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Review Article

Biodegradable Polymer Use in Drug Delivery Systems: A Comprehensive Review

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Abstract

Biodegradable polymers have revolutionized the field of drug delivery systems, offering a promising solution to the limitations of traditional drug administration techniques. These polymers can be designed to degrade at specific rates, releasing therapeutics in a controlled and sustained manner, thereby improving bioavailability and reducing side effects. This review provides an overview of biodegradable polymers, including natural polymers like collagen, albumin, and gelatin, as well as synthetic polymers like polyesters, polyorthoesters, and polyphosphoesters. Here discuss the types of biodegradable polymers, their mechanisms, and benefits in drug delivery systems, including controlled release, targeted release, transdermal delivery, gene delivery, and tissue engineering. The review also highlights the future prospects and trends in biodegradable polymers, including the development of new polymers, blends, and nanoparticles.

Keywords: Biodegradable polymers, Drug delivery systems, Controlled release, Targeted delivery, Regenerative medicine

Introduction:

Drug delivery systems (DDS), which aim to maximise therapeutic effectiveness while minimising side effects, are critical to therapy administration efficiency. Traditional drug administration techniques frequently have drawbacks such as systemic toxicity, rapid elimination, and low bioavailability. Because of their ability to release medicines in a controlled, sustained, and targeted manner, biodegradable polymers are now an essential component of sophisticated drug delivery systems [1]. Biodegradable polymers are materials that can be degraded by various environmental microorganisms, such as bacteria and fungi, to produce water and carbon dioxide [2]. Biodegradable polymers are being developed as an alternative to non-biodegradable polymer materials in a variety of applications [3]. Biodegradation of biodegradable polymers is defined as the chemical decomposition of substances accomplished through the enzymatic work of microorganisms, resulting in a change in chemical composition, mechanical and structural properties, and the formation of metabolic products, which are environmentally friendly materials such as methane, water, biomass, and carbon dioxide [4]. The most effective way to manage non-biodegradable plastic waste is to replace the usage of uneconomical non-biodegradable materials for recycling or reuse with biodegradable polymers, which are environmentally friendly [5]. Because of the environmental contamination caused by the usage of non-biodegradable materials, research and development on biodegradable materials has risen [6]. Biodegradable polymers are materials that can function for a limited period before disintegrating into easily disposed products following a regulated process [7]. They could be generated from a number of wastes or bioresources, including food, animal, and agro-waste, as well as other sources including starch and cellulose[4]. Biodegradable plastics and polymers were first developed in the 1980s [8]. Polyesters were the first successful biodegradable polymers created for suture materials [9]. Bioplastics made from renewable resources are frequently less expensive than those made from microbial resources, causing producers to focus on producing bioplastics from renewable resources [7]. The usage of biodegradable polymers has environmental benefits such as raw material regeneration, biodegradation, and reduced carbon dioxide emissions, which contribute to global warming [10]. Biodegradable polymers can be consumed by microorganisms like bacteria and fungi, which then transform them into

methane, CO2, and H2O. The composition of the substance determines the biodegradation process [11]. The biodegradation process is influenced by the polymer's molecular weight, shape, structure, and chemical and radiation treatments [12]. Biopolymers are another name for biodegradable polymers [13]. The use of biodegradable or renewable polymers offers an alternate option. Therefore, there is a considerable increase in the manufacture and use of bio-based and biodegradable polymer materials, which can help reduce environmental issues related to waste polymer materials [8]. Research on renewable resources focusses on using corn, soy, sugarcane, potato, rice, or wheat, as well as oil-rich seeds or fermentation products, as raw materials to manufacture biopolymeric polymers [14]. The use of biomass to make biopolymers offers numerous advantages, as biomass-derived polymers are biodegradable and very easy to recycle [8]. Experts estimate that polymer manufacture consumes up to 7% of global oil and gas supplies [15].

Biodegradable and Nonbiodegradable:

1 Biodegradable polymers:

Biodegradable polymers undergo degradation, non-enzymatically and enzymatically and generate a harmless, biocompatible by-product [16]. Biodegradable polymers have a notable emphasis on the chemistry in the scheme of new molecules in targeted drug delivery applications. The use of biocompatible polymers reduces the side effects of a given drug [17]. Biodegradable biomaterials have no constant inflammatory effect, good permeability, and good therapeutic properties [18]. Biodegradable polymers are materials that can be degraded by various environmental microorganisms, such as bacteria and fungi, into water and carbon dioxide [2]. Biodegradation methods or decomposition begin on the polymer surface as a result of the action of microorganisms' extracellular enzymes, which generate oligomers. These matching oligomers subsequently enter the microorganism cell, where they serve as carbon sources and are converted into CO2 and water [16].

2 Nonbiodegradable polymer:

Local antibody injection is carried out using clinically non-biodegradable polymers. Acrylic polymers, cellulose derivatives, and silicon are among the most common non-biodegradable polymers [17]. Polymethyl methacrylate (PMMA) is an acrylic-based, non-biodegradable polymer that is mostly employed in bone cement or PMMA beads [18]. Because of the drawbacks of non-biodegradable polymers, scientists are working on developing biodegradable, biocompatible polymer synthesis for a drug delivery system [16]. The usage of nonbiodegradable polymer materials is dangerous to human health because they contain phthalates, which are chemical substances found in thermoplastics [17]. Human exposure to these components comes through food consumption and has been linked to negative health impacts, including hormone disturbance [19]. The most effective way to manage non-biodegradable plastic waste is to replace the usage of uneconomical non-biodegradable materials for recycling or reuse with biodegradable polymers, which are environmentally friendly [5]. Because of the environmental contamination caused by the usage of non-biodegradable materials, research and development on biodegradable materials has risen [6].

Types of Biodegradable Polymer:

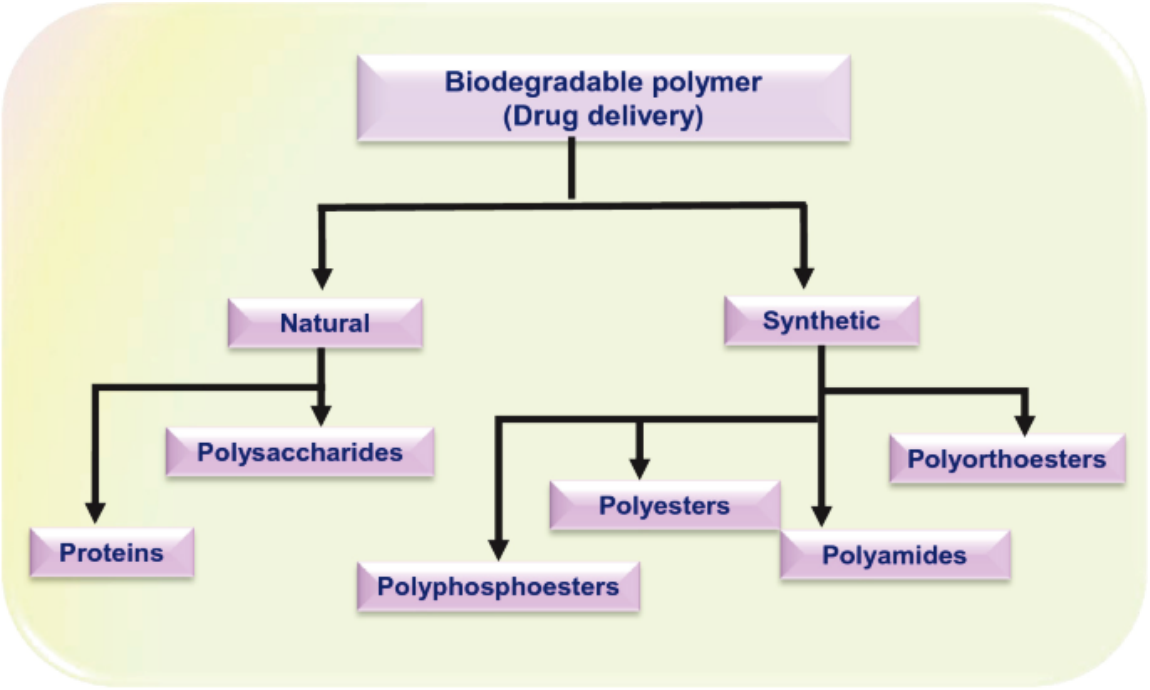

Figure 1: Types of biodegradable polymers [20].

Natural Polymer:

Protein based polymers: - Collagen, Albumin, Gelatin [21].

Polysaccharides: - Starch, Agarose, alginate, carrageenan, hyaluronic acid, dextran, chitosan, cyclodextrins [22].

Synthetic Polymer:

Polyesters: - Poly (lactic acid), poly (glycolic acid), poly (hydroxy butyrate), poly (ε-caprolactone), poly (β-malic acid), poly (dioxanones) [23].

Polyorthoesters: - Poly (sebacic acid), poly (adipic acid), poly (terephthalic acid) and various copolymers [24].

Polyamides: - Poly (amino carbonates), poly amino acids [25].

Polyphosphoesters: - Polyphosphates, poly phosphonates, poly phosphagens [26].

Others: - Poly (cyanoacrylates), polyurethanes, poly ortho esters, poly dihydropyrans, polyacetals [27].

Non-Biodegradable:

Cellulose derivatives: - Carboxymethyl cellulose, ethyl cellulose, cellulose acetate, cellulose acetate propionate, hydroxypropyl methyl cellulose [28].

Silicones: - Polydimethylsiloxane, colloidal silica [29].

Acrylic polymers: - Polymethacrylates, poly (methyl methacrylate), poly hydro (ethyl- methacrylate) [30].

Others: - Polyvinyl pyrrolidone, ethyl vinyl acetate, poloxamers, polyamines [31].

Natural Polymer

Protein-Based Polymer

1 Collagens:

The most prevalent proteins in mammals are collagens. There are 28 members of the collagen family that have at least one triple-helical domain [32]. Three distinguishing characteristics define the entire family of glycoproteins that are collectively referred to as "collagen." The amino acid repeating sequence [Gly–X–Y] n, both with and without breaks, is the first of these [33]. The second distinguishing property is that proline and its hydroxylated counterpart, hydroxyproline, respectively, occupy the X and Y locations. Third, collagen has a distinct quaternary structure due to the formation of the right-handed triple helix from three left-handed polyproline αchains of the same length [34]. The structure of the many collagen types, their splice variations, the existence of extra non-helical domains, their assembly, and their functions are all highly complex and diverse [35]. Although the peptides were heterogeneous polymers, the development of solid-state peptide synthesis allowed for the synthesis of peptides with specific lengths and sequences to simulate biological activity and elucidate triple-helix stability principles [36].

2 Albumin:

Albumin is the most prevalent plasma protein (35-50 g/L of human serum). Albumin is considered harmless, with low immunogenicity, biocompatibility, and biodegradability. Most critically, it acts as a transporter for many chemicals in the plasma [37]. Albumin improves drug solubility and targeting efficacy, and a number of nanoscale drug delivery methods have been investigated as anticancer agents [38]. Protein-polymer bioconjugates combine the strengths of both components to address challenges in biological applications [39].

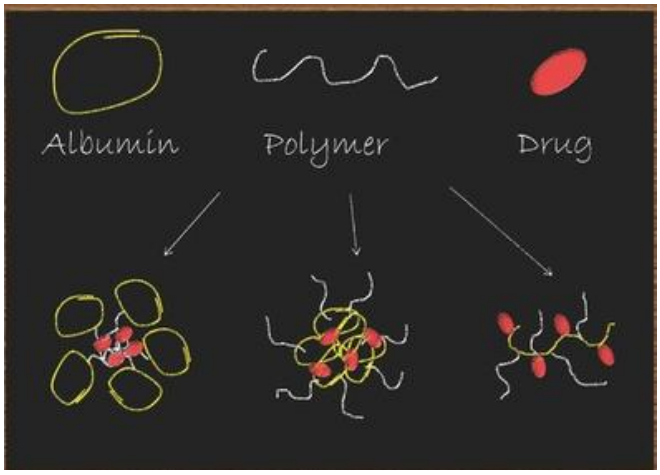

Figure 2: Activity of albumin polymer and drug [37]

3 Gelatin:

Gelatin derived from fish skin or bones is known for its biocompatibility, biodegradability, good solubility, non-immunogenicity, low cost, and biological origin. Its most notable feature is the abundance of arginine-glycine-aspartic acid (RGD) groups that promote cell adherence, migration, and differentiation [40]. Many researchers have turned their focus to gelatin, which is one of the most prominent natural polymers. Even though gelatin is made from collagen, it is less expensive than cell [41]. The cell polymer construct paradigm, which involves infusing a suspension of cells into an erodable porous scaffold, serves as the foundation for many tissue engineering techniques. Numerous characteristics of the developing tissue, such as food availability and growth kinetics, cell-cell interactions, extracellular matrix deposition, and morphological changes, are determined by the three-dimensional arrangement of cells implanted within the scaffold [42]. Scaffolds that combine bone cells with natural and synthetic biopolymers or composites are thought to be a promising way to get around the drawbacks of the traditional method of treating bone injuries [43].

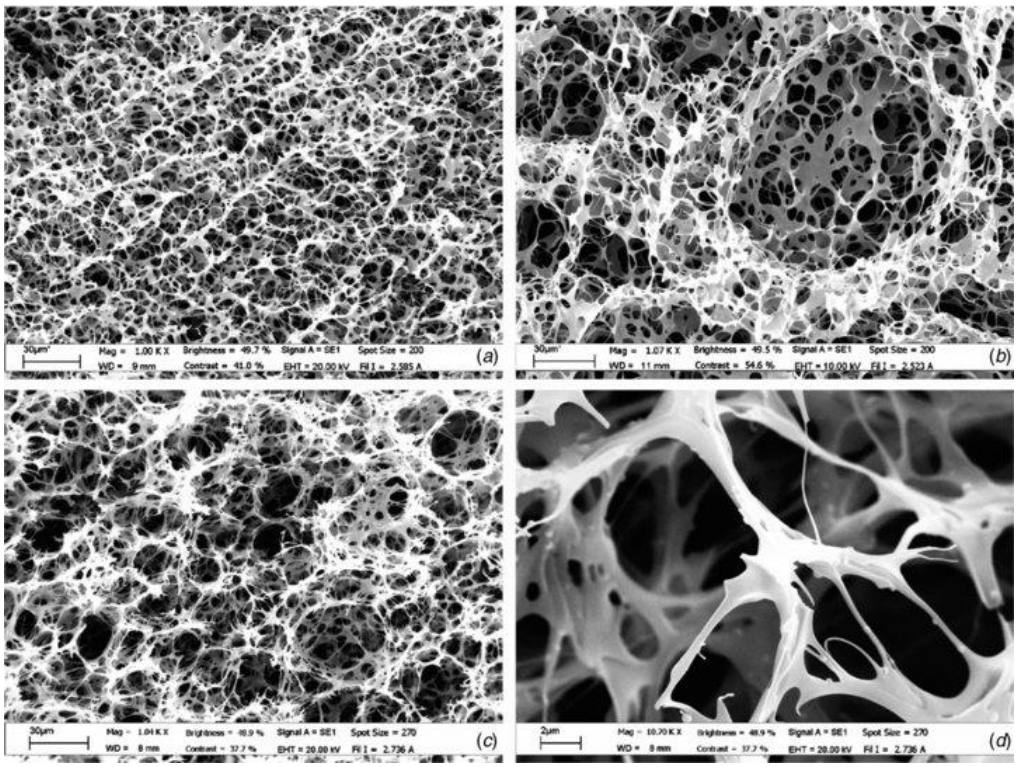

Figure 3: Cross-sectional SEM images of freeze-dried (A) GelMA, (B) GelMA-SF, (C) GelMA-SNAP, and (D) GelMA-SF-SNAP [40,41].

Polysaccharides:

1 Starch:

Starch is an emergent polymer in biomedical research due to its ease of availability, low cost, and biological properties [44]. Starch polymer has been employed as a powder and film in tissue engineering and haemostasis applications [45]. The starch is semicrystalline in form, with glucose units connected by glycosidic linkages [46]. Protein in starch is essential for creating a clean and transparent solution [47]. Phosphate in starch in the form of monophosphate improves solution stability and slows retrogradation rate [48].

2 Agarose:

Agarose is a well-known marine polysaccharide with reversible thermos gelling tendency, excellent mechanical characteristics, strong bioactivity, and switchable chemical reactivity for functionalisation [49]. The majority of polysaccharides display a high surface charge. This event occurs when the drug carrier hits an impediment during its circulation within the body, such as protein corona formation [50]. While agarose has a neutral surface charge at varying pH levels, this property allows agarose to transport drugs with little protein corona formation and improves delivery efficiency [51]. Drug carriers have low drug absorption, pharmacological leakage, inadequate targeting effects, and difficulties monitoring cellular events after administration; nonetheless, agarose and its derivatives are distinguished by their high efficacy in delivery processes [52].

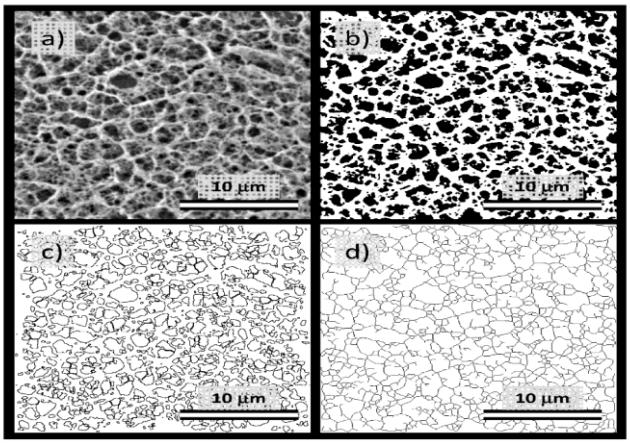

Figure 4 (a) Original image (1 wt.% agarose gel without any interpenetrating component). (b) Binary projection (grayscale thresholding using MaxEntropy algorithm) of the original image. (c) An image mask is provided by the application of the 'Analyze particles' tool. (d) Image mask is provided by the application of the 'Analyze skeleton' tool [53].

3 Chitosan:

Chitosan (Ch), derived from chitin deacetylation, is one of the most often utilised biopolymers. Chitin is a polysaccharide found in the exoskeletons of arthropods such as lobster and crab, as well as the endoskeletons of cephalopod molluscs such as squid, both of which are frequent fishing industry waste items [54]. Chitosan is the only known natural polycation with a greater DD%, increasing its charge density potential [55]. Functional chitosan derivatives can be classified into two groups based on their chemical structure: linker-containing derivatives and linker-free derivatives. Linkers are described as extra structural fragments between the

inserted functional substituent and the polymer backbone [56]. Some chitosan inhibits nematode growth and development, while others have antiviral action. Chitosan promotes plant growth and development, induces disease resistance, and improves abiotic stress tolerance [57]. Chitosan supports scar-free wound healing in animals and people, some appear to limit cancer cell proliferation, some may have anti-inflammatory or anti-oxidant potential, and a variety of other biomedically important bioactivities have also been described [58].

Synthetic Polymer:

Polyesters:

1 Polylactic Acid:

Polylactic acid polymer interference screws are commonly Q5 used in anterior cruciate ligament (ACL) reconstructions, especially in proximal tibia fixation [59]. However, several concerns have been raised, including the acid products during its degradation in vivo [60]. In recent years, biodegradable magnesium (Mg) based implants have become attractive because of their favourable mechanical properties, which are more similar to those of natural bone when compared with other degradable materials, such as polymers, apart from their alkaline nature during degradation [61].

2 Poly glycolic acid:

Poly (lactic-co-glycolic acid) (PLGA) is one of the most studied biodegradable polymers in a variety of biological applications, including drug delivery and tissue engineering [62]. Polymeric biomaterials have been widely employed in commercial biomedical goods for decades [63]. Poly (lactic-co-glycolic acid) or poly(lactide-co-glycolide) (PLGA) is a thermoplastic co-polyester composed of various monomer ratios that is hydrolysed in vivo into non-toxic lactic and glycolic acids, which are metabolised in the tricarboxylic acid cycle and eliminated via carbon dioxide and water [64]. According to research findings, increasing glycolic acid concentration in PLGA (PLA/PGA) results in faster degradation because to increased hydrophilicity [65].

Figure 5: Poly glycolic acid suture [66]

Polyorthoesters:

1 Poly sebacic acid:

Polyorthoesters are a type of biodegradable and biocompatible polymer utilised for long-term administration of bioactive substances [67]. The rate of polymer breakdown is greatly dependent on the device's molecular weight, hydrophobicity, pH, crystallinity, porosity, and surface area[68]. Biocompatible polyanhydrides, such as poly(sebacic acid) (PSA) derived from sebacic acid, breakdown more quickly than other biocompatible polymers, such as poly(esters) [69]. The PSA microparticles were spherical, ranging in size from many hundreds of nanometres to a few tens of micrometres [70]. PSA-based polymeric microparticles can be used as carriers for long-term, consistent nutrition delivery [71].

2 Poly adipic acid:

Poly(adipic anhydride) decomposed faster than its hydrophobic counterpart, poly(sebacic anhydride) [72]. In general, the polymer chain's breakdown rates slow down as its water solubility decreases [73]. Thin films are created from poly(adipic anhydride) blends in various ratios, and films are also made from the copolymer poly(salicylic acid-co-sebacic acid) [74]. These films are intended to serve as sacrificial layers for self-regenerating functional coatings, such as those that regenerate antibacterial surface activity [75].

Polyphosphoesteres:

Polyphosphate:

Polyphosphate (polyP) is a linear arrangement of inorganic phosphates that defies its structural simplicity by performing an astonishing number of distinct functions in the cell [76]. Polyphosphate (polyP), an extremely simple polyanion, has long been known to play a role in a wide range of cellular processes, from stress resistance, biofilm formation, and virulence in bacteria to bone mineralisation, blood clotting, and mammalian target of rapamycin (mTOR) signalling in mammals [77]. Inorganic polyphosphates (polyP) are linear polymers made of dozens to hundreds of phosphate residues [78]. Inositol polyphosphates (IPs) and inositol pyrophosphates (PP-IPs) control a variety of biological functions in eukaryotic cells [79]. Both bacteria and their eukaryotic hosts manufacture inorganic polyphosphate (polyP), which seems to have a number of significant functions in the interactions between those species [80].

Non Biodegredable Polymer:

Cellulose Derivative:

1 Carboxymethyl Cellulose:

Carboxymethyl cellulose (CMC) is a water-soluble cellulose derivative and a prominent type of cellulose ether formed by the chemical attack of alkylating reagents on activated non-crystalline areas of cellulose [81]. Carboxymethyl cellulose (CMC)-based wound dressing materials have sparked intense interest because to their noble qualities, which include biocompatibility, biodegradability, tissue resemblance, low cost, and non-toxicity [82]. It has a wide range of uses in the biomedical and pharmacological industries. CMC's hydrophilic nature allows it to be blended and crosslinked with other materials such as synthetic polymers, natural polymers, and inorganic materials, allowing for the development of novel wound dressing biomaterials [83]. Carboxymethyl cellulose (CMC) has been shown to be useful in the pharmaceutical sector and is used in a variety of drug delivery methods, such as hydrogels, quantum dots,

magnetic mesoporous nano carriers, and nanocomposites [84].

2 Ethyl Cellulose:

Ethyl cellulose (EC) is produced by chemically substituting the naturally occurring polymer cellulose [85]. Ethyl cellulose (EC), a water-insoluble polymer, could be employed to delay medication release and improve oral drug bioavailability [86]. EC is hydrophobic in nature and is widely employed as a coating material, tablet binder, in microcapsules and microspheres, and in the manufacture of matrix-type controlled release tablets [87]. Ethyl cellulose nanoparticles boosted oral bioavailability and could treat fungal infections safely and efficiently, avoiding the negative effects of some intravenous preparations [88].

Silicons:

Polydimethylsiloxane:

Polydimethylsiloxane (PDMS)-based elastomers have been widely employed in biological applications for many years [89]. PDMS is noted for its minimal toxicity, physiological inertness, high biocompatibility, and blood compatibility. PDMS-based devices include drainage implants for glaucoma patients, blood pumps, mammary prosthesis, cardiac pacemaker leads, medical adhesives, and denture liners [90]. Polydimethylsiloxane (PDMS) has become a microfluidics industry standard due to its simple construction technique and material properties like as gas permeability, optical transparency, and flexibility [91]. PDMS is a crosslinked polymer of hydrophobic dimethylsiloxane oligomers, which poses two problems for its application in cell culture systems [92].

Colloidal / Mesoporous Silica:

Mesoporous silica (MPS), created via the supramolecular polymer templating process, is one of the most appealing nanomaterials for biomedical applications such as drug administration, labelling, and tissue engineering [93]. Nanomaterial pore shapes have been identified as one of the primary factors contributing to nanotoxicity due to differences in cellular absorption and immune response [94]. Silica is generally thought to be non-cytotoxic [95]. MPS nanoparticles are more biocompatible than colloidal silica and show great promise for use in biomedical and biotechnological applications [96].

Acrylic Polymer: -

Polymethacrylate

Polymethacrylate is the most often utilised organic polymer for casting monoliths for biomolecular separation [97]. Polymethacrylate has long been employed in pharmaceutical preparations to produce controlled release in tablets, although it was only recently introduced into liposome modification [98]. Polymethacrylate monoliths generally perform well in chromatography, and in some situations, the efficiency improves with increasing flow rate [99]. Polymethacrylate monoliths have become increasingly popular in research applications, allowing for high throughput biomolecule purification on semi-preparative and preparative scales [100].

Mechanism And Benefits of Biodegradable Polymer in Drug Delivery System

Control Drug Release:

Mechanism:

Biodegradable polymers can be designed to disintegrate at certain rates, giving precise control over the timing and rate of drug release [101].

This regulated degradation allows therapeutic drugs to remain in the bloodstream or at the target site for longer periods of time [102].

Controlled release medication delivery uses drug-encapsulating devices that allow therapeutic agents to be released at controlled rates over long periods of time, ranging from days to months [103].

Benefits:

Medicine administration frequency is reduced since the medicine is released gradually [101].

Steady release eliminates the peaks and troughs associated with traditional dosage, resulting in optimal medication levels[102].

Controlled release minimises the likelihood of damage from large initial doses [103].

Total drug usage was reduced when compared to usual therapy [104].

Targeted Drug Release:

Mechanism:

Biodegradable polymers can be engineered to respond to specific stimuli (such as pH, temperature, and enzymes) found in the target tissue or disease site [105].

This targeting capability ensures that the medicine is released largely at the point of action [106].

Benefits:

Higher local medication concentrations can be achieved, improving the therapeutic efficacy [106].

Reduces drug distribution to non-target organs, lowering the possibility of systemic adverse effects [105].

Enhanced targeting can result in better therapeutic outcomes, particularly in cancer and localised infections [107].

Transdermal Drug Delivery System:

Mechanism

Polymers are utilised in patches or gels to transfer medications through the skin for systemic effects [108].

TDD is a painless way of systemically administering medications that involves putting a drug formulation to undamaged and healthy skin [109].

Benefits: **-**

Transdermal patches for consistent release of hormones [108].

Analgesic patches for the treatment of persistent pain [109].

Patches to help people quit smoking [108].

Gene Delivery Systems

Mechanism

Gene therapy is made easier by biodegradable polymers, which both shield and transport genetic material (DNA, RNA) to target cells [1].

The creation of superior drug delivery vehicles is crucial for the body's breakdown of gene therapy medications and their efficient distribution to target tissues, cells, and organelles [110].

Benefits

Delivery of genes that boost the immune system or cause cancer cells to undergo apoptosis [111].

Delivery of functional genes to correct genetic abnormalities [110].

Distribution of DNA vaccines that trigger robust immune reactions [112].

Tissue Engineering and Regenerative Medicine

Mechanism

In order to promote tissue regeneration, biodegradable scaffolds release growth factors and offer a supporting framework for cell growth [113].

A key component of tissue engineering is the creation of complex scaffolds that offer the support and signals required for cell growth and differentiation [114].

Benefits

Scaffolds including chondrogenic or osteogenic components [113].

Skin-graft and wound-healing scaffolds [115].

Scaffolds that supply neurotrophic nutrients and promote nerve development [114].

Future Prospective

Based on the present market size, share, growth, demand, and trends, it is predicted that biopolymer consumption and production patterns will increase over the next several years. However, one of the biggest obstacles to biopolymers capacity to compete with plastics generated from petroleum is still their high cost of manufacture [2].

Enhancing drug encapsulation and release kinetics methods to attain the best possible therapeutic results. Drug loading capacity and controlled release will be improved by advancements in formulation science and drug-polymer interactions [1].

Simplifying regulatory procedures to enable the commercialisation and approval of medication delivery devices based on biodegradable polymers. Industry, academics, and regulatory bodies working together will create uniform standards and hasten market access [116].

Future Trend [117]

Copolymers with hydrophilic/hydrophobic interactions.

Complexation networks responding via hydrogen or ionic bonding.

Polymers as nanoparticles for immobilization of enzymes, drugs, peptides, or other biological agents.

New biodegradable polymers.

New blends of hydrocolloids and carbohydrate-based polymers.

Conclusion:

Biodegradable polymers have transformed the field of drug delivery, offering a promising solution to the limitations of traditional drug administration techniques. Their ability to degrade at specific rates, releasing therapeutics in a controlled and sustained manner, has improved bioavailability and reduced side effects. As research continues to advance, we can expect to see the development of new biodegradable polymers, blends, and nanoparticles, which will further enhance the efficacy and safety of drug delivery systems. With ongoing innovation and collaboration between industry, academia, and regulatory bodies, biodegradable polymers will play a crucial role in shaping the future of drug delivery and regenerative medicine, ultimately improving patient outcomes and quality of life. The potential of biodegradable polymers in drug delivery systems is vast, and their impact will be significant, enabling the treatment of various diseases and improving human health.

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