toxicity while maximizing therapeutic efficacy.

Nanotechnology and Smart Carriers for Targeted Drug Delivery

Nanotechnology overcomes the limitations of conventional drug delivery by achieving targeted delivery, enhanced bioavailability, and controlled drug release. Intelligent or smart nanocarriers including liposomes, dendrimers, micelles, and polymeric nanoparticles have been engineered to target the site of action with minimum or no undesirable side effects[13]. These nanocarriers are engineered to deliver drugs through biological barriers to specifically accumulate at the site of action and exert their therapeutic effects.[14]

Targeting the site of action using smart or intelligent nanocarriers involves passive and active targeting mechanisms. Passive targeting of tumor tissues through the Enhanced Permeability and Retention (EPR) effect enables the accumulation of nanomedicines due to the leaky vasculature of tumor tissues.[15] On the other hand, active targeting employs targeting moieties such as ligands, antibodies, and peptides to specifically recognize and bind to tumor-specific receptors on the target cell surface, resulting in enhanced therapeutic efficiency and reduced off-target toxicity[16].

The recently developed stimulus-sensitive or intelligent nanocarriers have also been engineered to respond to specific physiological or biochemical cues in the target site, a property referred to as "on-demand drug delivery". Thus, these smart nanocarriers offer an enormous potential in drug delivery due to their ability to specifically deliver drugs to the target site with minimal or no premature degradation, thereby enhancing therapeutic efficiency.[17]

In addition to that, nanotechnology has been exploited to develop multifunctional nanocarriers for the targeted delivery of imaging agents to monitor drug delivery and therapeutic efficacy. Overall, nanotechnology offers a wide range of strategies for precision medicine and personalized patient-specific therapy.[18]

Polymers

A polymer is a substance having a large molecular structure formed totally of rings or chains of a large number of distinctive repeating elements (monomers). For easier understanding, the word polymer consists of two Greek words "poly" and "mer" meaning "many" and "parts". Synthetic and natural polymers are applied in various industries due to their wide range of properties. Most polymers are used and produced as plastics and resins. Actually, plastics are considered as polymers, with additional additives, created from long molecular chains formed by alkenes. A change, usually, replacement of one or more hydrogen atoms with another atom, occurs to form polymers of different kinds. Plastics are used in the packaging industry since they can be easily molded and shaped into different forms and sizes. Different types of plastics and their properties offer several packaging options such as shape, color, size, weight, content functionality, print, etc. Currently, polymers are an indispensable component of modern lifestyle because of their desirable properties such as stability, resilience, and cost-effectiveness. In other words, plastics are advantageous to manufacturers because they are lightweight and malleable or flexible; therefore, they can be formed into any desired shape using blowing, extrusion or coextrusion, casting, laminating processes among others. This allows packaging of unique items, which could not have been possible using traditional containers[19].

Polymers are advantageous for various food packaging applications because of the barrier properties, which help in food preservation, protection, and

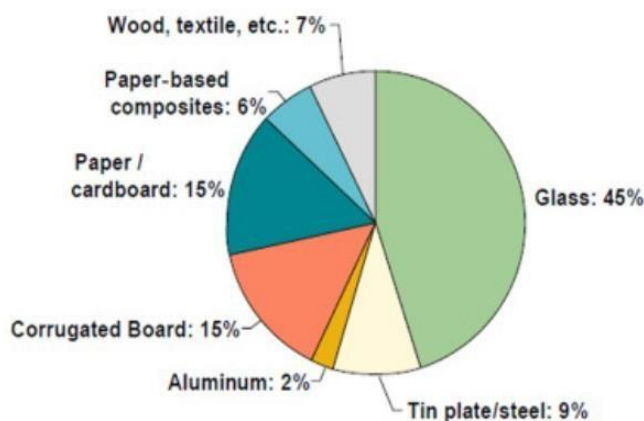
extension of shelf life. Polymer packaging can be regarded as eco-friendly because food industry manufacturers and companies can minimize waste since the food packaged using these materials lasts longer than the ones packed using traditional materials. For instance, Tajeddin et al. reviewed polymers useful for modified atmosphere packaging (MAP). These compounds are primarily used for flexible film packaging structures for the majority of MAP applications. However, the same materials can be formed into rigid or semi-rigid packaging solutions such as lidding on a tray. The polyolefin-based polymers include: PEs such as LDPE, linear LLDPE, HDPE; PP; PS; polyesters such as

PET or PETE; polycarbonate (PC); and polyethylene naphthalate; PVC; polyvinyl dichloride; PA or nylon; and ethylene vinyl alcohol; are the main polymer materials applied for MAP. On the contrary, researches are still underway to modify the structures of some of these polymers for specific applications. For instance, Kobayashi and Saito examined the morphological evolution of PC/PMM A blends via simultaneous biaxial stretching.[20]

The mechanical and gas barrier characteristics of polymer films can be effectively enhanced by employing the biaxial stretching process, which makes this polymer processing approach very attractive for creating high-performance films utilized in food and industrial packaging. For another example, Han et al. prepared polyvinyl formal (PVF) from polyvinyl alcohol (PVA) and formaldehyde. Comparative data demonstrate that the obtained PVF had an elevated decomposition and glass transition (T_g) temperatures and a decreased melting point relative to those of PVA. The synthesized PVF could be melt-processed at significantly lower temperatures than those needed for PVA. Polypropylene carbonates (PPC) and the obtained PVF were melt-blended in a Haake mixture to prepare PPC/PVF blends. The resulted PPC/PVF blends exhibited a high Vicat softening temperature and tensile strength compared to those of pristine PPC. In terms of thermogravimetric analysis, it was found that the thermal stabilities of PPC/PVF decrease with an increase in the PVF content. Scanning electron microscopy observations confirmed that the interfacial adhesion of the immiscible blends of PPC and PVA matrices was poorer than that of the PPC/PVF matrix. The PPC/PVF blends displayed enhanced multifunctional properties over those of the blend components suggesting that these materials could be employed as a new approach to extend the applicable area of PPC copolymers[21].

Polymers (plastic materials) are the most common materials in the packaging industry. For instance, for each of the analyzed categories, 95%–99% of plastics in North American packaging. Comparative to other packaging materials such as aluminum, glass, paper, and steel, plastic packaging materials comprise 39%–100% of total North American market demand for the packaging material category analyzed in this study. Nevertheless, the most significant challenge posed by plastics is that the production and processing of plastics require energy-intensive processes, resulting in the emission of greenhouse gases and consequent climate change. Moreover, Smith, as reported by Yadav et al. observes that upon burning plastics, toxic gases such as CO₂, chlorine, hydrochloric acid, dioxin, furans, amines, benzene, 1,3-butadiene, and acetaldehyde are generated, threatening the environment and human health. Similarly, plastic waste, like polyethylene bags, to-go food containers, plastic straws, and plastic water bottles, has been problematic for decades because they are nondegradable. Consequently, these plastic wastes are dangerous to the environment, wildlife, and, by extension, human health. In addition to that, they cause adverse effects to the ecosystems when thrown away in the wild. For example, plastics, including plastic bags, threaten marine life and eventually pollute oceans since they do not degrade easily. In addition, plastic bags contribute to the blockage of human respiratory tracts and cause lung cancer. Moreover, they lead to an increase in the risk of prostate cancer in men. In addition, it is estimated that by the year 2050, ocean plastic waste will outweigh fish in the world's oceans. Thus, plastic bags choke our planet, particularly the oceans. Furthermore, they contribute to lung diseases and prostate cancer in men. However, over 500 billion plastic bags are thrown away in landfills every year, and only three percent of these bags are recycled. In fact, most plastic bags are manufactured using PE. These bags can last for hundreds of years before decomposing if not properly disposed of, which is a challenge since there is no appropriate recycling technology. On the other hand, they emit harmful greenhouse gases, which intensify global warming. Therefore, it is essential to reduce the usage of these materials and utilize alternative materials[22].

Fig. 16.1 presents an example of the composition of materials that can replace plastic materials. In fact, Brandt and Pilz developed a model for a theoretical substitution of plastic packaging materials. The results obtained from their experiment are presented in Fig. 16.1, if plastic packaging (LDPE, LLDPE, HDPE, PP, PVC, PS, expanded polystyrene, and PET in this study) were replaced by other materials (tin plate and steel packaging, aluminum, glass, corrugated board, cardboard, paper and fiber cast, paper-based composites, and wood in this study). Fig 16.1 16.1. Material substitution options for the food packaging system in a theoretical scenario (replacing polyolefin-based flexible packaging materials such as low-density polyethylene (LDPE), linear low-density polyethylene (LLDPE), high-density polyethylene (HDPE), polypropylene (PP), polyvinyl chloride (PVC), polystyrene (PS), expanded polystyrene, polyethylene terephthalate (PET) and other materials (tinplate and steel packaging, aluminum, glass, corrugated board, cardboard, paper and fiber cast, paper-based composites, and wood)[23].



TYPES OF POLYMERS USED (BINDERS, COATING, CONTROLL RELEASED MATRIX, EXCIPIENTS)

These are several types of polymers used for the purposes of drug delivery, and their properties can be utilized according to the needs they have to resolve. Based on their application in the dosage forms, polymers can be divided into the following categories:

1. Binders and Excipients

Drug delivery polymers can serve as binders and excipients. In other words, HPMC and PVP are binding agents that ensure the strength and integrity of the formed dosage form. Moreover, they have an impact on its disintegration and flowability. Below is an illustration showing how polymers are used in the drug delivery system. It also demonstrates the types of polymers described in this article, such as coating agents, controlled release matrices, and excipients[24].

2. Coating Agents

Coating agents can be used to protect the drug from external factors (e.g., moisture or light), mask unpleasant taste, or provide enteric coating. Examples of polymers that can be used to coat tablets and capsules include CAP and methacrylic polymers. They are resistant to the acidic environment in the stomach and are dissolved in the alkaline environment of the intestine.

3. Controlled Release Matrices

To control the release rate of the active substance, it is possible to use hydrophobic polymers (such as Ethyl cellulose) or hydrophilic and swellable polymers (such as high viscosity HPMC). The latter category of polymers allows for decreasing the dose of the substance to be released and smoothing its pharmacokinetics.

4. Specialized Matrices

Biodegradable polymers such as Poly (lactic-co-glycolic acid), or PLGA, are used to make implants that are broken down by the body over a period of weeks or months. A similar effect is achieved by fillers in capsules, which are also absorbed by the body over time[25].

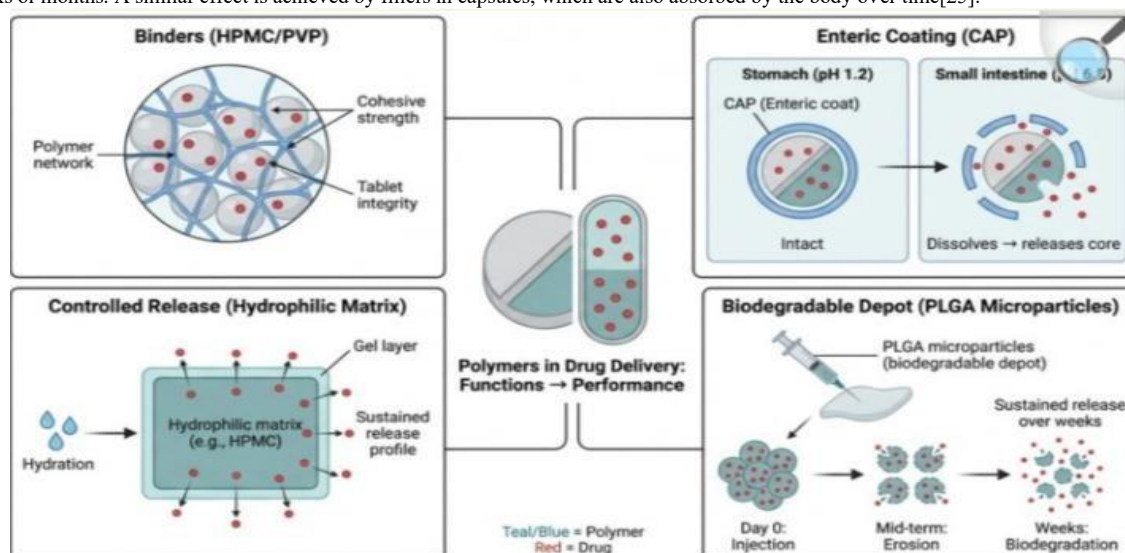


Fig. 1. How polymers affect different aspects of drug delivery.

Overview of polymers used in drug delivery systems, including their contribution to forming tablets with appropriate cohesion (as seen in the HPMC/PVP), enteric coating (CAP), and development of controlled release matrices or biodegradable depots (PLGA microparticles). In this figure, polymers are highlighted in blue and teal, whereas drugs are highlighted in red.

BIODEGRADABLE ALTERNATIVES TO CONVENTIONAL PLASTICS

Many bioplastics have mechanical properties similar to conventional plastics, such as polypropylene (PP), polystyrene (PS) and polyethylene (PE), and can be processed using standard polymer processing technologies, including compounding, film production, moulding, etc. They have been used in a variety of applications where short-term performance is required and biodegradability is a key requirement, such as consumer packaging (trays, pots, films, and bags for food packaging), convenience food packaging (cutlery/tableware), bags (shop, garden or household waste), mulch films in agriculture, personal care (nappies), and even golf tees. On the other hand, bioplastics have been used in more durable products, such as textiles, consumer goods, automotive components, and building materials, with a focus on the sustainable use of renewable resources, and inherent biodegradability, if any, masked or controlled[26].

PLA is an eco-friendly material that is 100% bio-based and biodegradable under specific conditions and is industrially compostable. On the other hand, PLA has been proved to be a biocompatible material that does not cause carcinogenic or toxic effects on local tissues. Compared to other polymers such as polycaprolactone (PCL), PLA is characterized by better thermal processability. In addition, PLA is a highly hydrophobic polymer with slower degradation. According to table 10, PLA has mechanical properties similar to PET polymer. In particular, the elastic modules and tensile strength were found to be comparable to PET. On the other hand, high-molecular weight PCL polymers exhibit mechanical properties similar to those of polyethylene (PE), including high density, modulus, and tensile strength. Specifically, the tensile strength was found to be in the range of 12-30 MPa, and the elongation at break was 400-900%. At the same time, PCL has some shortcomings, such as a very low glass transition temperature (-60 °C) and a melting point (60-

65 °C), which restricts its use at elevated temperatures. PCL is often blended with other polymers, including polypropylene (PP), polycarbonate (PC), polyethylene oxide (PEO), and starch, to prepare composite materials with characteristic properties.

Due to their plastic-like properties and biodegradability, polyhydroxyalkanoates (PHAs) can serve as promising substitutes for non-degradable conventional polymers, such as PE and PP. For example, PHB homopolymer has a set of physical properties, including a glass transition temperature (T_g) of 15 °C, a degree of crystallinity of 80%, and a tensile strength of 40 MPa, close to those of PP. At the same time, PHB is significantly more brittle than PP (the elongation at break of PHB is 6% compared to 400% for PP). Another bioplastic is PBS, which is at the same time biodegradable, mostly fossil-based, but presented to become 100% bio-based. This polymer has mechanical properties similar to PE and PP, a melting point of 90-120 °C, and a glass transition temperature of -45 to -10 °C. In turn, PBS has good processability, which is better than that of PLA. On the other hand, the mechanical properties of BioPBSTM are similar to those of low-density polyethylene (LDPE). To date, PBAT is mostly fossil-based polymer; its commercial name is Ecoflex (produced by BASF, Germany). The PBAT grade Ecoflex F Blend C1200 exhibits properties similar to those of low-density polyethylene (PE-LD) due to the high molecular weight and long-chain branched structure of PBAT.

Cellulose and starch are biodegradable alternatives to conventional plastics such as polypropylene (PP) and polystyrene (PS). In particular, cellulose acetate (CA) is the most important cellulose derivative among cellulose plastics with tensile strength comparable to polystyrene. Starch blends are totally biodegradable; they can contain up to 100% bio-based materials. At the same time, the content of starch in such polymers can vary from 25 to 100%, depending on the characteristics of the matrix in which it is found[27].

BENEFITS OF BIODEGRADABLE POLYMERS FOR DRUG DELIVERY SYSTEM:

Biodegradable polymers offer numerous benefits of drug delivery, including controlled release and targeted delivery. This includes the advantages of controlling the release rate and targeting specific cells or tissues. In addition, biodegradable polymers are often biocompatible and can break down into harmless substances within the body. The main advantages of biodegradable polymers in drug delivery are discussed below

1. Controlled release of drugs Biodegradable drug delivery systems:

allow for the controlled release of therapeutics overtime. This means that the drug is delivered to the body at a constant rate, ensuring that the drug remains therapeutically active for as long as possible. This feature of biodegradable polymers allows for predictable and controlled drug release and eliminates the need for frequent doses [28]

Mechanism:

Biodegradable polymers break down over time, allowing for slow and controlled release of the drug. Controlled breakdown ensures that drug concentrations in the body remain constant. Benefits Improved patient compliance. Patients do not have to take the drug as frequently since it is released slowly and continuously.

Reduced side effects:

Constant drug concentration reduces fluctuating levels of the drug in the body, thereby minimizing side effects.

2. Targeted drug delivery:

One of the major advantages of biodegradable drug delivery systems is that they can be engineered to deliver drugs to specific cells or tissues within the body. For example, biodegradable nanoparticles can have targeting ligands attached to their surface that recognize specific cell types, such as cancerous cells or immune cells. Targeted delivery allows for increased precision in drug delivery while reducing unnecessary exposure of healthy cells to the drug.

Mechanism:

Biodegradable polymers can be engineered to respond to specific biochemical or physical cues in the target tissue or cell.

Benefits:

Increased drug concentration at the target site:

Targeted delivery can increase the concentration of the drug at the desired location, thereby improving its therapeutic effect.

Reduced toxicity to healthy cells:

Targeted delivery reduces the exposure of healthy tissues to the drug, thereby minimizing potential side effects.

3. Biocompatibility:

When biodegradable polymers are used correctly, they can be broken down into harmless byproducts by the body. Specifically, these polymers can break down into carbon dioxide and water, which can be easily eliminated from the body[29].

Mechanism:

Biodegradable polymers can be made to break down into biocompatible and non-toxic byproducts that can be easily eliminated by the body.

Benefits:

Minimized toxicity:

The by-products of biodegradable polymers are typically not harmful to the body. Increased safety: Unlike conventional non-biodegradable polymers, biodegradable polymers do not require surgical removal after the drug has been delivered.

Synthesis methods

The synthesis of biodegradable polymers typically involves various polymerization processes, depending on the desired characteristics of the polymer. Below are some of the most common methods used in the synthesis of biodegradable polymers:

1. Ring-opening polymerization(ROP):

ROP is a popular method used primarily for the synthesis of polyesters such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and poly(lactic-co-glycolic acid) (PLGA). ROP is known for its ability to produce polymers with well-defined molecular weights.[30]

2. Condensation polymerization:

This method is used to synthesis polyamides and polyurethanes. It typically involves the condensation of monomers that contain specific functional groups.

3. Microbial synthesis:

Microbial synthesis involves the use of microorganisms to produce polyhydroxyalkanoates (PHAs), which are biodegradable and biocompatible polymers. This method is considered more sustainable and efficient compared to other synthesis methods. Properties of biodegradable polymers typically display various advantageous properties, including good biocompatibility, biodegradability, mechanical robustness, and the ability to be fabricated into different physicochemical forms. Some common properties of biodegradable polymers include:

Bio compatibility:

They can be safely used in the body without elicit unwanted immune responses.

Biodegradability:

They break down into non-toxic by-products that can be eliminated from the body.

Controlled drug release:

They allow for the controlled and sustained release of drugs.

Mechanical strength:

They can exhibit good mechanical properties that are suitable for various biomedical applications.

Versatility:

They can be produced in various forms, including nanoparticles, microspheres, hydrogels, and implants.

Applications of Biodegradable polymer

1. Controlled and Sustained Drug Delivery

Biodegradable polymers are of great interest in the field of controlled and sustained drug delivery because of their ability to degrade in a controlled manner in the biological environment so as to release drugs at a desired rate. Drug release can be achieved by a combination of mechanisms including diffusion, swelling, erosion, and degradation. Polymers such as Polylactic acid (PLA), Poly(lactic-co-glycolic acid) (PLGA), Polycaprolactone (PCL) and Poly anhydrides are used extensively in the field of controlled drug delivery due to the ability of these polymers to control the rate of degradation and hence drug release rate. The degradation rate and hence the drug release from a polymer can be varied by varying the molecular weight of the polymer, the crystallinity, polymer: drug ratio and the monomer composition (in case of copolymers like PLGA). By using such biodegradable polymers, a constant and desirable concentration of drug can be maintained in the body for a long time.[31]

2. Biodegradable Polymeric Nanoparticles and Microparticles

Biodegradable polymers are key materials for the development of polymeric nanoparticles and microparticles used in drug delivery applications. They offer versatility in designing formulations with enhanced stability, bioavailability and tissue-targeting capabilities. Polymeric systems such as poly(lactic acid) (PLA), poly(lactic-co-glycolic acid) (PLGA) and natural biodegradable polymers have been widely explored for the fabrication of nano- and microparticulate systems. These systems enable the controlled release of encapsulated bioactive compounds while protecting them from degradation and exerting their biological effects. The surface of such particles may be further functionalized with targeting moieties to enhance their recognition by specific cell types or tissues. This property is particularly advantageous for the development of therapeutics targeting hard-to-reach sites, such as the central nervous system. Overall, biodegradable polymeric nanoparticles and microparticles represent a promising platform for the next generation of drug delivery systems.

3. Biological Polymers for the Synthesis of Hydrogels

Hydrogels are three-dimensional networks of polymers that can absorb and retain large amounts of water. Hydrogels made from biodegradable polymers such as chitosan, alginates, or hyaluronic acid, are particularly attractive materials for drug delivery, since their degradation rate and degree of swelling can be tailored to control the release of a therapeutically active moiety. Such hydrogels can be used to provide long-term local drug delivery or develop responsive systems that allow stimulus-induced drug release. Moreover, biodegradable hydrogels can serve as vehicles for growth factors and drugs in the context of advanced wound healing therapies or regenerative medicine due to their capacity to mimic the biomechanical microenvironment of native tissues[32].

4. Biodegradable Implants and Drug-Eluting Devices

Biodegradable polymers are used in the development of implantable drug-delivery systems, which permit prolonged drug release at a specific site. PLGA and other biodegradable polyesters can be formulated into drug-loaded implants and depot systems, which can provide either localized or systemic drug delivery. Such drug delivery systems were investigated for various applications, including the treatment of cancer, pain management, contraception and antiviral therapy. An important advantage of the polymer-based systems is their potential to gradually degrade after release of the drug, thereby possibly obviating the need for surgical removal after the drug has been released.

5. Pharmaceutical Coatings

Biodegradable polymers can be used as materials for coating pharmaceutical dosage forms. Polymer coatings can provide a protective barrier against environmental influences, such as moisture, light and oxidation, and can also be used to control the release rate of the active pharmaceutical ingredient. The choice of polymer for coating depends on the desired release profile, and polymers with differing degrees of polymerization and permeability can be selected to produce either delayed, enteric or sustained-release coatings. Bio-based and biodegradable polymers are also being developed as an alternative to conventional petroleum-based polymers.

6. Mucoadhesive and Transmucosal Drug Delivery

Biodegradable polymers with mucoadhesive properties may be used to prolong the residence time of drug formulations at mucosal surfaces. Chitosan and its modified derivatives are of particular interest due to their mucoadhesive properties and interaction with biological tissues. Such systems can increase drug retention and absorption, and may be useful for oral, nasal, buccal, ocular and other transmucosal routes. Biodegradable polymer-based ocular systems have also been explored for prolonged drug retention and controlled release.

7. 3D-Printed Biodegradable Drug Delivery Systems

Three-dimensional printing is an emerging technology for the fabrication of personalized drug delivery systems composed of biodegradable polymers. This technique permits exquisite control over dosage, geometry, internal architecture, porosity and drug-elution profiles. A variety of complicated morphologies, including hollow, porous, lattice and buoyant structures, can be designed to tailor drug release and residence time in the gastrointestinal

tract. Consequently, 3D printing offers an opportunity to develop patient-specific biodegradable dosage forms and sophisticated controlled-release systems [33].

8. Polymer Modification for Advanced Medical Applications

The modification of biodegradable polymers can be used to improve their functional and therapeutic properties. Chemical modifications, blending and inclusion of functional groups can alter the hydrophilicity, biodegradation rate and mucoadhesive properties, drug-loading capacity and stimulus responsiveness of such molecules. Polymers that have been modified in this manner can be designed to target specific physiological conditions that require pH-, temperature-, enzyme- or redox-responsive drug release. Modified polymers can also be used to improve targeted delivery and interactions with biological barriers. Thus, polymer modifications can serve as a valuable strategy for developing advanced drug-delivery, wound healing and regenerative-medicine systems.

9. Tissue Engineering and Regenerative Medicine

Biodegradable polymers are used as temporary scaffolding in tissue engineering. These polymers can provide a structural support as new tissue forms and then degrade. Polymers such as PLA, PLGA, PCL, chitosan and alginate have been investigated as scaffolds for the regeneration of bone, cartilage, skin and other tissues. The degradation rate, mechanical properties and biocompatibility can be tailored to meet the needs of the tissue being regenerated.

10. Wound Healing and Wound Dressings

Biodegradable polymers find applications also in wound-management systems, ranging from films and hydrogels, nanofibers and polymeric dressings. They can be used to provide a protective environment for the wound and can be engineered to allow a controlled release of antimicrobial or therapeutic agents. Natural biodegradable polymers, such as chitosan, are of interest also due to their biocompatibility and potential wound-healing properties.

Advantages of Biodegradable Polymers as Drug Carriers

Polymers are large molecular structures consisting of many identical or similar molecules connected by covalent bonds. Apart from being resorbable, the five main advantages of polymeric pharmaceutical products include

- Localized delivery of the pharmaceutical,
- Prolonged delivery of the pharmaceutical,
- Protection of the pharmaceutical,
- Less dependence of the rate of drug release on the physicochemical properties of the drug, and constant release of the drug.

Thus, the product can be implanted directly at the site of action, which reduces systemic exposure and enables targeting, which is especially valuable for toxic pharmaceuticals such as chemotherapeutic drugs. Second, the drug is delivered to the target tissues constantly and can be sustained for a relatively long time through the polymeric chains, which spares the patient the frequent injections, especially for protein-deficient individuals. The polymer shields the drug from the surrounding medium, thereby ensuring that they are not degraded, which is a significant advantage in delivering vulnerable pharmaceuticals like proteins. Fourth, in diffusion-controlled systems, the release of the drug typically decreases over time, while it is constant in the case of the degradation of polymers for which the increase in polymer porosity and chain scission can compensate for the decrease in drug solubility. Indeed, the controlled biodegradation of lactide polymers can provide a continuous release of the drug over time. Finally, the degradation rate of polymers determines the duration of the drug release, which is critical for the treatment of chronic diseases.

The five factors that affect the rate of biodegradation of lactide polymers include

- The chemical composition of the starting material
- The degree of crystallinity
- The hydrophobic character of polymers
- Hydrolytic biodegradation of polymers
- Molecular weight of the polymer

Disadvantages of Biodegradable Polymers as Drug Carriers:

Biodegradable polymers as drug carriers have various disadvantages over traditional drugcarrier systems:

- ✦ These include high production cost relative to conventional carriers.
- ✦ Low drug loading capacity for certain drugs.
- ✦ Inconsistent degradation rates that may compromise drug release profiles.
- ✦ An initial burst release of the encapsulated drug.
- ✦ Potential for irritation or toxicity caused by degradation by-products.
- ✦ Instability during storage.
- ✦ Challenging formulation process that requires optimization.
- ✦ Loss of drug potency during polymer manufacturing.
- ✦ Difficulties in scaling up the production process.
- ✦ Limited shelf-life for certain biodegradable polymer formulations.

Factor affecting biodegradation of polymers:

- Chemical structure
- Chemical composition
- Distribution of repeat units in multimers
- Presents of ionic groups
- Presence of unexpected units or chain defects
- Configuration structure
- Molecular weight
- Molecular-weight distribution

- Morphology (amorphous/semi crystalline, microstructures, residual stresses).
- The presence of low molecular weight compounds
- Processing
- Annealing
- Sterilization process
- Storage history
- Shape
- Site of implantation
- Adsorbed and absorbed compounds (water, lipids, ions, etc
- Physicochemical factors (ion exchange, ionic strength, pH
- Physical factors (shape and size changes, variations of diffusion coefficients, mechanical stresses, stress- and solvent-induced cracking, etc.)
- Mechanism of hydrolysis (enzymes versus water)

Current Trends and Challenges in the Field of Biodegradable Polymers:

One of the key challenges in scientific research worldwide is the development of methods for rapid biodegradation of synthetic polymers. Bioplastics can be either bio-based (i.e., derived from biomass) or biodegradable. The promising direction to solve the problem is the creation of additives or modifiers that will actively participate in the regulation process of biodegradation and accelerate the degradation of polyolefin, polystyrene, phthalates, and other plastics.

The absence of biodegradability for one polymer does not necessarily mean its inferiority over polymers with this ability because, in nature, all types of polymers are subject to powerful physicochemical forces. Thus, they are hydrolyzed by water, oxidized by oxygen, and become an excellent substrate for microorganisms. A biofilm is a large community of bacteria associated with a solid surface covered with water and polymers that swell when heated. According to Donlan and others, the formation of a biofilm leads to the swelling of the polymer surface, which makes it more susceptible to biodegradation[34].

At present, scientists are focusing on three main tracks:

1. Introduction of functional groups into biodegradable polymers for their photodegradation; 2. Creation of composite materials of conventional and biodegradable polymers for the initiation of biodegradation;

3. Synthesis of polymers of biodegradable plastics from standard industrial polymers. There are several methods for equipping conventional plastics with biodegradability:

1. The use of agro-industrial wastes (beet Pulp, oat, buckwheat, corn mash) as additives in synthetic polymers;
2. Composite materials based on synthetic and natural polymers (starch, cellulose, polylactic acid);
3. The addition of oxo-biodegradable additives to synthetic polymers, which contain metal salts that accumulate radicals hydroperoxides, peroxides, and radicals, which are transformed into hydroperoxide during biodegradation.
4. The production of PGA using hydrogen is a well-known technology. It involves the gasification of organic waste (natural polymers) into synthesis gas (a mixture of CO and H₂). The resulting gas is further transferred to photosynthetic bacteria, where it is synthesized into biomass through an anaerobic fermentation process. Another way to obtain hydrogen is the acidogenic fermentation of organic waste, which is a promising technology due to the high hydrogen yield. It is further used to create bioplastics.
5. The creation of biodegradable bioplastics with the help of biotechnological methods falls under the concept of “green plastics”. Green plastic is a biodegradable polymer obtained from renewable resources. It is of great interest as an alternative to conventional plastics from petroleum.

Today, mixed cultures of microorganisms can be used in the process of producing raw bioplastics, since the use of a single culture in the absence of strict sterility control is fraught with unpredictable consequences. The organic acids produced as a result of the acidogenic fermentation of municipal solid waste (MSW) can serve as a carbon source for the synthesis of raw bioplastics.

The advantages of the described technology for recycling organic waste include:

- Reduction of the amount of waste burned;
- Reduction of the amount of ash sent to landfills;
- The possibility of using seawater in the process of MSW separation.

Bio-based polyamides account for about 12% of the world market for bioplastics. Commercially available bio-based polyamides are produced from sebacic acid or undecanoic acid derived from castor oil. The most common bioplastic today is polyamide 11 (PA11). However, it is also possible to produce polymers such as PA610, PA1010, PA510, PA6, PA66, PA12 in a partly or fully bio-based composition.

The products presented in the first two categories are predominantly packaging materials: bags. Other products include food packaging: bags, wrappers, paper, cup wraps. Tableware (plates, cups), egg cartons, dairy packaging, and cosmetics packaging (sanitary napkins, tampon applicators) are also used. Degradation is relevant only if such products are not disposed of in an appropriate way. Otherwise, their presence in the natural environment is demoted. The production of plastic materials with photo- and biodegradability is associated with the introduction of photo- and bioactivating additives into the polymer chain, which are equipped with a mechanism for breaking down under the action of UV radiation, or the action of bacteria under anaerobic condition.

Bioplastics made of PHAs can be used in various sectors of the economy, including construction and agriculture. However, there are two technological challenges associated with the processing of raw PHA-based nanocomposite bioplastics. The first challenge is the relatively high melting temperature of PHAs, which is usually in the range of 160-180 °C[35]. The melting temperature of PHB is close to the temperature of its thermal degradation (Td). For comparison, the temperatures of protein, polysaccharides, and polynucleotide degradation are similar to the Td values. Thus, this value is a critical indicator for the thermal processing of any biopolymer material, as the proximity of the melting point (Tm) to Td indicates a decrease in the temperature

stability of the biopolymer. Fortunately, plant biomass contains a number of natural antioxidants that are able to inhibit the process of thermal degradation of bioplastics. It is also known that protein can act as a thermoplastic material when mixed with certain plasticizers that suppress crosslinking reactions. This technology allows the creation of thermoplastic materials instead of thermosetting ones. Therefore, the temperature and time regimes when processing composite bioplastics from raw PHA-containing matrices should be optimized to exclude excessive thermal degradation of PHA and other bacterial biopolymers contained in it.

At the moment, four main tracks of scientific research have been established, allowing the creation of such bioplastics. The first is the partial modification of natural polymers (starch, cellulose, pullulan). The second is the preparation of monomers from scratch or from natural polymers using fermentation technology, followed by their chemical polymerization (PLA, polyethylene). The third is the modification of selected microorganisms or the use of derived strains (PHA, PHB). The fourth option is the production of polymers with partial biodegradability (PBT, PBAT, PBS, PU). However, biodegradable bioplastics currently available on the market are characterized by rather long biodegradation periods under the action of microorganisms, despite the presence of specific conditions for their destruction.

FUTURE TRENDS:

Future advancements in biodegradable polymers are expected to focus on the development of copolymers with hydrophilic and hydrophobic interactions, enabling better control of drug release and enhanced therapeutic efficacy. Complexation networks responding through hydrogen bonding or ionic interactions are also being explored to improve the stability and responsiveness of drug delivery systems. Furthermore, biodegradable polymers are increasingly being developed as nanoparticles for the immobilization and delivery of enzymes, drugs, peptides, and other biological agents. The discovery of new biodegradable polymer and the development of novel blends of hydrocolloids and carbohydrate-based polymers are expected to expand the scope of biomedical and pharmaceutical applications. Advances in nanotechnology, smart polymers, and biomaterials are anticipated to improve target specificity, drug encapsulation efficiency, controlled release mechanisms, and patient compliance, making biodegradable polymers an integral part of future drug delivery technologies[36].

Recommendations for Future Research:

Through this review of biodegradable biobased polymers and their potentiality to become an alternative to petroleum-based polymers, we recommend below the future research directions

Improving Biodegradation Processes

Due to the many restrictions in the degradation of most common polymers, improvements must be made to existing degradation processes. Most current research proves the anaerobic and aerobic degradation process by mixing the polymers with pro-oxidants or natural polymers to increase the degradation rate. Furthermore, UV rays, heat, and light have pretreated the polymer. However, there have been few studies and data collected on how much these methods have improved the degradation rates of most used polymers (such as PLA or polyglycolic acid). With a better understanding of the effects of pretreatment processes and pro-oxidants on the degradation rates of polymers, one can improve the efficiency of the degradation of common plastics.

Reducing Microplastics and Subsequent Impacts on Environments:

One danger in the degradation of plastics is the formation of microplastics, which take longer to degrade. Although the early stages of degradation are fast, once they become microplastics, the degradation rate slows. The development of microplastics can cause many environmental issues, as they harm most living organisms. Because most common plastics used in packaging and plastic bottles are oxo-degradable plastics, further research must be conducted to improve the degradation process of these plastics to reduce the amount of microplastics in the environment[37].

Developing a Standardized Testing Procedure for Bioplastic Degradation:

As the need for waste reduction and lowered plastic consumption rises over the next decade, a common testing procedure must be developed to produce the most consistent and metric results. Agreed, there are common standards among which the degradation tests are run, but few draw important comparisons even among the same material, which can be challenging. This leads to inefficient data reporting and collection, and cross-comparisons between studies are not nearly as accurate, which causes a wider range of results. For example, a 28-day period for compost-degrading bioplastic should be employed, and it should have a set temperature, environment, and moisture, among other things. Only one degradation measure should also be employed, such as CO₂ evolution. CO₂ evolution provides more accuracy, as there is a direct measure of how much plastic has been degraded. SEM could be a useful, more in-depth measure, but the degradation assessment is more subjective due to its multifaceted nature.

Analyzing Compost Compositions and Environments

Composting is one of the most effective yet challenging methods of biodegradation for biopolymers. However, the compost's temperature, moisture, and environment must be monitored very closely for degradation to take place for a lot of bioplastics due to the nature of the microbial activity that occurs. Especially considering PLA, these factors must be given attention; otherwise, it could result in no mass change. Throughout many of the studies presented, some plastics resulted in minimal to no degradation. Further research should be pursued into what compost composition and environments best suit a given bioplastic[38].

Developing an End-to-End Production Process

While the general appeal of bioplastics is that they can be degraded in nature and not cause environmental harm, an end-to-end production process that utilizes bioplastics' byproducts, instead of letting it degrade, would be far more efficient. Facilities that accept used bioplastic products and convert them back into commercial-ready bioplastics and the optimization of its production processes could be revolutionary for the bioplastic industry. Despite decades of research, bioplastics have not been implemented in everyday plastic usage. A more efficient production and recycling method can potentially change this.

Identifying and Focusing on Materials with the Highest Potential

Based on viability and mechanical performance, certain materials, such as PLA, should be focused on more. PLA is one of the highest potential bioplastic materials because of how relatively easy and cheap it is to produce. Although PLA could degrade slower than some other materials in most environments,

such as PHB or PCL, it has been developed more as a material, researched extensively, and produced on a larger scale. PLA-based and starch-based biopolymer materials should be emphasized further in the literature to make an initial shift to a larger bioplastic economy possible, with more realistic techno-commercial production models being developed for practical applications. Bioplastics have been written about and researched for multiple decades now; a shift toward bringing this to every consumer is the next step, and progressing this idea further with a few bioplastic materials with the highest potential would allow for the idea to become closer to turning into a reality.

Conclusion:

Biodegradable polymers have become an important source of materials for pharmaceutical and biomedical engineering due to their possibility to control degradability, biocompatibility, mechanical properties, and drug-release rate. Their ability to gradually erode away offers a number of benefits over non-degradable polymers, including reduced invasiveness and the possibility to obtain the prolonged activity of a drug in the targeted location. The polymers that have been considered include PLA, PLGA, PCL, PHAs, chitosan, alginate, and others. They can be used for controlled and sustained drug delivery, nanoparticles, microparticles, hydrogel, implants, pharmaceutical coatings, transmucosal drug delivery, 3D-printed tablets, tissues engineering, and wound healing.

The characteristics of polymer implants largely depend on the properties of a polymer, such as its composition, molecular weight, crystal structure, morphology, hydrophobicity, and others, as well as the processing method, sterilization, storage, and the environment in which the implant is placed or embedded. Therefore, a careful selection of materials and conditions is required for obtaining the desired rate of degradation and drug-release profile. However, the clinical utility of biodegradable polymers in pharmaceutical technology is limited by some factors, including high cost, burst release, inconsistent degradability, low drug loading, instability during processing, poor storage, and scale-up difficulties.

Advanced methods for modifying commercial polymers, new approaches in nanotechnology, smart biomaterials, and individualized medicine allow for developing new effective treatment methods and reducing the amount of toxic system ingredients. Therefore, future research should be focused on the creation of new polymers with predictable degradation properties, high drug loading, and targeting ability. It is also important to develop new approaches to the degradation of biodegradable polymers and study the mechanisms of microplastic formation. Moreover, the standardization of biodegrading studies and the establishment of the requirements for materials with reduced environmental impact will also help to ensure the safety of biodegradable polymers and address current sustainability concerns. In general, the development of biodegradable polymers will allow creating new pharmaceutical and biomedical technologies with unique properties.

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