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Review

Applications of Bioengineered Polymer in the Field of Nano-Based Drug Delivery

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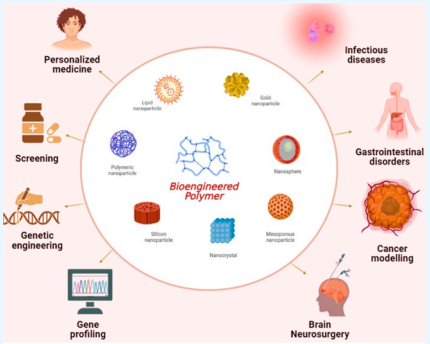
ABSTRACT: The most favored route of drug administration is oral administration; however, several factors, including poor solubility, low bioavailability, and degradation, in the severe gastrointestinal environment frequently compromise the effectiveness of drugs taken orally. Bioengineered polymers have been developed to overcome these difficulties and enhance the delivery of therapeutic agents. Polymeric nanoparticles, including carbon dots, fullerenes, and quantum dots, have emerged as crucial components in this context. They provide a novel way to deliver various therapeutic materials, including proteins, vaccine antigens, and medications, precisely to the locations where they are supposed to have an effect. The promise of this integrated strategy, which combines nanoparticles with bioengineered polymers, is to address the drawbacks of conventional oral medication delivery such as poor solubility, low bioavailability, and early degradation. In recent years, we have seen substantially increased interest in bioengineered polymers because of their distinctive qualities, such as biocompatibility, biodegradability, and flexible physicochemical characteristics. The different bioengineered polymers, such as chitosan, alginate, and poly(lactic-*co*-glycolic acid), can shield medications or antigens from degradation in unfavorable conditions and aid in the administration of drugs orally through mucosal delivery with lower cytotoxicity, thus used in targeted drug delivery. Future research in this area should focus on optimizing the physicochemical properties of these polymers to improve their performance as drug delivery carriers.



Potential Applications of Bioengineered Polymers

INTRODUCTION

Drug delivery is delivering medicine to the target site to obtain safer and more effective therapeutic results.[1] One of the key goals that clinicians seek to achieve is drug release at the site of action. However, safe medication deliveries to pathogenic areas and regulated release are the primary difficulties facing drug delivery systems. By the creation of therapeutically relevant formulations, drug delivery research ultimately aims to benefit patients. Controlled drug delivery technology has improved dramatically over the past few decades, enabling the creation of numerous therapeutic formulations that increase patient compliance and convenience.[2] Conventional drug delivery systems release the drug from the formulation at an uncontrolled rate, causing many disadvantages in the field of drug therapeutics. Current drug delivery approaches allow for delivery of the drug at a determined rate, increasing the bioavailability of the drug, reducing the side effects, and reducing the dosing regimen. Drugs are typically administered orally or transdermally, significantly increasing treatment efficacy and reducing side effects.[3] Drugs can be locally delivered for months or even years through implantable systems.[4] Even though they play a key role in drug delivery, there are possible areas where they can be considered clinically relevant. Targeted medication delivery to solid tumors is one such topic. The capacity to specifically target a medicine or drug carrier to reduce drug-originating systemic adverse effects makes targeted drug delivery clinically meaningful. The efficacy of medications intended to provide prevention or, more frequently, therapeutic relief of clinical diseases is governed by a wide range of intricate and interrelated parameters.[5] This comprises inherent pharmacological characteristics, such as the specificity of the drug's action and its molecular size and chemical makeup, which determine its general solubility in bodily fluids, penetration into tissues, and cell uptake.

The effectiveness of the treatment is significantly influenced by several physiological processes of the body, including drug clearance by specific organs, potential metabolic transformation, degradation, disposal, and drug circulation half-life. The process of creating a new medicine molecule is time-

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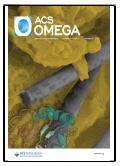

consuming, costly, and frequently unsuccessful, so employing older medications in clinics may be more efficient if their bioavailability, targetability, efficiency, or safety is improved. Numerous approaches, such as individualized drug therapy, chemical conjugates, therapeutic drug monitoring, nanoparticle-based drug delivery systems, and stimuli-sensitive targeted therapy, are being thoroughly researched for these reasons.[6] Over the past few decades, several studies have been done on nanoparticular drug delivery systems with particular emphasis on the outcome.

BIOENGINEERED POLYMER AND ADVANTAGES

In living organic systems, polymers, such as proteins, polysaccharides, and nucleic acids, are present as fundamental elements. To suit the needs of both industrial and scholarly applications, synthetic polymers that are intended to resemble these biopolymers have been produced in a range of functional forms. Synthetic polymers can be divided into various types based on their chemical characteristics. Few unique polymers have evolved into a very practical class with unique chemical properties and usage in various contexts. Based on the changes in their physical and chemical properties per the desired activities, their polymers are categorized as stimuli-responsive or smart polymers.[7] The trait that genuinely distinguishes them as "smart" is their propensity to react to even the smallest environmental alterations. While the introduction of smart-responsive polymers in this context is a pivotal development, it is essential to recognize that not all bioengineered polymers require smart or responsive properties. These materials, often meticulously tailored for biocompatibility, biodegradability, and maintenance of a stable environment, serve as the backbone for drug delivery and tissue engineering applications. In these scenarios, the priority is the provision of a secure and consistent platform for drug release and tissue regeneration. Smart or responsive behavior, such as adapting to external stimuli, becomes indispensable only when precise control and adaptation are necessitated by the specific goals of an application. For example, in drug delivery, responsive polymers can be engineered to release drugs in a targeted and controlled manner, thus optimizing therapeutic efficacy. Likewise, in tissue engineering, smart polymers can mirror native tissue behavior, responding to mechanical or biochemical forces, thus facilitating improved integration.[8] Therefore, the choice of incorporating smart or responsive properties in bioengineered polymers is unequivocally guided by the distinct objectives of the application, emphasizing that such characteristics are advantageous but not universally imperative. "These materials are special not only because of the rapid changes in their structure at the macroscopic level but also because these changes are reversible. Responses can take the form of modifications in shape, surface properties, and solubility; the development of complex molecular assemblies; a sol-to-gel transition; and other factors. These transitions can be triggered by changes in temperature or pH, an increase in ionic strength, the presence of specific metabolic chemicals, the addition of an oppositely charged polymer, or the development of polycation−polyanion complexes. The physiological features of water-soluble smart polymers typically change in response to external stimuli, and some are responsive to numerous stimuli. Their organization, solubility, or hydrophobic−hydrophilic balance are all affected by this alteration.[9] The thermosensitive polymers have undergone extensive research, and at a key solution temperature known as the cloud point, they exhibit a volume phase transition that is responsive to changes in the solvation state. At crucial onset points, physical inputs such as temperature, electric, or magnetic fields and mechanical stress will change the level of different energy sources and modify molecular connections. They quickly and irreversibly transfer from a hydrophilic to a hydrophobic state in terms of microstructure.[10] The production of precipitates from solutions or changes in the size and water content of stimuli-responsive hydrogels are two examples of how these changes manifest at the macroscopic level. The phase transition is thought to need a proper balance of hydrophobicity and hydrophilicity in the polymer's molecular structure. The basic advantages of bioengineered polymer usage are shown in Figure 1.

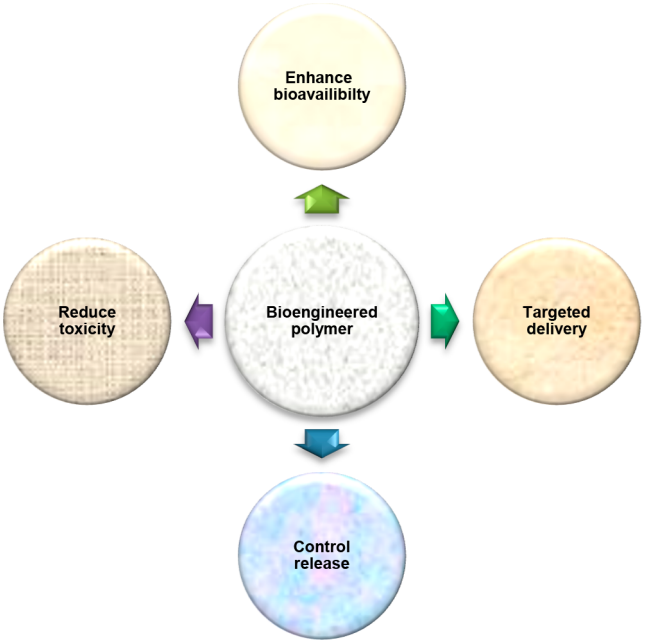

Figure 1. Advantages of bioengineering polymer. Adapted from ref 11. CC BY 4.0, 2022, MDPI.

SYNTHESIS AND PROPERTIES OF BIOENGINEERED POLYMERS

The process of developing polymer materials designed for particular biomedical uses is termed the synthesis of bioengineered polymers. These polymers are designed to have particular characteristics and capabilities that make them appropriate for use in tissue engineering, drug delivery, and other biomedical uses. Selecting particular monomers that can be chemically linked together through polymerization is the normal approach to creating bioengineered polymers.[12] The final polymer can be altered to improve specific characteristics, such as its mechanical strength, biocompatibility, and degradation rate.

Biopolymers, derived from biological resources, possess unique qualities such as biodegradability, high thermal stability, nontoxicity, and antibacterial and antifungal properties, making them versatile and eco-friendly for various applications. These biopolymers are synthesized through various methods including esterification, dehydration, polycondensation, hydrolysis, and granulation. Esterification allows for the modification of biopolymers such as cellulose, starch, and

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Table 1. Steps to Synthesize the Polymers

S. No.	Step	Description	Ref.
1.	Selection of monomer	It is crucial to choose the right monomers for biosynthesis. For example, lactide and lactic acid are polylactic acid (PLA) synthesis monomers.	26
2.	Polymerization	After choosing the monomers, they are polymerized using various techniques, such as ring-opening polymerization. Utilizing a catalyst like stannous octoate, lactide monomers are ring-opened polymerized in the case of PLA.	27
3.	Modification	The characteristics of the synthesized polymer can be modified. For example, various ratios of lactic acid and lactide can be added during the PLA synthesis to change the polymer's molecular weight.	28
4.	Characterization	The characteristics of the synthesized polymer, such as its molecular weight, thermal stability, and biocompatibility, are then determined through characterization. For example, differential scanning calorimetry is used to evaluate the thermal properties of PLA, while gel permeation chromatography is used to find the molecular weight.	29
5.	Formulation and development	The synthesized polymer is then processed into a scaffold for tissue engineering applications or a drug delivery system. For example, PLA can be used as a scaffold for bone tissue engineering or as nanoparticles for drug delivery.	30

hemicelluloses, leading to products with applications in plastics, coatings, explosives, and more. Microbial poly(β,L-malic acid) methyl esters with different conversion degrees of 25, 50, 75, and 100% were synthesized, leading to copolyesters with reduced crystalline characteristics, degradation rates that depend on methylation level, and decreased heat stability. The 100% methylated product was effectively used for producing erythromycin microspheres, and drug release was mostly based on the hydrolysis of the host polymer. Dehydration techniques, using agents such as trehalose and cyclodextrins, preserve the structural integrity of biopolymers and enhance enzyme stability, with applications in areas such as adhesives, coatings, and drug delivery systems. Microbial poly(β,L-malic acid) methyl esters with different conversion degrees of 25, 50, 75, and 100% were synthesized, leading to copolyesters with reduced crystalline characteristics, degradation rates that depend on methylation level, and decreased heat stability. The 100% methylated product was effectively used for developing erythromycin microspheres, and drug release was mostly based on the host polymer hydrolyzing.[13]

Polycondensation enables the development of specialized polymers, including phosphorus-containing polymers, melamine/formaldehyde microspheres, and flexible foam and fiber resins, finding use in pharmaceuticals and tissue engineering. Synthetic biopolymers, with their distinct characteristics and versatile synthesis methods, play a pivotal role in various industries, from medicine to environmental protection.[14]

Poly(D,L-lactic acid) (PDLLA) was synthesized using D,L-acid and $SnCl_2$ as a catalyst through melt polycondensation, with a resulting Mη of 4100 Da. PDLLA was used for drug delivery, producing effective microspheres for lung targeting with good in vitro and in vivo performance for erythromycin and ciprofloxacin with a sustained release profile. Tamarind gum graft copolymers of polyacrylamide, synthesized using ceric ammonium nitrate and microwave exposure, exhibited enhanced properties, including increased swelling index, thermal stability, and antibacterial activity.[15] A multistep procedure, including monomer selection, polymerization, modification, characterization, and formulation, is required to create bioengineered polymers, as shown in Table 1.

TARGETED DRUG DELIVERY OF BIOENGINEERING POLYMER-BASED NANOFORMULATIONS

Paul Ehrlich first proposed the concept of drug targeting at the beginning of the 20th century. Ehrlich used the term "magic bullet" to describe a hypothetical creature made up of a therapeutic substance connected to a component capable of identifying a disease target and allowing accurate medication delivery. Targeted drug delivery, independent of route and manner of drug administration, is the accumulation of the majority independent of the route and manner of drug administration and the accumulation of most of the drug inside a target zone.[16] The particular molecular interaction between medication and its receptor is known as a target−agonist interaction. Bioengineered polymers have been developed to improve the efficacy and safety of drug delivery to the various sites of the gastrointestinal tract. These polymers can be modified with various functional groups to allow targeted delivery to particular cells or tissues along with various drug release mechanisms like possessing gastro-retention or mucoadhesion properties.[17] The four essential elements of retention, evasion, targeting, and release are necessary for efficiently targeted drug delivery systems. For formulations meant for intravenous administration, this entails effective drug loading into a delivery vehicle, enough time spent in the circulation to reach the body's intended sites, retention by particular characteristics within those sites (i.e., targeting), and release of drugs at the target site within a window of time that enables the drug to function as intended.[18] According to the drug delivery method chosen, multiple delivery systems are needed for drugs that target specific areas of the body. An adaptable system for the targeted delivery of drugs and other therapeutic agents to treat different diseases of the gastrointestinal tract is provided by bioengineered polymers.

Chitin, present in crab exoskeletons, is the source of chitosan, a biocompatible and biodegradable polymer.[19] Due to its mucoadhesive qualities, which enable it to bind to the mucus layer lining the stomach, chitosan has been widely researched for drug delivery to the stomach. Chitosan-based nanoparticles have been developed to deliver chemotherapeutic and anti-inflammatory drugs.[20] Chitosan is widely utilized to enhance drug absorption due to its mucoadhesion property and tendency to interact and open tight junctions between mucosal cells.[21]

Coating of nanoparticles with advanced engineered polymers possesses a smaller size that allows for the release of the medication at the intended site in the brain following intravenous administration, circumventing the blood−brain barrier. Compared to free paclitaxel, the albumin-coated polymeric formulation of paclitaxel (Abraxane) has demonstrated superior response in the treatment of aggressive breast cancer lately.[22]

The receptor for the oligopeptide sequence is exclusively expressed by tumor cells, making it extremely selective to it. The first cell-targeting polypeptide discovered was the polypeptide known as RGD, which is composed of arginine, glycine, and aspartic acid. It has a great affinity for $\alpha v\beta 3$ integrins, which are overexpressed by both tumor cells and angiogenic endothelial cells.[23]

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Alginate is a natural polysaccharide derived from brown seaweed that is used for drug delivery to the stomach. Alginate forms a gel-like matrix in the presence of calcium ions, which can encapsulate drugs and protect them from degradation in the stomach's acidic environment.[24] Alginate-based hydrogels have been developed to sustain drug release to the stomach. PLGA is a biodegradable polymer extensively studied for drug delivery to the stomach due to its biocompatibility, biodegradability, and flexible release kinetics[25] Drugs such as anti-inflammatory and chemotherapeutic drugs can be delivered to the stomach precisely using PLGA-based nanoparticles and microparticles.

Utilizing bioengineered polymers to target particular cells or tissues of any organ system is known as targeted medication delivery. This strategy can be accomplished by adding ligands, antibodies, or other targeted molecules to the polymer matrix. Examples of targeted drug delivery systems include antibody-conjugated nanoparticles and peptide-targeted microparticles.[31] Bioengineered polymers have shown great promise in developing targeted drug delivery systems for various diseases that affect the stomach and other parts of the gastrointestinal tract. A potential strategy for generating therapeutic applications in the stomach is the development of bioengineered polymers. These polymers are artificial or organic substances that were developed to resemble the composition and traits of biological substances. They are ideal for developing therapies for various stomach-related conditions because they can be engineered to have specific characteristics, like biodegradability, biocompatibility, and targeted drug delivery.[32]

Drug delivery systems that adhere to the ulcer site and release drugs such as ranitidine slowly can be developed using bioengineered polymers. These systems may be developed to deliver drugs over an extended period, boosting the rate of ulcer healing. The polymers used in this application can be made specifically to meet the needs of the drug being given.[33] The lower esophageal sphincter (LES) can be strengthened, and the opening through which acid enters the stomach can be reduced by implanting devices made of bioengineered polymers. To aid in the recovery of LESs and stop acid reflux, these devices may be made of biodegradable materials that release drugs gradually. For this purpose, the polymers must be robust.[34] Drug delivery methods that target stomach cancer cells while minimizing the risk to healthy cells can be developed using bioengineered polymers. These devices can be made to release the drug gradually over time, allowing for sustained drug delivery to the cancerous tissue. The polymers used in this application can be tailored to meet the particular needs of the drug being given.[35]

Drug delivery methods for targeting the stomach can also be developed with the help of bioengineered polymers. To increase treatment effectiveness and reduce side effects, these systems can be engineered to release medication gradually at the targeted site. The polymers used for this can be customized to meet the needs of the drugs being administered and are biocompatible and biodegradable.[35,36] Bioengineered polymers can be used to develop drug delivery systems that particularly target the inflammatory tissue in inflammatory bowel disease. These systems can be made to release the drug gradually over time, allowing for sustained drug delivery to the inflammatory site. Devices implanted in the stomach to help functional dyspepsia can be developed using bioengineered polymers that can release drugs gradually, helping to control gastric motility and reduce symptoms.[37]

BIOENGINEERED MATERIALS

Bioengineering is the application of principles and methods from engineering, biology, and other fields to solve problems in healthcare, agriculture, environmental science, and other areas.[38] Bioengineered materials are created or modified by using biological processes or materials. These special materials have been used in biosensors, tissue engineering, drug delivery, and other fields.[39] Tissue engineering is one of the most exciting uses of bioengineered materials. Creating new organs or tissues in a lab and then transplanting them into the body to substitute diseased or damaged tissue is known as tissue engineering.[40] New cells can be grown on scaffolds made from bioengineered materials. These scaffolds serve as a structure for cells to develop and arrange themselves into useful tissue. Hydrogels, manufactured polymers, and natural polymers can all be used to create tissue engineering materials (Figure 2). In

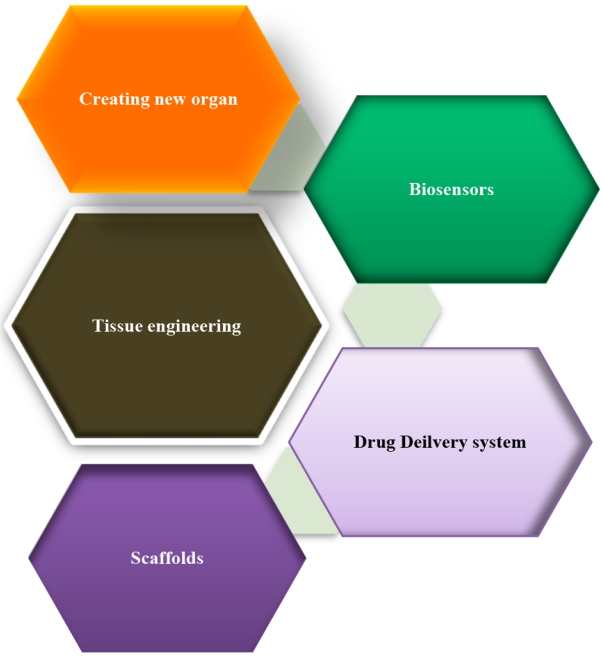

Figure 2. Application of tissue engineering. Adapted from ref 48. CC BY 4.0, 2021, MDPI.

the laboratory, synthetic polymers are made and can be modified to have particular characteristics, such as strength and flexibility.[41,42] Collagen and fibrin are natural polymers that can be extracted from the body and treated as scaffolds. A form of material called hydrogel can absorb a lot of water and has characteristics similar to those of natural tissue.[43] In addition to scaffolds, bioengineered materials can be used as coverings for medical devices such as stents and implants. These coatings can help prevent the body from rejecting the device and promote tissue growth around the device. Drug distribution is another use for bioengineered materials.[44] A liposome is an illustration of a bioengineered drug delivery mechanism. Liposomes are tiny lipid-based spheres that can contain medicines.[45] The drug will gradually be released into the bloodstream after the liposome has been injected. Liposomes can release drugs at particular body places such as tumor sites. Biosensors are tools that can identify and quantify biological

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elements such as DNA and proteins. A few biosensor applications include food safety, environmental monitoring, and medical diagnostics.[46] Bioengineered biosensors can be developed by attaching living molecules to a surface. In addition to other materials, polymers, metals, and semiconductors can be employed to create biosensors. A bioengineered biosensor is an example, such as a glucose monitor.[47] Some of the bioengineered materials are as follows.

Gold Nanoparticles. Gold nanoparticles (AuNPs) are a form of a bioengineered material. They are a particular class of nanoparticle with a size between 1 and 100 nm with a crystalline arrangement of gold atoms.[49] The amazing optical, electrical, and catalytic capabilities that gold nanoparticles have been found to possess have made them valuable in a variety of applications. The optical characteristics of gold nanoparticles are among their characteristics. When subjected to electromagnetic radiation, they display a phenomenon called surface plasmon resonance (SPR), which is the collective oscillation of electrons on the surface of the particle's surface. The size and shape of the nanoparticle affect the SPR frequency, and this characteristic can be utilized to identify distinct molecules in a sample. As a result, biosensors using gold nanoparticles to identify biological components, including DNA and proteins, have been developed. The electrical characteristics of the gold nanoparticles are also significant. They are very conductive and can be an ideal substrate for electron transfer reactions. Due to this characteristic, gold nanoparticles can be used for electrochemical catalysis and sensing. Various biomolecules, including proteins, peptides, and antibodies, can be functionalized onto these AuNPs. This allows them to be used in various applications, including cancer therapy and drug delivery. They can be functionalized for drug delivery by adding medicines and ligands that can target particular cells or tissues. This can lessen the drug's toxicity while increasing its effectiveness. Gold nanoparticles can be functionalized with antibodies that target cancer cells for use in cancer therapy.[50] The nanoparticles produce heat when exposed to light, which can specifically destroy cancer cells. Gold nanoparticles have unique optical properties, making them useful as contrast agents in imaging. Gold nanoparticles have found uses in several fields, including imaging and photothermal therapy, in addition to their employment in biosensors, medication transport, and cancer therapy.[51]

Iron Oxide Nanoparticles. Iron oxide nanoparticles (IONPs) are a class of bioengineered materials that have garnered much interest due to their distinctive magnetic characteristics. They are a particular type of iron oxide nanoparticle with a 5−100 nm diameter, frequently magnetite (Fe_3O_4) or maghemite ($-Fe_2O_3$). Since IONPs may be synthesized in various shapes, sizes, and protein functionalization, they are well-suited for a wide range of biological applications. The main characteristics of IONPs are their magnetic properties. They keep their magnetism when exposed to an external magnetic field due to their superparamagnetic nature, but they lose it when the field is removed. Because of this property, they have been used in several applications, including cardiology, medicine administration, and magnetic hyperthermia.[52,53] Cancer cells can be killed during hyperthermia by being selectively heated by IONPs, while the surrounding healthy cells are left unharmed. By creating heat when exposed to an external magnetic field, IONPs can be used to target heat cancer cells.[54] This might lessen side effects while enhancing the efficacy of cancer treatment. They are biocompatible and can be functionalized with specific proteins, such as antibodies, to target particular cells or tissues. When subjected to an external magnetic field, the IONPs create a magnetic moment that the MRI scanner can detect and use for high-resolution imaging.[55] Adding drugs can be functionalized for drug delivery, and ligands can then be employed to target specific cells or regions. When exposed to an external magnetic field, the IONPs are drawn to the target cells or tissues, making it possible for the medication to be delivered to the desired location. This might improve the drug's effectiveness while lowering its toxicity.[56]

Additionally, IONPs have been applied in some industries including tissue engineering and biosensors. IONPs are utilized as scaffolds in tissue engineering to promote the growth of cells and tissues. IONPs can be employed as labels in biosensors to find specific molecules, including proteins and DNA. Stability, biocompatibility, and targeting capabilities are the areas to expand on for their usefulness in clinical settings.[57,58]

Quantum Dots. Quantum dots (QDs), a subclass of semiconductor nanoparticles, have unique optical properties. They are commonly built of semiconductors like indium phosphide (InP) or cadmium selenide (CdSe), and their diameter ranges from 1 to 10 nm. Depending on their size, the QDs' optical properties can produce light either at higher energy or shorter wavelengths. QDs release light at specific wavelengths and have a high luminosity, depending on their size. This property makes them potentially useful fluorescent probes for imaging and sensing applications.[59] QDs can be functionalized with specific proteins, such as antibodies, to enable targeted imaging of certain cells or tissues. They can also be used as sensors to identify certain ions or chemicals in biological samples.

Numerous biomedical fields, including tissue engineering, medication delivery, and the detection and therapy of cancer, have found applications for them.[60] For cancer diagnosis, QDs can be used as contrast agents for imaging techniques, such as computed tomography (CT) and fluorescence imaging. Drug delivery and therapy can also be enhanced by functionalizing drugs with them and directing them toward cancer cells. QDs can be functionalized with delivered drugs and targeted with ligands to specific cells or tissues. This might improve the effectiveness of the drug while reducing its toxicity. QDs have also been used as scaffolds in tissue engineering to promote the growth of cells and tissues.[61] To improve the efficiency of light absorption, energy conversion, and color accuracy in solar cells, QDs can be used. Additionally, they offer super optical properties used in solar cells. QDs may have benefits, but there are concerns about their toxicity, especially since some QDs contain heavy metals like cadmium. Scientists are working to develop nontoxic QDs and studying how QDs impact biological systems to assuage these concerns.[62,63]

Fullerenes. Fullerenes are a particular class of carbon molecules that Sir Harold W. Kroto, Smalley, and Curl, Jr. first identified in 1985. They were honored with the 1996 Nobel Prize in Chemistry for their work. A hollow sphere, ellipsoid, or tube made completely of carbon atoms organized in a three-dimensional lattice makes up the distinctive structure of fullerenes.[64] The buckminsterfullerene (C_{60}), which has a spherical shape resembling a football, is the most prevalent fullerene. Due to their distinctive electrical and optical characteristics, fullerenes can be used in various applications. Due to their capacity to pass through cell membranes and biocompatibility, fullerenes can be employed in medication

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delivery as carriers for pharmaceuticals or biomolecules. To improve their biocompatibility and targeted specificity, fullerenes can also be functionalized with different compounds such as amino acids, sugars, and peptides. Fullerenes can be employed as contrast agents in bioimaging because of their high electron density and outstanding imaging resolution.[65,66] Photodynamic therapy, which involves turning on a photosensitive chemical to cause cell death, has also been utilized as a photosensitizer. They serve as electron acceptors in organic solar cells used in photovoltaic systems. An electrical current can be produced by transferring electrons to the fullerene molecule. They could also be used in nanotechnology and materials science. Due to their distinctive structure and electrical characteristics, they are appealing for use in creating nanoscale materials and devices, including sensors and batteries.[67,68]

Carbon Dots. Carbon dots are a specific type of carbon nanoparticle that are attractive for a range of applications in materials science and biomedical engineering due to their distinctive photoluminescence characteristics. These nanoparticles can be functionalized with different molecules and made from various carbon sources such as carbon nanotubes, graphene, and diamonds. They are intriguing candidates for numerous biomedical applications because of their excellent biocompatibility, low toxicity, and great stability.[69,70] Typically, they have a diameter of under 10 nm. With excellent sensitivity and resolution, carbon dots can be used as fluorescent probes in bioimaging to scan cells and tissues. Due to their tiny size and adjustable photoluminescence capabilities, they are ideal for several imaging techniques, including confocal microscopy and flow cytometry. Carbon dots can be functionalized with various biomolecules, such as antibodies and enzymes, to detect specific analytes such as glucose, DNA, and proteins. Due to their photoluminescence properties, which enable the sensitive and exact detection of these analytes, carbon dots are the preferred material for biosensors.[71] They can also be functionalized with drug molecules and directed to particular cells or tissues for controlled drug release when used in medication delivery. Carbon dots' small size and biocompatibility enable effective drug administration with minimal toxicity and adverse effects. Carbon dots have potential usages in energy conversion and storage, such as in solar cells and batteries, in addition to their medicinal applications. These devices' special photoluminescence features can be leveraged to improve their functionality, resulting in greater efficiency and stability. There are significant difficulties in the synthesis and functionalization of carbon dots despite their promising uses.[72] Further study is required to improve the production processes, comprehend the biocompatibility and toxicity of these nanoparticles, and create applications for them that are both safe and efficient.

Graphene. The 2D substance, known as graphene, is composed of a single layer of carbon atoms organized in a hexagonal lattice. Andre Geim and Konstantin Novoselov, who shared the 2010 Nobel Prize in Physics for their research, were the ones who first isolated and studied the molecule in 2004. Due to its exceptional qualities, including its high thermal conductivity, electrical conductivity, and good mechanical strength, graphene has attracted a lot of attention.[73] Graphene's mechanical strength is one of its most impressive characteristics. It is more than 100 times stronger than steel and the strongest substance yet discovered with a tensile strength of over 130 gigapascals. Its flexibility, low weight, and strength make it a desirable material for use in the aircraft industry and other fields where weight and strength are crucial.[74] These graphenes have very good electrical conductivity. Due to its rapid electron mobility and low resistance, it is the perfect material for use in electronics, including transistors, sensors, and conductive coatings. Graphene's distinct electrical characteristics also make it appropriate for quantum computing and other cutting-edge technologies. Graphene is a promising material for heat management applications due to its high thermal conductivity and combination of mechanical, electrical, and mechanical characteristics. Due to its substantial surface area and potency to conduct heat effectively, it is a desired material for thermal management systems, such as heat sinks and thermal interface materials.

Graphene has shown promise as an energy storage material in batteries and supercapacitors. Its enormous surface area and great electrical conductivity make it desirable for electrode materials, enabling high-capacity and high-performance energy storage systems.[75] They are two-dimensional materials with excellent mechanical, electrical, and thermal properties, enabling a wide range of applications in industries, including aircraft, electronics, and thermal management. Due to its distinctive qualities, it offers a promising application for cutting-edge technology and developing sectors.[76] To fully realize the potential of graphene in the coming years, research is currently concentrated on addressing the difficulties of large-scale production and the incorporation of graphene into useful applications.[77]

Nanodiamonds. Nanodiamonds, an interesting subset of diamond nanoparticles, have garnered a great deal of interest in nanotechnology. These nanoparticles, which typically have sizes between 2 and 10 nm, are composed of crystalline diamonds and have special optical and mechanical capabilities. Particularly biocompatible, nanodiamonds are excellent for various biological applications.[78] Nanodiamonds' versatility in being functionalized with other biomolecules such as proteins or peptides is one of their main benefits. They can therefore be utilized as targeted drug delivery systems, enabling the release of medications directly to particular cells or tissues within the body. Nanodiamonds can also pass through cell membranes due to their small size, which increases their potential in drug delivery applications.[79] The use of nanodiamonds in biosensing and bioimaging is also significant. Nanodiamonds are excellent fluorescent probes for monitoring the movement of biomolecules in biological systems due to their strong fluorescence and high refractive index.

Additionally, biosensing applications can take advantage of the luminous characteristics of nanodiamonds to identify certain proteins or analytes in intricate biological samples. Many industrial applications are attracted by the special mechanical qualities of nanodiamonds.[80,81] Nanodiamonds are excellent coatings for cutting tools and wear-resistant surfaces due to their extreme hardness and wear resistance. Due to their great electrical conductivity, they are also being researched for quantum computing and other electronic applications. However, further study in this area is anticipated to produce innovative new uses for these extraordinary nanoparticles.

Carbon Nanotubes. Due to their exceptional physical and chemical characteristics, carbon nanotubes (CNTs) are a special type of nanoparticle that have recently attracted much attention. All carbon atoms in these cylinder-shaped formations give them tremendous mechanical strength,

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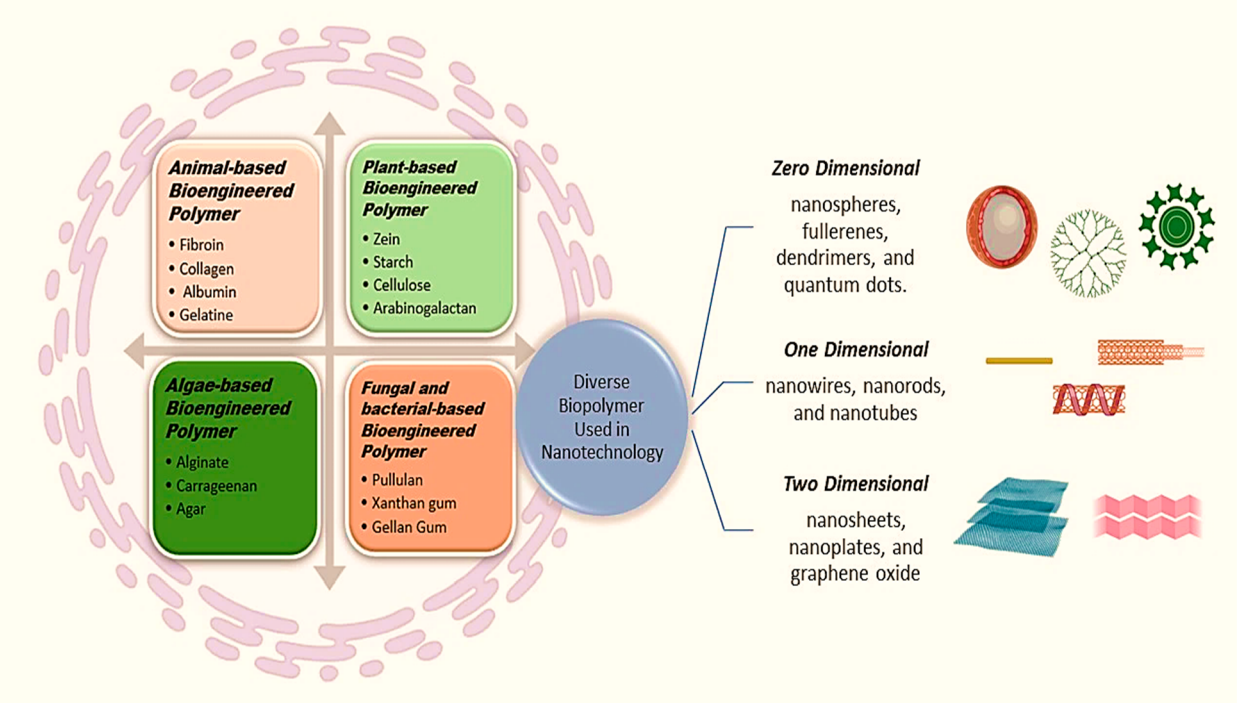

Figure 3. Diverse bioengineered materials used in drug delivery systems.

electrical conductivity, and thermal stability.[82] Biomedical engineering is one of the most fascinating fields in which CNTs are used. These nanoparticles can be functionalized with a range of biomolecules, such as peptides or proteins, and it has been demonstrated that they have high biocompatibility. This makes them ideal for use in targeted drug delivery systems, where they can deliver drugs directly to specific cells or tissues within the body.

CNTs' small size makes it possible to pass through cell membranes, increasing their potential in drug delivery applications.[83] Bioimaging is a possible area of use for CNTs. These nanoparticles can be used as fluorescent probes and imaging agents because of their distinctive optical characteristics. Researchers may detect the movement of biomolecules in living cells or tissues in real time because of the ability of these devices to generate light at precise wavelengths. In addition to their uses in biomedicine, CNTs have been introduced to several other industries.[84,85] They have been employed in creating cutting-edge materials including composites, energy storage systems, and electronic parts. They constitute a great contender for usage in the aerospace and defense industries due to their superior mechanical strength and electrical conductivity.[86] Nanomaterials perform exceptionally well in many applications because they differ from bulk materials in their physicochemical features including size, reactivity, surface area, and shape. There are various criteria by which nanomaterials can be categorized.[87] All of these bioengineered materials used in drug delivery systems with their target are shown in Figure 3.

PHYSIOCHEMICAL PROPERTIES OF BIOENGINEERED POLYMER-BASED NANOTECHNOLOGY

Nanoparticles can be used in a long list of applications due to their unique physiochemical properties listed below:

Catalytic Properties. The size, shape, composition, interparticle spacing, oxidation state, and support of the NPs all affect their catalytic capabilities. The NPs become smaller as their catalytic activity increases.[88] The shape also has an impact on the reactivity and the selectivity of the NPs. Hemispherical NPs were discovered to be more active than spherical ones for oxidation of CO by Au NPs.[89] The use of alloys increases the catalytic activity of NPs because the alloying impact alters the catalyst's electrical characteristics, reduces poisoning effects, and produces various selectivity.[90]

Electronic and Optical Properties. Metallic and semiconductor nanoparticles (NPs) have fascinating electrical and optical capabilities as a result of phenomena like localized surface plasmon resonance (LSPR) effect and quantum confinement.[91] When the frequency of the light photons equals the collective excitation of the conducting electrons, the LSPR phenomenon takes place. In noble metal NPs, a substantial size-dependent UV−visible extinction band results from this phenomenon that is not present in bulk metals. Size, shape, and the surrounding dielectric environment all have an impact on NPs' optical characteristics.[92]

Magnetic Properties. All magnetic compounds have a "magnetic element", such as Fe, Co, or Ni (at room temperature), in their formula. Sc_3In, $ZrZn_2$, and $TiBe_{2-x}Cu_x$ are the only three exceptions to mixed diamagnetic elements that are currently known. Otherwise, diamagnetic elements, such as Pd, Au, or Ag, exist. On the nanoscale, everything is altered. Uneven electrical dispersion leads to the formation of NPs from various materials. For instance, FeAl is not magnetic in the bulk but becomes magnetic when it is in the form of NPs. The magnetic anisotropy energy per NP reduces as NP size decreases.[93] The energy that maintains the magnetic moment in a specific orientation is known as the magnetic anisotropy energy. The anisotropy energy equals the thermal energy at a characteristic size for each type of NP, allowing the

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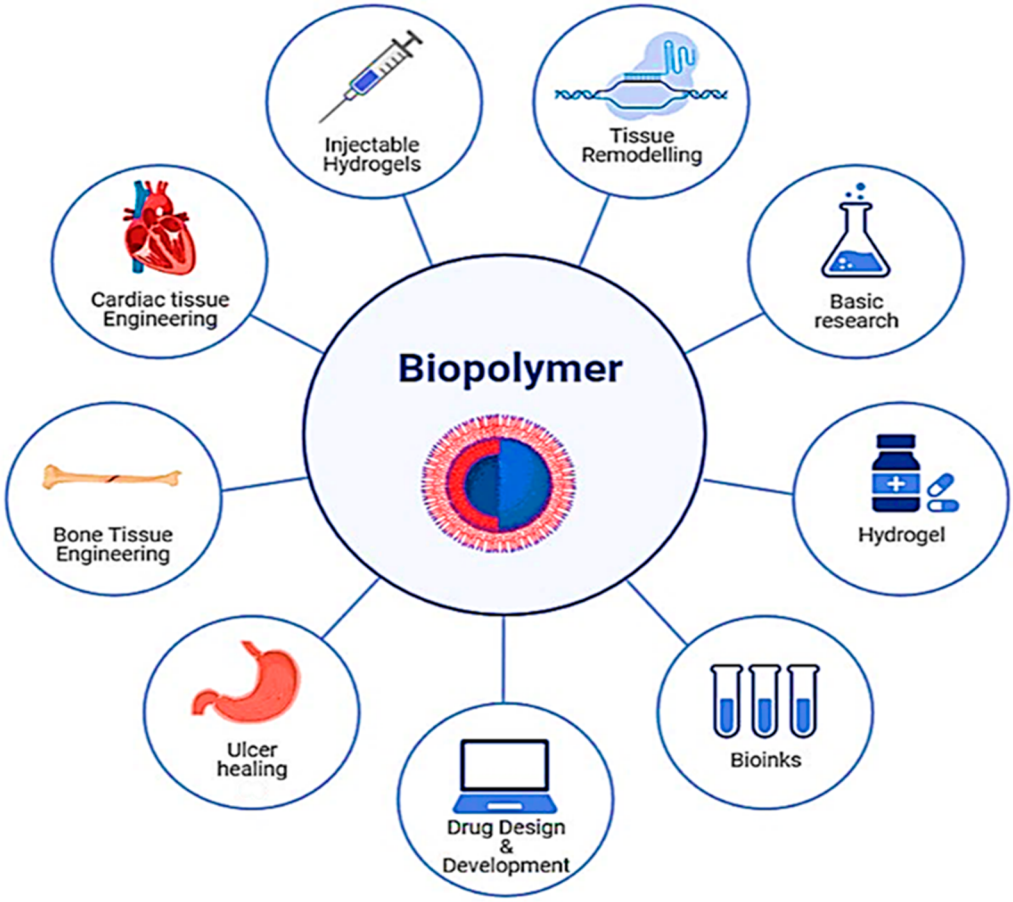

Figure 4. Application of biopolymers in various fields. Adapted from ref 100. CC BY 4.0, 2021, MDPI.

random flipping of the magnetic moment, in which case the NP is referred to as superparamagnetic.[94]

APPLICATION OF BIOENGINEERED POLYMER IN VARIOUS FIELDS OF HEALTHCARE

The healthcare field is evolving quickly, and the ideas of tissue engineering and regenerative medicine are helping to move the focus from replacement to regeneration. For thousands of patients yearly, tissue engineering promises amazing medical treatment at lower medical costs. The growing newer technologies of tissue engineering and regenerative medicine will address the limitations of the existing healthcare approaches, such as organ transplantation. Engineered organs could avoid the issues with organ transplantation, which could be a boon to healthcare in the future.[95] Tissue engineering and cell therapy have recently been developing as viable treatments for heart disorders. Research activities have sought to restore the ailing heart through the epicardial implantation of a bioengineered tissue patch preseeded with bone marrow cells or BM-derived mesenchymal stem cells. Natural and synthetic polymers such as collagen, fibrin, PGA, PLGA, etc. are employed for these uses. Recently, the infracted myocardium has been repaired using in situ cardiac tissue engineering and injectable biomaterials. This strategy has several benefits, such as being less intrusive and encouraging repair by enhancing donor cell retention and neo-angiogenesis.[96] An alternative cell source is adipocyte stem cells, which can spontaneously develop into functional cardiomyocytes.[97]

Large numbers of disposable medical devices fabricated from nondegradable biomaterials pose a serious environmental and economic issue. With the advances in technology, this is putting a huge burden on our environment on a global scale. Advanced technologies in bioengineering and biomaterials can be applied to tailor the biodegradability of materials to render them nontoxic to our environment. Biodegradable polymers like PLA, poly(glycolide), poly D-, and L-(lactic-*co*-glycolide) have emerged as promising materials for use as disposable medical devices and are environmentally friendly.[98] Biodegradable polymers can be used as medical devices since they deteriorate by the straightforward hydrolysis of ester linkages, and their hydrolytic byproducts are not hazardous to mammalian tissue. Synthetic degradable polyesters have been employed as bone fixation tools, suture materials, etc. Compared to metallic implants, absorbable systems have several advantages, such as avoiding a second surgery. Further developments in biomaterials and polymer technology (as shown in Figure 4) may result in more promising biodegradable medical devices that significantly advance healthcare.[99]

Some examples of bioengineered polymers that can be used in the treatment of various diseases are as follows:

Cancer. Bioengineered polymers can deliver chemotherapy drugs directly to cancer cells in the stomach while minimizing damage to healthy tissue. For example, researchers have developed chitosan-based nanoparticles that can deliver doxorubicin, a chemotherapy drug, specifically to gastric cancer cells. The nanoparticles are modified with folate,

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Table 2. Different Areas Where Bioengineered Polymers Can Be Used

S. No.	Field	Details	Ref.
1.	Medical devices	Medical equipment like sutures, stents, and catheters are made from bioengineered polymers. Polymers are ideal for various devices because they can be engineered to have particular mechanical properties.	111
2.	Diagnostics	In diagnostics, bioengineered polymers can be utilized to develop sensors and assays that can identify particular biomolecules in body fluids like blood and urine.	112
3.	Organ on a chip	For use in drug testing and research, bioengineered polymers are used to make microfluidic devices that can imitate the functionality of organs.	113
4.	Neuroprosthetics	To develop implants that can interact with the nervous system for use in treating conditions like Parkinson's disease and spinal cord injuries, bioengineered polymers can be used.	114
5.	Tissue engineering	Scaffolds composed of bioengineered polymers are used to assist the development of new tissues like skin, bone, and cartilage.	115
6.	Dental material	Dental materials like fillings, crowns, and bridges can be made from bioengineered polymers.	116
7.	Orthopedics	Orthopedic implants like spinal fusion devices and joint replacements are made from bioengineered polymers. It is possible to design the polymers to have particular mechanical characteristics similar to those of natural bone and cartilage.	117

which targets the folate receptor expressed on the surface of many cancer cells.[101] According to the study, aminocellulose-grafted polymeric nanoparticles contain LCS-1 for synthetic targeting of checkpoint kinase 2 (CHEK2). Aminocellulose (AC), a highly biocompatible and biodegradable hydrophilic polymer, was grafted over polycaprolactone (PCL), and a nanoprecipitation method was employed for formulating nanoparticles containing LCS-1. In this study, they used LCS-1-loaded PCL-AC NPs to specifically inhibit CHEK2-deficient HCT116 CRC cells by taking advantage of the synthetic lethal interaction between SOD1 and CHEK2. Additionally, the size, cellular absorption, and survival of PCL-AC nanoparticles were evaluated in relation to the impacts of protein corona formation. Using a zeta sizer, LCS-1-loaded NPs were measured for size, zeta potential, and the polydispersity index. Transmission electron microscopy, scanning electron microscopy, and atomic force microscopy analyses were used to examine the morphological features. Confocal imaging demonstrated cellular internalization and uptake of nanoparticles by HCT116 cells. Also, nanoparticles were cytocompatible as they did not induce cytotoxicity in hTERT and HEK-293 cells.[102]

Diabetes. Diabetes is a chronic disease that affects millions of people worldwide. One of the key challenges in diabetes management is the delivery of insulin or other medications to the appropriate site in the body. Bioengineered polymers can be used to overcome this challenge by providing a targeted and sustained delivery of drugs to the site of action. One promising approach for diabetes management is the delivery of insulin to the stomach.[103] The stomach is an important site of drug absorption, and insulin delivered to the stomach can be rapidly absorbed into the bloodstream. However, the stomach's acidic environment might cause insulin to break down, reducing its effectiveness. In a study reported by Zhang et al. a novel oral protein−drug delivery system composed of starch nanoparticles (SNPs) and poly (L-glutamic acid) (PGA) was successfully synthesized via click reaction.[104] The copolymer, SNP-g-PGA, exhibited efficient grafting and structural confirmation. This copolymer formed amphiphilic aggregates with pH-dependent properties. In vitro insulin release experiments demonstrated that insulin was released more slowly in acidic conditions (pH 1.2) due to the copolymer's excellent stability, making it a promising candidate for controlled insulin release.[105,106] Researchers have also created a bioengineered hydrogel that can carry insulin to the stomach and keep it from degrading to solve this problem. Alginate and chitosan, two biocompatible and biodegradable polymers, comprise the hydrogel. Natural polymers that are produced from chitin, such as chitosan, have mucoadhesive properties, while alginate is a polysaccharide that naturally forms a gel when divalent cations are present. Chitosan Protects the pancreatic β-cells and promotes insulin secretion.[107] After being transported to the stomach, the hydrogel is filled with insulin and forms a gel that releases insulin over time. The alginate component of the hydrogel protects against deterioration in the acidic environment of the stomach, while the chitosan component improves the hydrogel's attachment to the stomach lining. The hydrogel was well-tolerated and had no negative effects as previously reported.[108]

Gastrointestinal Disorders. A variety of symptoms can be caused by digestive disorders, such as inflammatory bowel disease and irritable bowel syndrome, which can be difficult to manage adequately. A promising method of delivering medications or treatments directly to the affected area of the gastrointestinal tract is provided by bioengineered polymers. This method can enhance treatment outcomes and lessen the adverse effects. To treat ulcerative colitis, an inflammatory bowel disease that damages the colon, mesalamine is a frequently prescribed medication. Creating a PLGA-based polymer that can carry mesalamine to the colon is one instance of a bioengineered polymer that can be used to treat gastrointestinal disorders. A bile acid derivative was added to the PLGA polymer to enable it to target the colon precisely. The polymer can release mesalamine locally in the colon because of the bile acid derivative's improvement of the polymer's solubility in the colonic fluid. The change also makes the polymer more adherent to the intestinal epithelium, which increases medication absorption.[109]

Infectious Diseases. *Helicobacter pylori* (*H. pylori*) is a Gram-negative bacterium that can colonize the stomach lining and cause gastritis, peptic ulcers, and gastric cancer. Conventional antibiotic therapies for *H. pylori* infections often have low efficacy and can lead to antibiotic resistance. Therefore, there is a need for alternative therapies that can specifically target *H. pylori* while minimizing the side effects on normal microbiota. Bioengineered polymers can be a promising approach to deliver antimicrobial agents directly to the stomach and combat *H. pylori* infections. One example is using chitosan-based polymers that can deliver lysozyme, an enzyme that can disrupt the cell walls of bacterial pathogens.[110] Some examples of how bioengineered polymers are used in various healthcare fields are listed in Table 2.

Patents. The unique characteristics of bioengineered polymers, such as biocompatibility, controllable mechanical properties, and controlled degradation, have drawn much attention. These materials are widely used in many healthcare

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Table 3. Patent Related to the Bioengineered Polymer

S. No.	Patent title/No.	Description	Ref.
1.	Bioengineered formulations, methods of making, and embodiments thereof (CN114761544A)	The present disclosure introduces bioengineered formulations for treating corneal defects. These formulations consist of modified collagen peptides and modified hyaluronic acid with specific characteristics. The compressive modulus of the formulation falls within a defined range. A method for obtaining the formulation involves combining the modified collagen peptides and modified hyaluronic acid and treating the mixture with a photoinitiator solution. The resulting formulation can be applied to the corneal defect and exposed to white light for a specific duration to treat the condition. Additionally, the disclosure presents a formulation containing exosomes derived from corneal stromal stem cells or mesenchymal stem cells, along with a clinically approved eye drop formulation, as a treatment approach for corneal defects.	118
2.	Single-step heparosan *n*-deacetylation and depolymerization for making bioengineered heparin (WO2012116048A1)	This invention addresses the challenge of producing bioengineered heparin that is chemically identical to pharmaceutical heparin. The method involves treating heparosan in a single-step, base-catalyzed reaction to achieve optimal N-deacetylation and depolymerization. The reaction conditions, including NaOH concentration, reaction time, and temperature, are determined using equations. The resulting partially N-deacetylated and depolymerized product can be further processed to obtain bioengineered heparin. This includes selective N-sulfonation, C5-epimerization/2-O-sulfonation, 6-O-sulfonation, and 3-O-sulfonation. The bioengineered heparin produced exhibits similar levels of *N*-acetylglucosamine and *N*-sulfoglucosamine, as well as comparable number-average molecular weight, weight-average molecular weight, and polydispersity index to pharmaceutical heparin. The invention also encompasses pharmaceutical compositions containing bioengineered heparin for disease treatment.	119
3.	Method of fabricating bioengineered product using three-dimensional bioprinting (WO2019162790A1)	The disclosed method involves fabricating a bioengineered product using three-dimensional bioprinting. The process includes preparing a bioink composition by mixing a cell carrier, serum-based nutritional supplement, and cryoprotectant. The viscosity of the bioink is adjusted by modifying its temperature. The bioink is then deposited onto a print plate to create a scaffold, and one or more cross-linkers are added to the scaffold. This cross-linking step helps stabilize the structure of the scaffold. Overall, the method enables the precise printing of complex three-dimensional structures using bioink, which can potentially be utilized in tissue engineering and regenerative medicine applications.	120
4.	Methods of producing bioengineered neuronal organoids (benos) and uses thereof (US2020208105A1)	The present invention describes a method for producing bioengineered neuronal organoids (BENOs) from pluripotent stem cells (PSCs). The method involves several steps: (A) providing a source of PSCs, (B) culturing the PSCs embedded in a matrix in cell culture medium, (C) culturing the PSCs in the matrix with a Rho-associated kinase inhibitor (ROCKi) and FGF-2, (D) culturing the developing BENO in cell culture medium containing retinoic acid and inhibitors of SMAD signaling to induce neurogenesis, (E) culturing the forming BENO in cell culture medium with TGF-beta and FGF-2 to enhance the generation of stromal cells and neurogenesis, and (F) culturing the developing BENO in cell culture medium with TGF-beta and inhibitors of notch signaling to further promote the formation of stromal cells and neurodifferentiation. This method enables the production of complex bioengineered neuronal organoids with potential applications in neuroscience research and regenerative medicine.	121
5.	Biopolymer-bioengineered cell sheet construct (US2009263465A1)	The present invention introduces a biopolymer-bioengineered cell sheet construct for corneal tissue reconstruction. It comprises a deformable and bioresorbable biopolymer carrier and a bioengineered cell sheet composed of interconnected cells with uniform orientation. The cell sheet is attached to the carrier with the cell surfaces facing the carrier, and an extracellular matrix is present at the basal surfaces of the cells. The cells used can be human corneal endothelial cells or human corneal epithelial cells. Gelatin is the preferred material for the biopolymer carrier, with a weight-average molecular weight of 10,000 to 200,000 Da and an isoelectric point of 1−10 (preferably 5−9). In one embodiment, the gelatin has a weight-average molecular weight of 100,000 Da and an isoelectric point of 5, and it carries a negative charge. The construct offers a novel technique for directly transplanting cultivated HCECs as a cell sheet onto corneas without the need for permanent cell carriers. It allows for regeneration of the endothelial sheet while maintaining corneal deturgescence.	122
6.	Bioengineered particulate material (WO2017125396A1)	The conducted experiments demonstrate that the presence of clay in a sand matrix has a significant impact on scour dynamics. As the clay content increases, there is a gradual reduction in the depth and lateral extent of scour, resulting in less excavated material. Additionally, the addition of clay promotes irregularity in the shape of the scour pit, transforming it from a classical conical shape to a more irregular and blocky appearance. Regardless of the extent and nature of the scour zone, the experiments show that clean sand separates from the clay fraction and gets deposited behind the monopile. The experiments also confirm that biological cohesion, particularly in the form of EPS (extracellular polymeric substances), plays a crucial role in shaping scour morphology. When EPS is present at a certain concentration, there is minimal change in surface morphology compared to initial conditions. On the other hand, higher EPS concentrations result in similar scour patterns, indicating that EPS has a much greater influence in restricting scour development. These findings directly contradict the theory proposed by Briaud et al. (1999) that the equilibrium scour depth remains the same for both clay and sand, with only the scour rate differing. The observed increase in shear strength caused by clay content does not simply account for the differences in scour behavior between substrates. Instead, it is the clay content itself that correlates better with key parameters describing scour evolution. The reduction in equilibrium scour depth and excavation area at higher clay concentrations can be attributed to a shift from grain-supported to matrix-supported substrates. In matrix-supported cases, the sand particles are not in direct contact with each other, and the clay component controls the erodibility of the sediment mixture. The study also indicates that winnowing, the process of selectively removing fine particles, including clay, from the sediment surface, plays a vital role in governing the rate and extent of scour. The presence of clay on sand grain surfaces does not necessarily prevent sand from being transported as bedload, but the increasing abundance of clay particles with higher clay concentrations leads to a higher prevalence of residual clay particles.	123
7.	Tubular bioengineered smooth muscle structures (US2014379083A1)	The disclosed methods involve generating tubular, bioengineered smooth muscle structures for the repair or replacement of tubular organs. The process includes obtaining smooth muscle cells and culturing them to form a construct of directionally oriented smooth muscle cells. This construct is then placed around a tubular scaffold and cultured in a growth media until a mature smooth muscle cell structure is formed. Autologous smooth muscle cells can be obtained from the same subject. In one approach, the smooth muscle cells are deposited around a central post, facilitating the development of a tubular smooth muscle structure. The muscle cells can be suspended in collagen, allowed to gel into a muscle construct, and then placed around a tubular scaffold-like chitosan. These methods allow for connecting multiple tubular smooth muscle structures to create an elongated composite structure. This composite structure can be stimulated to produce a wave of contractions, enabling coordinated movement through the individual tubular smooth muscle structures.	124
8.	Three-dimensional bioengineered smooth muscle tissue and sphincters and methods, thereof (US2006134076A1)	The invention addresses the need for functional in vitro models of sphincters to understand smooth muscle degenerative diseases. It introduces bioengineered sphincters composed of contractile smooth muscle cells, enabling the investigation of sphincter malfunction mechanisms and the development of treatments for sphincter dysfunction and weakened smooth muscle contractile force. The bioengineered sphincters are generated by culturing smooth muscle cells in a cell culture vessel with a cylindrical mold coated with fibrin, an extracellular matrix protein. The cells reorganize into parallel arrays and contract in response to contractile agonists. Methods are provided for identifying agents that modulate smooth muscle cell contraction and sphincter function by measuring changes in peak isometric contraction in the presence of test agents. These methods have implications for disorders such as fecal incontinence, gastroesophageal reflux disease, urinary incontinence, and biliary dyskinesia. Identified stimulators or inhibitors of smooth muscle cell contraction can serve as potential therapeutics. The invention also encompasses methods of treating sphincter dysfunction by administering modulators of smooth muscle cell contraction or replacing defective sphincters with bioengineered ones. Co-culturing smooth muscle cells with embryonic nerve cells or stem cells is explored to create bioengineered rings for studying colonic or airway disorders. This invention highlights the chaperone protein HSP27, particularly phosphorylated HSP27, as a stimulator of smooth muscle cell contraction. Phospho-HSP27 shows promise in restoring contractile response in bioengineered sphincters and aged smooth muscle cells. Thus,	125

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Table 3. continued

S. No.	Patent title/No.	Description	Ref.
		phospho-HSP27 may serve as a therapeutic for reinstating contractile force in age-related sphincter dysfunction. The invention suggests methods of stimulating or reinstating smooth muscle contractile force by administering phosphor-HSP27 or its pharmaceutical compositions.	
9.	Bioengineering retinal nerve scaffold with cell tracing function and preparation method of bioengineering retinal nerve scaffold (CN105641750A)	The present invention aims to provide a method for creating a bioengineered retinal nerve scaffold with cell tracing capabilities, allowing for the direct marking and tracking of bioengineered retinal nerve scaffold cells. This facilitates the detection of cell migration, proliferation, differentiation, and prognosis in vivo, serving as an important indicator for evaluating the transplantation of engineered retinal nerve scaffold cells in living organisms. The method involves transfecting the GFP gene into human induced pluripotent stem cells (hiPSc) to obtain GFP-hiPSc. The nerve fiber layer of the 3D retina induced by GFP-hiPSc is digested into single cells, which are then used as seed cells. The seed cells are suspended in a medium and inserted into a polylactic acid-glycolic acid polymer scaffold coated with Matrigel. Subsequently, the cells are induced to differentiate in a differentiation medium, resulting in the formation of a bioengineered retinal nerve scaffold with a cell tracing function. The differentiation medium consists of a neurotrophic factor and a maintenance concentration of retinal differentiation nutrient solution. The induced differentiation medium typically includes bFGF, BDNF, CNTF, and N2 supplement, nonessential amino acids, heparin, and DMEM/F12 medium. The digestion of the nerve fiber layer into single cells involves placing the tissue in D-Hanks solution, separating the tissue, discarding pigmented portions, retaining the nerve fiber layer, washing with PBS, digesting with accurate cell digestion solution, terminating digestion with differentiation medium, and centrifuging to obtain seed cells. Transfection of the GFP gene into hiPSc is achieved using a retroviral vector carrying the GFP gene. The retroviral GFP-packaged PT67 cells are screened with a G418-containing medium, and the collected supernatant is combined with the hiPSc using the 3000Reagent to obtain GFP-hiPSc. By incorporating cell tracing capabilities into the bioengineered retinal nerve scaffold, this method enables more accurate tracking of transplanted cells, providing valuable information on their migration, proliferation, differentiation, and transformation in vivo. This advancement contributes to the evaluation and monitoring of cell transplantation in retinal nerve regeneration research.	126
10.	Use of biological material containing cells supported on three-dimensional scaffolds comprising hyaluronic acid derivatives, for autologous and/or allogenic graft preparation for implantation by arthroscopy (IT1320141B1)	The invention includes an independent claim for a surgical instrument kit for implanting the biological material. The kit consists of a sterilization tray, a cannula with sterile valves for arthroscopy access, and various instruments such as a mapper-sampler, guide wire, cutter-abrasion, and hollow plunger. The mapper-sampler is used to create a circular imprint and extract cartilage tissue of the same shape. The cutter-abrasion prepares the implantation site within the imprint, and the hollow plunger is used to insert the biological material into the prepared lesion.	127
11.	Dynamic bionanoparticle platforms (US11096901B2)	The invention introduces the concept of nanoscale elements formed from isolated, synthetic, or recombinant amino acid residues, including various isoforms of Clathrin and Coatomer I/II proteins. These elements can take the form of cages, vesicles, or minimalist structures, offering a wide range of configurations and applications. The nanoparticles can carry cargo or act as efficacious agents on their own, with the ability to penetrate cells, fuse with cell membranes, and perform various cellular processes. The invention also emphasizes the flexibility, stability, functionality, and low antigenicity of these nanoparticles, enabling applications in drug delivery, diagnostics, therapy, and regenerative medicine. Furthermore, the nanoparticles can cross the blood−brain barrier, exhibit self-modifying behavior, utilize quantum mechanical effects, and serve as platforms for biomedical, biomolecular, and information-processing applications.	128
12.	Smart bionanoparticle elements (US2007141163A1)	The invention presents a nanoscale smart bionanoparticle (SBN) element that can be utilized in a scalable platform for various applications, including biomedical, electronics, telecommunications, and information processing. The SBN element is formed by self-assembling protein cages containing nanoscale cargo elements, which can include metals, gases, drugs, optics, and polymers. The invention overcomes the limitations of the prior art by inhibiting charge transfer, preventing cage distortion, and allowing for the precise placement of cargo elements. It offers advantages such as reduced hydrophobicity, selective uptake, integration with patient factors, dynamic dosing, intelligent monitoring, and the ability to attack multiple targets. The SBN element maintains structural integrity, accommodates a wide variety of cargo elements, and can be bioengineered. It provides a basis for complex delivery systems and can exploit biological control laws, integrate with other smart devices, and utilize self-directed behaviors. The SBN platform enables safer and more efficient drug discovery and information processing at the nanoscale.	129
13.	Plasmonic nanoparticle-doped silk materials (US2013310908A1)	The present invention combines silk-based materials, specifically silk fibroin, with plasmonic nanoparticles to create an improved light-activated heating element. This combination offers superior features compared to existing devices in the field. Silk-based materials provide biocompatibility, biodegradability, and conformability, expanding the range of applications for plasmonic nanoparticles and enabling enhanced tunability and precision. The photothermal elements described in the invention consist of a distribution of plasmonic nanoparticles within a silk fibroin matrix, capable of generating heat when exposed to electromagnetic radiation. The plasmonic nanoparticles can be of various types, shapes, sizes, and materials, including metal particles like gold, silver, and iron oxide. The invention's applications include therapeutic uses such as hyperthermia for tissues, wound healing, pain relief, cell/bacteria killing, and even converting generated heat to other forms of energy like electricity for wireless powering of devices. These materials hold the potential for implantable and biodegradable heating elements in biomedical and wireless power applications	130

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industries such as tissue engineering, drug delivery systems, medical equipment, and regenerative medicine. Table 3 enumerates various patents relating to bioengineered polymers and their uses in various healthcare fields.

FUTURE PERSPECTIVE

There is still much to learn about these materials and their potential uses, even though bioengineered polymers have tremendous promise for treating gastrointestinal disorders. Future research and development in this area may focus on a variety of significant areas to further improve the effectiveness and safety of bioengineered polymers. There may be other materials with even higher potential for drug delivery in the stomach than the current bioengineered polymers, such as PLGA and chitosan, which have shown encouraging outcomes in preclinical studies. For example, new studies have investigated protein-based polymers for drug delivery, including silk fibroin and polypeptides that resemble elastin.[131] These substances' distinctive qualities may improve drug stability, absorption, and targeting of the gut. Furthermore, there is a need for more research on the behavior and biocompatibility of bioengineered materials. Although many bioengineered polymers have shown encouraging results in vitro and preclinical studies, much more research is needed to understand how they behave in vivo.

Further research could examine the biodistribution, biodegradation, and immune response of bioengineered polymers in animal models and human clinical trials to confirm their effectiveness and safety. Advanced imaging methods must be further developed to track the bioengineered polymers' distribution and utility in vivo. In preclinical studies, modern imaging methods like MRI and CT have shown promise, but there is still much to learn about how well they can monitor drug delivery and trace disease progression in individuals.[132] For better tracking of drug−polymer formulations in vivo, additional studies might investigate the development of novel imaging techniques such as molecular imaging and positron emission tomography (PET).

LIMITATIONS

Due to their biocompatibility, biodegradability, and adaptable properties, bioengineered polymers have shown potential as drug delivery systems. However, several restrictions must be considered when delivering therapeutic substances through the stomach. For bioengineered polymers used in medication administration, the stomach's acidic environment poses a challenge because it can result in their breakdown and decreased efficiency.[133] Before these polymers reach their intended target site, digestive enzymes in the stomach can degrade them. The mucus barrier that protects the stomach lining and the rapid stomach emptying may also prevent bioengineered polymers from being delivered to the desired area and releasing their contents. Furthermore, these polymers' limited drug load capacity limits their potential to deliver more potent or various therapeutic agents. A practical restriction could be the expense and difficulty of synthesizing and bioengineering polymers for medication delivery. Last but not least, using bioengineered polymers carries a danger of immunological responses or allergic reactions, hence necessitating a primary quality control system before the administration.[134]

CONCLUSION

Bioengineered polymers have shown considerable promise in drug delivery, especially for the transfer of therapeutic drugs through the stomach. These polymers have better drug stability, controlled release, and targeted distribution than those of conventional drug delivery systems. Bioengineered polymers can improve drug stability, which helps protect drugs from degradation and enhances their shelf life. These polymers can also be designed to control the release of drugs, allowing for sustained drug release over an extended period, which can enhance the therapeutic efficacy and reduce side effects. Another critical advantage of bioengineered polymers is their ability to target specific tissues or cells within the body, which is crucial for delivering drugs to the intended site of action while minimizing their impact on healthy tissues. Researchers can produce polymers that specifically bind to target cells by altering the polymer structure or incorporating targeting ligands, which increase medication uptake and lower the necessary drug dose. They can be utilized safely inside the human body without tissue irritation or toxicity because they are also biocompatible and biodegradable. These polymers are made to degrade over time, and the byproducts of their decomposition are nontoxic and easily excreted from the body through physiological processes. Bioengineered polymers can efficiently deliver a variety of therapeutic agents such as proteins, peptides, and small molecules. Thus, compared with conventional delivery methods, bioengineered polymers have been utilized to transport insulin, a protein hormone used to treat diabetes. Additionally, chemotherapeutic medicines for cancer treatment have been delivered using bioengineered polymers. These polymers are projected to become more important with further research and development in enhancing the efficacy and safety of medicine delivery, which will in the long run enhance health outcomes and life quality.

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Author Contributions

The manuscript was written through the contributions of all authors. All authors have approved the final version of the manuscript. These authors contributed equally.

Notes

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■ ABBREVIATIONS

DDS, Drug Delivery System; PLA, Poly(lactic acid); PLGA, Poly(lactic-*co*-glycolic acid); LES, Lower Esophageal Sphincter; AuNPs, Gold Nanoparticles; DNA, Deoxyribonucleic Acid; RNA, Ribonucleic Acid; GFP, Green Fluorescent Protein; hiPSc, Human Induced Pluripotent Stem Cells; bFGF, Basic Fibroblast Growth Factor; BDNF, Brain-Derived Neurotrophic Factor; CNTF, Ciliary Neurotrophic Factor; D-MEM/F12, Dulbecco's Modified Eagle Medium/Nutrient Mixture F-12; Rocki, Rho-Associated Kinase Inhibitor; TGF-beta, Transforming Growth Factor-beta; EPS, Extracellular Polymeric Substances

■ REFERENCES

(1) Wen, H.; Jung, H.; Li, X. Drug Delivery Approaches in Addressing Clinical Pharmacology-Related Issues: Opportunities and Challenges. *AAPS J.* **2015**, *17* (6), 1327−1340.
(2) Adepu, S.; Ramakrishna, S. Controlled Drug Delivery Systems: Current Status and Future Directions. *Molecules.* **2021**, *26*, 5905.
(3) Dahan, A.; Hoffman, A. Rationalizing the Selection of Oral Lipid Based Drug Delivery Systems by an in Vitro Dynamic Lipolysis Model for Improved Oral Bioavailability of Poorly Water Soluble Drugs. *J. Controlled Release* **2008**, *129*, 1−10.
(4) Pons-Faudoa, F. P.; Ballerini, A.; Sakamoto, J.; Grattoni, A. Advanced Implantable Drug Delivery Technologies: Transforming the Clinical Landscape of Therapeutics for Chronic Diseases. *Biomed. Microdevices* **2019**, *21* (2), 47.
(5) Manzari, M. T.; Shamay, Y.; Kiguchi, H.; Rosen, N.; Scaltriti, M.; Heller, D. A. Targeted Drug Delivery Strategies for Precision Medicines. *Nat. Rev. Mater.* **2021**, *6*, 351.
(6) Dara, S.; Dhamercherla, S.; Jadav, S. S.; Babu, C. M.; Ahsan, M. J. Machine Learning in Drug Discovery: A Review. *Artif. Intell. Rev.* **2022**, *55* (3), 1947−1999.
(7) Salit, M. S. Biopolymer. *Engineering Materials* **2014**, 39−52.
(8) Png, Z. M.; Wang, C. G.; Yeo, J. C. C.; Lee, J. J. C.; Surat'man, N. E.; Tan, Y. L.; Liu, H.; Wang, P.; Tan, B. H.; Xu, J. W.; Loh, X. J.; Zhu, Q. Stimuli-Responsive Structure-Property Switchable Polymer Materials. *Molecular Systems Design and Engineering* **2023**, *8*, 1097−1129.
(9) Kumar, A.; Srivastava, A.; Galaev, I. Y.; Mattiasson, B. Smart Polymers: Physical Forms and Bioengineering Applications. *Progress in Polymer Science (Oxford)* **2007**, *32*, 1205−1237.
(10) Wang, W. J.; Qiu, Z. S.; Zhong, H. Y.; Huang, W. A.; Dai, W. H. Thermo-Sensitive Polymer Nanospheres as a Smart Plugging Agent for Shale Gas Drilling Operations. *Pet. Sci.* **2017**, *14* (1), 116−125.
(11) Baranwal, J.; Barse, B.; Fais, A.; Delogu, G. L.; Kumar, A. Biopolymer: A Sustainable Material for Food and Medical Applications. *Polymers* **2022**, *14*, 983.
(12) Nagase, Y.; Okamura, Y. Synthesis of New Biocompatible Polymers and Fabrication of Nanosheets. *Advances in Bioengineering* **2015**, DOI: 10.5772/59633.
(13) Portilla-Arias, J. A.; García-Alvarez, M.; de Ilarduya, A. M.; Holler, E.; Galbis, J. A.; Muñoz-Guerra, S. Synthesis, Degradability, and Drug Releasing Properties of Methyl Esters of Fungal Poly(β, L-Malic Acid). *Macromol. Biosci.* **2008**, *8* (6), 540−550.
(14) Das, A.; Ringu, T.; Ghosh, S.; Pramanik, N. A Comprehensive Review on Recent Advances in Preparation, Physicochemical Characterization, and Bioengineering Applications of Biopolymers. *Polymer Bulletin*; Springer Science and Business Media Deutschland GmbH, July 1, 2023; pp 7247−7312. DOI: 10.1007/s00289-022-04443-4.
(15) Jha, S.; Malviya, R.; Fuloria, S.; Sundram, S.; Subramaniyan, V.; Sekar, M.; Sharma, P. K.; Chakravarthi, S.; Wu, Y. S.; Mishra, N.; Meenakshi, D. U.; Bhalla, V.; Djearamane, S.; Fuloria, N. K. Characterization of Microwave-Controlled Polyacrylamide Graft Copolymer of Tamarind Seed Polysaccharide. *Polymers (Basel)* **2022**, *14* (5), 1037.
(16) Ulbrich, K.; Holá, K.; Šubr, V.; Bakandritsos, A.; Tuček, J.; Zbořil, R. Targeted Drug Delivery with Polymers and Magnetic Nanoparticles: Covalent and Noncovalent Approaches, Release Control, and Clinical Studies. *Chem. Rev.* **2016**, *116*, 5338−5431.
(17) Liechty, W. B.; Kryscio, D. R.; Slaughter, B. V.; Peppas, N. A. Polymers for Drug Delivery Systems. *Annu. Rev. Chem. Biomol. Eng.* **2010**, *1*, 149−173.
(18) Bae, Y. H.; Park, K. Targeted Drug Delivery to Tumors: Myths, Reality and Possibility. *J. Controlled Release* **2011**, *153*, 198−205.
(19) Kamble, S. S. Chitin and Chitosan Polymer: A Review of Recent Advances and Prospective Applications. *Paintindia* **2018**, *68* (7), 69−78.
(20) Ways, T. M. M.; Lau, W. M.; Khutoryanskiy, V. V. Chitosan and Its Derivatives for Application in Mucoadhesive Drug Delivery Systems. *Polymers* **2018**, DOI: 10.3390/polym10030267.
(21) Garg, U.; Chauhan, S.; Nagaich, U.; Jain, N. Current Advances in Chitosan Nanoparticles Based Drug Delivery and Targeting. *Advanced Pharmaceutical Bulletin*; Tabriz University of Medical Sciences 2019; pp 195−204. DOI: 10.15171/apb.2019.023.
(22) Kunde, S. S.; Wairkar, S. Targeted Delivery of Albumin Nanoparticles for Breast Cancer: A Review. *Colloids and Surfaces B: Biointerfaces. Colloids Surf. B Biointerfaces* **2022**, *213*, 112422.
(23) Gong, Z.; Liu, X.; Zhou, B.; Wang, G.; Guan, X.; Xu, Y.; Zhang, J.; Hong, Z.; Cao, J.; Sun, X.; Gao, Z.; Lu, H.; Pan, X.; Bai, J. Tumor Acidic Microenvironment-Induced Drug Release of RGD Peptide Nanoparticles for Cellular Uptake and Cancer Therapy. *Colloids Surfaces B Biointerfaces* **2021**, *202*, 111673.
(24) Lee, K. Y.; Mooney, D. J. Alginate: Properties and Biomedical Applications. *Progress in Polymer Science (Oxford)* **2012**, *37*, 106.
(25) Lee, K. Y.; Mooney, D. J. Progress in Polymer Science Alginate : Properties and Biomedical Applications. *Prog. Polym. Sci.* **2012**, *37* (1), 106.
(26) Qin, Y.; Summerscales, J.; Graham-Jones, J.; Meng, M.; Pemberton, R. Monomer Selection for in Situ Polymerization Infusion Manufacture of Natural-Fiber Reinforced Thermoplastic-Matrix Marine Composites. *Polymers (Basel)* **2020**, *12* (12), 2928.
(27) Zagho, M. M.; Hussein, E. A.; Elzatahry, A. A. Recent Overviews in Functional Polymer Composites for Biomedical Applications. *Polymers* **2018**, *10*, 739.
(28) Rani, R.; Singh, G.; Batra, K.; Minakshi, P. Bioengineered Polymer/Composites as Advanced Biological Detection of Sorbitol: An Application in Healthcare Sector. *Curr. Top. Med. Chem.* **2020**, *20* (11), 963−981.
(29) Gil, M. S.; Cho, J.; Thambi, T.; Giang Phan, V. H.; Kwon, I.; Lee, D. S. Bioengineered Robust Hybrid Hydrogels Enrich the Stability and Efficacy of Biological Drugs. *J. Controlled Release* **2017**, *267*, 119−132.
(30) Guo, B.; Ma, P. X. Synthetic Biodegradable Functional Polymers for Tissue Engineering: A Brief Review. *Sci. China Chem.* **2014**, *57* (4), 490−500.
(31) Borin, D. Targeted Patterning of Magnetic Microparticles in a Polymer Composite. *Philos. Trans. R. Soc. A Math. Phys. Eng. Sci.* **2020**, *378* (2171), 20190256.

https://doi.org/10.1021/acsomega.3c07356
ACS Omega 2024, 9, 81−96

(32) Birajdar, M. S.; Joo, H.; Koh, W. G.; Park, H. Natural Bio-Based Monomers for Biomedical Applications: A Review. *Biomaterials Research* **2021**, DOI: 10.1186/s40824-021-00208-8.
(33) Yang, W. W.; Pierstorff, E. Reservoir-Based Polymer Drug Delivery Systems. *Journal of Laboratory Automation* **2012**, *17*, 50−58.
(34) Rinsma, N. F.; Bouvy, N. D.; Masclee, A. A. M.; Conchillo, J. M. Electrical Stimulation Therapy for Gastroesophageal Reflux Disease. *J. Neurogastroenterol. Motil.* **2014**, *20* (3), 287−293.
(35) Xia, W.; Tao, Z.; Zhu, B.; Zhang, W.; Liu, C.; Chen, S.; Song, M. Targeted Delivery of Drugs and Genes Using Polymer Nanocarriers for Cancer Therapy. *Int. J. Mol. Sci.* **2021**, *22* (17), 9118.
(36) Zhang, W.; Michalowski, C. B.; Beloqui, A. Oral Delivery of Biologics in Inflammatory Bowel Disease Treatment. *Frontiers in Bioengineering and Biotechnology* **2021**, DOI: 10.3389/fbioe.2021.675194.
(37) Stewart, S. A.; Domínguez-Robles, J.; Donnelly, R. F.; Larrañeta, E. Implantable Polymeric Drug Delivery Devices: Classification, Manufacture, Materials, and Clinical Applications. *Polymers* **2018**, *10*, 1379.
(38) Javaid, M.; Haleem, A.; Singh, R. P.; Suman, R. Sustaining the Healthcare Systems through the Conceptual of Biomedical Engineering: A Study with Recent and Future Potentials. *Biomed. Technol.* **2023**, *1*, 39−47.
(39) Gao, J.; Yu, X.; Wang, X.; He, Y.; Ding, J. Biomaterial−Related Cell Microenvironment in Tissue Engineering and Regenerative Medicine. *Engineering* **2022**, *13*, 31−45.
(40) Andorko, J. I.; Jewell, C. M. Designing Biomaterials with Immunomodulatory Properties for Tissue Engineering and Regenerative Medicine. *Bioeng. Transl. Med.* **2017**, *2* (2), 139−155.
(41) Gomez-Florit, M.; Pardo, A.; Domingues, R. M. A.; Graça, A. L.; Babo, P. S.; Reis, R. L.; Gomes, M. E. Natural-Based Hydrogels for Tissue Engineering Applications. *Molecules* **2020**, *25*, 5858.
(42) Taghipour, Y. D.; Hokmabad, V. R.; Del Bakhshayesh, A. R.; Asadi, N.; Salehi, R.; Nasrabadi, H. T. The Application of Hydrogels Based on Natural Polymers for Tissue Engineering. *Curr. Med. Chem.* **2020**, *27* (16), 2658.
(43) Ahmed, E. M. Hydrogel: Preparation, Characterization, and Applications: A Review. *J. Adv. Res.* **2015**, *6*, 105−121.
(44) David, A.; Day, J.; Shikanov, A. Immunoisolation to Prevent Tissue Graft Rejection: Current Knowledge and Future Use. *Exp. Biol. Med.* **2016**, *241* (9), 955−961.
(45) Akbarzadeh, A.; Rezaei-Sadabady, R.; Davaran, S.; Joo, S. W.; Zarghami, N.; Hanifehpour, Y.; Samiei, M.; Kouhi, M.; Nejati-Koshki, K. Liposome: Classification, Preparation, and Applications. *Nanoscale Res. Lett.* **2013**, DOI: 10.1186/1556-276X-8-102.
(46) Mehrotra, P. Biosensors and Their Applications - A Review. *Journal of Oral Biology and Craniofacial Research* **2016**, *6*, 153−159.
(47) Fritea, L.; Banica, F.; Costea, T. O.; Moldovan, L.; Dobjanschi, L.; Muresan, M.; Cavalu, S. Metal Nanoparticles and Carbon-Based Nanomaterials for Improved Performances of Electrochemical (Bio)Sensors with Biomedical Applications. *Materials (Basel)* **2021**, *14* (21), 6319.
(48) Rezuş, E.; Burlui, A.; Cardoneanu, A.; Macovei, L. A.; Tamba, B. I.; Rezuş, C. From Pathogenesis to Therapy in Knee Osteoarthritis: Bench-to-Bedside. *International Journal of Molecular Sciences*; Multidisciplinary Digital Publishing Institute (MDPI), March 1, 2021; pp 1−24. DOI: 10.3390/ijms22052697.
(49) Hammami, I.; Alabdallah, N. M.; Jomaa, A. Al; Kamoun, M. Gold Nanoparticles: Synthesis Properties and Applications. *Journal of King Saud University - Science* **2021**, *33*, 101560.
(50) Sztandera, K.; Gorzkiewicz, M.; Klajnert-Maculewicz, B. Gold Nanoparticles in Cancer Treatment. *Mol. Pharmaceutics* **2019**, *16*, 1−23.
(51) Gao, Q.; Zhang, J.; Gao, J.; Zhang, Z.; Zhu, H.; Wang, D. Gold Nanoparticles in Cancer Theranostics. *Frontiers in Bioengineering and Biotechnology* **2021**, DOI: 10.3389/fbioe.2021.647905.
(52) Zhao, W.; Li, C.; Chang, J.; Zhou, H.; Wang, D.; Sun, J.; Liu, T.; Peng, H.; Wang, Q.; Li, Y.; Whittaker, A. K. Advances and Prospects of RAFT Polymerization-Derived Nanomaterials in MRI-Assisted Biomedical Applications. *Prog. Polym. Sci.* **2023**, *146*, No. 101739.
(53) Vítková, L.; Kazantseva, N.; Musilová, L.; Smolka, P.; Valášková, K.; Kocourková, K.; Humeník, M.; Minařík, A.; Humpolíček, P.; Mráček, A.; Smolková, I. Magneto-Responsive Hyaluronan Hydrogel for Hyperthermia and Bioprinting: Magnetic, Rheological Properties and Biocompatibility. *APL Bioeng.* **2023**, *7* (3), 36113.
(54) Dussán, K. J.; Giese, E. C.; Vieira, G. N. A.; Lima, L. N.; Silva, D. D. V. Pharmaceutical and Biomedical Applications of Magnetic Iron-Oxide Nanoparticles. *Metal Nanoparticles in Pharma* **2017**, 77−99.
(55) Liu, J.; Huang, C.; He, Q. Pharmaceutical Application of Magnetic Iron Oxide Nanoparticles. *Sci. Adv. Mater.* **2015**, *7* (4), 672−685.
(56) Silva, A. K. A.; Espinosa, A.; Kolosnjaj-Tabi, J.; Wilhelm, C.; Gazeau, F. Medical Applications of Iron Oxide Nanoparticles. *Iron Oxides: From Nature to Applications* **2016**, 425−471.
(57) Attia, N. F.; El-Monaem, E. M. A.; El-Aqapa, H. G.; Elashery, S. E. A.; Eltaweil, A. S.; El Kady, M.; Khalifa, S. A. M.; Hawash, H. B.; El-Seedi, H. R. Iron Oxide Nanoparticles and Their Pharmaceutical Applications. *Applied Surface Science Advances* **2022**, *11*, 100284.
(58) Bruschi, M. L.; de Toledo, L. de A. S. Pharmaceutical Applications of Iron-Oxide Magnetic Nanoparticles. *Magnetochemistry* **2019**, *5*, 50.
(59) Iravani, S.; Varma, R. S. Green Synthesis, Biomedical and Biotechnological Applications of Carbon and Graphene Quantum Dots. A Review. *Environmental Chemistry Letters* **2020**, *18*, 703−727.
(60) Zhao, C.; Song, X.; Liu, Y.; Fu, Y.; Ye, L.; Wang, N.; Wang, F.; Li, L.; Mohammadniaei, M.; Zhang, M.; Zhang, Q.; Liu, J. Synthesis of Graphene Quantum Dots and Their Applications in Drug Delivery. *J. Nanobiotechnol.* **2020**, DOI: 10.1186/s12951-020-00698-z.
(61) Matea, C. T.; Mocan, T.; Tabaran, F.; Pop, T.; Mosteanu, O.; Puia, C.; Iancu, C.; Mocan, L. Quantum Dots in Imaging, Drug Delivery and Sensor Applications. *Int. J. Nanomedicine* **2017**, *12*, 5421−5431.
(62) Iannazzo, D.; Pistone, A.; Salamò, M.; Galvagno, S.; Romeo, R.; Giofré, S. V.; Branca, C.; Visalli, G.; Di Pietro, A. Graphene Quantum Dots for Cancer Targeted Drug Delivery. *Int. J. Pharm.* **2017**, *518* (1−2), 185−192.
(63) Dey, N.; Rao, M. Quantum Dot: Novel Carrier for Drug Delivery. *Int. J. Res. Pharm. Biomed. Sci.* **2011**, *2* (2), 448−458.
(64) Rananaware, P.; Brahmkhatri, V. P. Fullerene Derivatives for Drug Delivery Applications. *Advanced Porous Biomaterials for Drug Delivery Applications* **2022**, 373−393.
(65) Ganji, M. D.; Yazdani, H.; Mirnejad, A. B36N36 Fullerene-like Nanocages: A Novel Material for Drug Delivery. *Phys. E Low-Dimensional Syst. Nanostructures* **2010**, *42* (9), 2184−2189.
(66) Al-Tamimi, B. H.; Farid, S. B. H. Fullerenes and Nanodiamonds for Medical Drug Delivery. *Nanocrystals [Working Title]* **2021**, DOI: 10.5772/intechopen.97867.
(67) Bolskar, R. D. Fullerenes for Drug Delivery. *Encyclopedia of Nanotechnology* **2016**, 1267−1281.
(68) Labille, J.; Pelinovskaya, N.; Botta, C.; Bottero, J.-Y.; Masion, A.; Joag, D. S.; Forbes, R. G.; Burger, S.; Pomplun, J.; Schmidt, F.; Veronis, G.; Sukharev, M.; Alam, M. A.; Kumar, S.; Matsui, S.; Arnold, W.; Schirmeisen, A.; Schwarz, U. D.; Hölscher, H.; Baumgartner, W.; Bolskar, R. D.; Tobias, G.; Mendoza, E.; Ballesteros, B.; Lu, J. G. Fullerenes for Drug Delivery. *Encyclopedia of Nanotechnology* **2012**, 898−911.
(69) Yan, P.; Ai, F.; Yan, X.; Liu, D. Biological Applications of Carbon Quantum Dots: Bioimaging, Drug Delivery and Toxicity. *Cailiao Daobao/Materials Rev.* **2017**, *31* (10), 35−42.
(70) Mondal, S.; Pan, A. Quantum Dots in Biosensing, Bioimaging, and Drug Delivery. *Application of Quantum Dots in Biology and Medicine* **2022**, 165−190.
(71) Jana, P.; Dev, A. Carbon Quantum Dots: A Promising Nanocarrier for Bioimaging and Drug Delivery in Cancer. *Mater. Today Commun.* **2022**, *32*, 104068.

(72) Calabrese, G.; De Luca, G.; Nocito, G.; Rizzo, M. G.; Lombardo, S. P.; Chisari, G.; Forte, S.; Sciuto, E. L.; Conoci, S. Carbon Dots: An Innovative Tool for Drug Delivery in Brain Tumors. *International Journal of Molecular Sciences* **2021**, *22*, 11783.
(73) Song, S.; Shen, H.; Wang, Y.; Chu, X.; Xie, J.; Zhou, N.; Shen, J. Biomedical Application of Graphene: From Drug Delivery, Tumor Therapy, to Theranostics. *Colloids Surf., B* **2020**, *185*, 110596.
(74) Hoseini-Ghahfarokhi, M.; Mirkiani, S.; Mozaffari, N.; Abdolahi Sadatlu, M. A.; Ghasemi, A.; Abbaspour, S.; Akbarian, M.; Farjadain, F.; Karimi, M. Applications of Graphene and Graphene Oxide in Smart Drug/Gene Delivery: Is the World Still Flat? *Int. J. Nanomed.* **2020**, *15*, 9469−9496.
(75) Pumera, M. Graphene-Based Nanomaterials for Energy Storage. *Energy Environ. Sci.* **2011**, *4* (3), 668−674.
(76) Wang, B.; Ruan, T.; Chen, Y.; Jin, F.; Peng, L.; Zhou, Y.; Wang, D.; Dou, S. Graphene-Based Composites for Electrochemical Energy Storage. *Energy Storage Materials* **2020**, *24*, 22−51.
(77) Oliveira, A. M. L.; Machado, M.; Silva, G. A.; Bitoque, D. B.; Tavares Ferreira, J.; Pinto, L. A.; Ferreira, Q. Graphene Oxide Thin Films with Drug Delivery Function. *Nanomaterials* **2022**, *12*, 1149.
(78) Xing, Y.; Dai, L. Nanodiamonds for Nanomedicine. *Nanomedicine* **2009**, *4*, 207−218.
(79) Qureshi, S. A.; Hsiao, W. W. W.; Hussain, L.; Aman, H.; Le, T. N.; Rafique, M. Recent Development of Fluorescent Nanodiamonds for Optical Biosensing and Disease Diagnosis. *Biosensors* **2022**, *12*, 1181.
(80) Zhang, W.; Patel, K.; Schexnider, A.; Banu, S.; Radadia, A. D. Nanostructuring of Biosensing Electrodes with Nanodiamonds for Antibody Immobilization. *ACS Nano* **2014**, *8* (2), 1419−1428.
(81) Chukhaeva, S. I. Synthesis, Properties, and Applications of Fractionated Nanodiamonds. *Phys. Solid State* **2004**, *46* (4), 625−628.
(82) Pandey, R. R.; Chusuei, C. C. Carbon Nanotubes, Graphene, and Carbon Dots as Electrochemical Biosensing Composites. *Molecules* **2021**, *26*, 6674.
(83) Rajabathar, J. R.; Periyasami, G.; Alanazi, A. M.; Govindasamy, M.; Arunachalam, P. Review on Carbon Nanotube Varieties for Healthcare Application: Effect of Preparation Methods and Mechanism Insight. *Processes* **2020**, *8*, 1654.
(84) Gruner, G. Carbon Nanotube Transistors for Biosensing Applications. *Anal. Bioanal. Chem.* **2005**, *384* (2), 322−335.
(85) Kumar, S.; Rani, R.; Dilbaghi, N.; Tankeshwar, K.; Kim, K. H. Carbon Nanotubes: A Novel Material for Multifaceted Applications in Human Healthcare. *Chem. Soc. Rev.* **2017**, *46*, 158−196.
(86) Ramachandran, K.; Boopalan, V.; Bear, J. C.; Subramani, R. Multi-Walled Carbon Nanotubes (MWCNTs)-Reinforced Ceramic Nanocomposites for Aerospace Applications: A Review. *J. Mater. Sci.* **2022**, *57*, 3923−3953.
(87) Kučuk, N.; Primožič, M.; Knez, Ž.; Leitgeb, M. Sustainable Biodegradable Biopolymer-Based Nanoparticles for Healthcare Applications. *International Journal of Molecular Sciences*; Multidisciplinary Digital Publishing Institute; February 6, 2023; p 3188. DOI: 10.3390/ijms24043188.
(88) Cuenya, B. R.; Baeck, S. H.; Jaramillo, T. F.; McFarland, E. W. Size- and Support-Dependent Electronic and Catalytic Properties of Au 0/Au3+ Nanoparticles Synthesized from Block Copolymer Micelles. *J. Am. Chem. Soc.* **2003**, *125* (42), 12928−12934.
(89) Haruta, M. Nanoparticulate Gold Catalysts for Low-Temperature CO Oxidation. *J. New Mater. Electrochem. Syst.* **2004**, *35*, 163−172.
(90) Cuenya, B. R. Synthesis and Catalytic Properties of Metal Nanoparticles: Size, Shape, Support, Composition, and Oxidation State Effects. *Thin Solid Films* **2010**, *518*, 3127−3150.
(91) Pelli Cresi, J. S.; Silvagni, E.; Bertoni, G.; Spadaro, M. C.; Benedetti, S.; Valeri, S.; D'Addato, S.; Luches, P. Optical and Electronic Properties of Silver Nanoparticles Embedded in Cerium Oxide. *J. Chem. Phys.* **2020**, DOI: 10.1063/1.5142528.
(92) Khan, I.; Saeed, K.; Khan, I. Nanoparticles: Properties, Applications and Toxicities. *Arabian Journal of Chemistry* **2019**, *12*, 908−931.
(93) Joudeh, N.; Linke, D. Nanoparticle Classification, Physicochemical Properties, Characterization, and Applications: A Comprehensive Review for Biologists. *J. Nanobiotechnol.* **2022**, DOI: 10.1186/s12951-022-01477-8.
(94) Sangeetha, G.; Usha, N.; Nandhini, R.; Kaviya, P.; Vidhya, G.; Chaithanya, B. A Review on Properties, Applications and Toxicities of Metal Nanoparticles. *International Journal of Applied Pharmaceutics* **2020**, 58−63.
(95) Zou, Y.; Zhang, L.; Yang, L.; Zhu, F.; Ding, M.; Lin, F.; Wang, Z.; Li, Y. Click" Chemistry in Polymeric Scaffolds: Bioactive Materials for Tissue Engineering. *J. Controlled Release* **2018**, *273*, 160−179.
(96) Bolívar-Monsalve, E. J.; Alvarez, M. M.; Hosseini, S.; Espinosa-Hernandez, M. A.; Ceballos-González, C. F.; Sanchez-Dominguez, M.; Shin, S. R.; Cecen, B.; Hassan, S.; Di Maio, E.; Trujillo-De Santiago, G. Engineering Bioactive Synthetic Polymers for Biomedical Applications: A Review with Emphasis on Tissue Engineering and Controlled Release. *Materials Advances* **2021**, *2*, 4447.
(97) Choi, Y. S.; Dusting, G. J.; Stubbs, S.; Arunothayaraj, S.; Han, X. L.; Collas, P.; Morrison, W. A.; Dilley, R. J. Differentiation of Human Adipose-Derived Stem Cells into Beating Cardiomyocytes. *J. Cell. Mol. Med.* **2010**, *14* (4), 878−889.
(98) Song, R.; Murphy, M.; Li, C.; Ting, K.; Soo, C.; Zheng, Z. Current Development of Biodegradable Polymeric Materials for Biomedical Applications. *Drug Design, Development and Therapy* **2018**, *12*, 3117−3145.
(99) Middleton, J. C.; Tipton, A. J. Synthetic Biodegradable Polymers as Orthopedic Devices. *Biomaterials* **2000**, *21* (23), 2335−2346.
(100) Kalirajan, C.; Dukle, A.; Nathanael, A. J.; Oh, T. H.; Manivasagam, G. A Critical Review on Polymeric Biomaterials for Biomedical Applications. *Polymers*; Multidisciplinary Digital Publishing Institute, September 6, 2021; p 3015. DOI: 10.3390/polym13173015.
(101) Mansur, A. A. P.; Carvalho, S. M.; Oliveira, L. C. A.; Souza-Fagundes, E. M.; Lobato, Z. I. P.; Leite, M. F.; Mansur, H. S. Bioengineered Carboxymethylcellulose−Peptide Hybrid Nanozyme Cascade for Targeted Intracellular Biocatalytic−Magnetothermal Therapy of Brain Cancer Cells. *Pharmaceutics* **2022**, *14* (10), 2223.
(102) Ahmad, A.; Ansari, M. M.; Verma, R. K.; Khan, R. Aminocellulose-Grafted Polymeric Nanoparticles for Selective Targeting of CHEK2-Deficient Colorectal Cancer. *ACS Appl. Bio Mater.* **2021**, *4* (6), 5324−5335.
(103) Zeynaloo, E.; Stone, L. D.; Dikici, E.; Ricordi, C.; Deo, S. K.; Bachas, L. G.; Daunert, S.; Lanzoni, G. Delivery of Therapeutic Agents and Cells to Pancreatic Islets: Towards a New Era in the Treatment of Diabetes. *Mol. Aspects Med.* **2022**, *83*, 101063.
(104) Kumar Reddy Sanapalli, B.; Tyagi, R.; Shaik, A. B.; Pelluri, R.; Bhandare, R. R.; Annadurai, S.; Venkata Satyanarayana Reddy Karri, V. L-Glutamic Acid Loaded Collagen Chitosan Composite Scaffold as Regenerative Medicine for the Accelerated Healing of Diabetic Wounds. *Arab. J. Chem.* **2022**, *15* (6), No. 103841.
(105) Mukhopadhyay, P.; Sarkar, K.; Bhattacharya, S.; Bhattacharyya, A.; Mishra, R.; Kundu, P. P. PH Sensitive N-Succinyl Chitosan Grafted Polyacrylamide Hydrogel for Oral Insulin Delivery. *Carbohydr. Polym.* **2014**, *112*, 627−637.
(106) Zhang, Z.; Shan, H.; Chen, L.; He, C.; Zhuang, X.; Chen, X. Synthesis of PH-Responsive Starch Nanoparticles Grafted Poly (l-Glutamic Acid) for Insulin Controlled Release. *Eur. Polym. J.* **2013**, *49*, 2082−2091.
(107) Tzeng, H. P.; Liu, S. H.; Chiang, M. T. Antidiabetic Properties of Chitosan and Its Derivatives. *Marine Drugs*. Multidisciplinary Digital Publishing Institute (MDPI), December 1, 2022. DOI: 10.3390/md20120784.
(108) Zhao, R.; Lu, Z.; Yang, J.; Zhang, L.; Li, Y.; Zhang, X. Drug Delivery System in the Treatment of Diabetes Mellitus. *Frontiers in Bioengineering and Biotechnology* **2020**, DOI: 10.3389/fbioe.2020.00880.
(109) Gao, C.; Liu, L.; Zhou, Y.; Bian, Z.; Wang, S.; Wang, Y. Novel Drug Delivery Systems of Chinese Medicine for the Treatment of

Inflammatory Bowel Disease. *Chinese Medicine (United Kingdom)* **2019**, DOI: 10.1186/s13020-019-0245-x.
(110) Liou, J. M.; Lee, Y. C.; El-Omar, E. M.; Wu, M. S. Efficacy and Long-Term Safety of h. Pylori Eradication for Gastric Cancer Prevention. *Cancers* **2019**, *11*, 593.
(111) Baranwal, J.; Barse, B.; Fais, A.; Delogu, G. L.; Kumar, A. Biopolymer: A Sustainable Material for Food and Medical Applications. *Polymers*; Multidisciplinary Digital Publishing Institute (MDPI), March 1, 2022. DOI: 10.3390/polym14050983.
(112) Flynn, C. D.; Chang, D.; Mahmud, A.; Yousefi, H.; Das, J.; Riordan, K. T.; Sargent, E. H.; Kelley, S. O. Biomolecular Sensors for Advanced Physiological Monitoring. *Nat. Rev. Bioeng.* **2023**, *1* (8), 560−575.
(113) Ahmed, T. Organ-on-a-Chip Microengineering for Bio-Mimicking Disease Models and Revolutionizing Drug Discovery. *Biosensors and Bioelectronics: X*; Elsevier, September 1, 2022; p 100194. DOI: 10.1016/j.biosx.2022.100194.
(114) Gupta, A.; Vardalakis, N.; Wagner, F. B. Neuroprosthetics: From Sensorimotor to Cognitive Disorders. *Communications Biology*; Nature Publishing Group, December 1, 2023. DOI: 10.1038/s42003-022-04390-w.
(115) Chan, B. P.; Leong, K. W. Scaffolding in Tissue Engineering: General Approaches and Tissue-Specific Considerations. In *European Spine Journal*; Springer, 2008; Vol. *17*, p 467. DOI: 10.1007/s00586-008-0745-3.
(116) Sharma, S.; Srivastava, D.; Grover, S.; Sharma, V. Biomaterials in Tooth Tissue Engineering: A Review. *Journal of Clinical and Diagnostic Research* **2014**, 309−315.
(117) Al-Shalawi, F. D.; Azmah Hanim, M. A.; Ariffin, M. K. A.; Looi Seng Kim, C.; Brabazon, D.; Calin, R.; Al-Osaimi, M. O. Biodegradable Synthetic Polymer in Orthopaedic Application: A Review. *Mater. Today Proc.* **2023**, *74*, 540−546.
(118) Bioengineered formulations, methods of making and embodiments thereof. Chinese patent CN114761544A. Google Patents https://patents.google.com/patent/CN114761544A/en?oq=Bioengineered+formulations%2C+methods+of+making+and+embodiments+thereof+(CN114761544A) (accessed 2023-05-26).
(119) Single Step Heparosan N-Deacetylation and Depolymerization for Making Bioengineered Heparin. U.S. patent WO2012116048A1, 2012.
(120) Method of Fabricating Bioengineered Product Using Three Dimensional Bioprinting. U.S. patent US9855369B2, 2019.
(121) Zaiferiou, M.-P.; Zimmermann, W.-H. Methods of Producing Bioengineered Neuronal Organoids (BENOs) and Uses Thereof. U.S. patent US9855369B2, 2018.
(122) Hsiue, G.-H.; Jui-Yang, L. Biopolymer-Bioengineered Cell Sheet Construct. U.S. patent US20080050423A1, 2009.
(123) Malarkey, J.; Baas, J. H.; Hope, J. A.; Aspden, R. J.; Parsons, D. R.; Peakall, J.; Paterson, D. M.; Schindler, R. J.; Ye, L.; Lichtman, I. D.; Bass, S. J.; Davies, A. G.; Manning, A. J.; Thorne, P. D. The Pervasive Role of Biological Cohesion in Bedform Development. *Nat. Commun.* **2015**, DOI: 10.1038/ncomms7257.
(124) Bitar, K. Tubular Bioengineered Smooth Muscle Structures. U.S. patent WO2013116446A1, January 31, 2013.
(125) Three Dimensional Bioengineered Smooth Muscle Tissue and Sphincters and Methods Therefore. U.S. patent US2006134076A1, 2005.
(126) GE Jian, C. N.; LI Kang-jun, C. N.; ZHONG Xiu-feng, C. N. *Bioengineering Retinal Nerve Scaffold with Cell Tracing Function and Preparation Method of Bioengineering Retinal Nerve Scaffold*; Zhongshan Ophthalmic Center, February 22, 2016.
(127) Use of Biological Material Containing Cell Supported on Three-Dimensional Scaffolds Comprising Hyaluronic Acid Derivatives, for Autologous and/or Allogenic Grafts Preparation for Implantation by Arthroscopy. Italian patent IT1320141B1, 2000.
(128) Dynamic bio-nanoparticle platforms. U.S. patent US11096901B2. Google Patents https://patents.google.com/patent/US11096901B2/en?oq=US11096901B2 (accessed 2023-06-19).
(129) Smart Bio-Nanoparticle Elements. U.S. patent US7393924B2, December 30, 2004.
(130) Plasmonic nanoparticle-doped silk materials. U.S. patent. US20130310908A1. Google Patents https://patents.google.com/patent/US20130310908A1/en?oq=US2013310908A1 (accessed 2023-06-19).
(131) Bajracharya, R.; Song, J. G.; Back, S. Y.; Han, H. K. Recent Advancements in Non-Invasive Formulations for Protein Drug Delivery. *Computational and Structural Biotechnology Journal* **2019**, *17*, 1290−1308.
(132) Ding, H.; Wu, F. Image Guided Biodistribution and Pharmacokinetic Studies of Theranostics. *Theranostics* **2012**, *2*, 1040−1053.
(133) Mahapatro, A.; Singh, D. K. Biodegradable Nanoparticles Are Excellent Vehicle for Site Directed In-Vivo Delivery of Drugs and Vaccines. *J. Nanobiotechnol.* **2011**, *9*, 55.
(134) Date, A. A.; Hanes, J.; Ensign, L. M. Nanoparticles for Oral Delivery: Design, Evaluation and State-of-the-Art Graphical Abstract HHS Public Access. *J. Controlled Release* **2016**, *240*, 504−526.

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