第 49 卷第 10 期
2022 年 月

湖南大学学报（自然科学版）
Journal of Hunan University（Natural Sciences）

Vol. 49. No. 10
October 2022

Open Access Article

BIOPOLYMERS FOR DRUG DELIVERY: PROPERTIES, PROCESSING, AND APPLICATIONS

[1]Dr A. Kishore Babu*, [2]Dr. Cheepurupalli Prasad, [3]Dr M Pradeep Kumar, [4]Dr. Virendra Singh, [5]Dr. Gulzar Alam, [6]Dr. Rohit Mohan*

[1]School of Pharmacy, KPJ healthcare University, Persiaran Seriemas, Nilai, Negeri Sembilan, Malaysia- 71800.

[2]Pydah college of Pharmacy, Kakinada, Andhra Pradesh, India- 533003.

[3]Department of Pharmaceutics, Vasavi Institute of Pharmaceutical Sciences Kadapa-516247

[4]Geetanjali Institute of Pharmacy, Geetanjali University, N.H 8 Bypass, Manwakhera, Udaipur-313001.

[5]Shiv Bali Singh Group of Educational & Training Institute, College of Pharmacy, Malwan, Fatehpur- 212664, UP, India.

[6]Dept. of Pharmacy Nandlal Prabhu Devi Professional Institute, Village-Alapur, Near Subhash Adarsh Inter College, Barabanki, Uttar Pradesh 225001.

Abstract

Biopolymers provide a plethora of applications in the pharmaceutical and medical applications. A material that can be used for biomedical applications like wound healing, drug delivery and tissue engineering should possess certain properties like biocompatibility, biodegradation to non-toxic products, low antigenicity, high bio-activity, processability to complicated shapes with appropriate porosity, ability to support cell growth and proliferation and appropriate mechanical properties, as well as maintaining mechanical strength. This paper reviews biodegradable biopolymers focusing on their potential in biomedical applications. Biopolymers most commonly used and most abundantly available have been described with focus on the properties relevant to biomedical importance.

Introduction

Biopolymer development provides a platform that fits into the paradigm of achieving an eco-friendly environment while reducing dependence on the limited fossil fuel components for the fabrication of everyday products in a world that canopies numerous opportunities to advance towards a green sustainable life. As a result of current technological advancements, biopolymer end products are now being used for more demanding applications and may soon perform on par with synthetic polymers derived from petroleum. This paper's goal is to shed some light on several biopolymer-related topics, including their classes, characteristics, composites, and uses. Numerous fascinating polymer composition chemistries can be supported depending on the sort of class based on different categories. By changing the chemical configuration and synthesis process, as well as concentrating on the biopolymer's functional purpose, essential features can be added to the resulting material. Modern biopolymer composites use the benefits of two different biopolymers to create a component with

Received: August,18, 2022 / Revised: September,11, 2022 / Accepted: 28, September, 2022 / Published: 20, October, 2022

About the authors：Dr A. Kishore Babu

Email:

improved properties and standout explicit characteristics. There are several ways to produce biopolymer composites, but in-situ, infiltration, and electrospinning technologies have garnered a lot of attention. The biomedical, packaging, agricultural, and automotive industries have all experienced enthralling advancements because to biopolymers and its composites. Biopolymers have made a distinctive mark that will stimulate the development of new materials for many years to come, even though their effectiveness has not yet caught up to that of their fossil fuel counterparts. Classification of biopolymers is shown in fig.1[1-2].

Uses and production of biopolymers

Living things have the capacity to create a diverse spectrum of polymers, and in the majority of species, these biopolymers make up the majority of the dry matter in the cells. Most of the time, biopolymers serve vital roles for cells and have a wide range of functions to match their complex structural makeup. Many different purposes are served by these biopolymers [3].

The organisms' several necessary processes include:

1. The expression and conservation of genetic data.
2. Reaction catalysis, carbon storage, energy storage, and other nutrient storage.
3. Defending and safeguarding against the assault of other cells, potentially dangerous environmental variables,
4. Biotic and abiotic elements being sensed.
5. Interaction with other organisms and the environment.
6. Controlling other creatures' or non-living materials' adhesion to surfaces, among many other things.

Enzymatic processes take place in the many types of cytoplasm, where all the biopolymers are created. the cytoplasmic membrane or cell wall components, at the surface, or in cellular compartments or organelles. Synthesis of a biopolymer can begin in one area of a cell and can continue elsewhere in the cell or even extracellularly in another section as it develops [4].

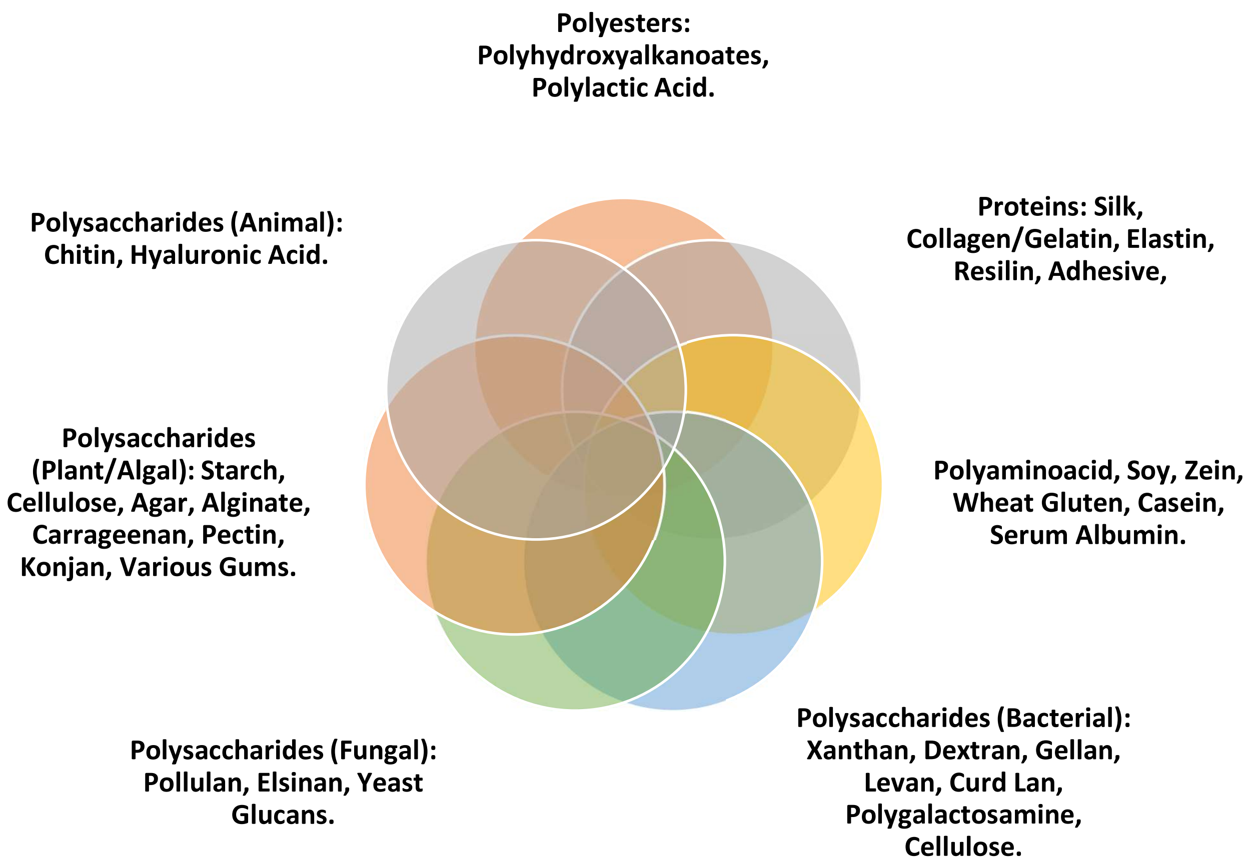

Fig.1 Classification of biopolymers

Production of Biopolymer

To make biopolymers available for a range of uses, many methods of production can be used:

(i)Many biopolymers can be extracted from plants and algae that grow in the wild since they are found in large quantities there. Red algae from the genus Gelidium as well as different brown algae, often known as seaweeds, are used to separate agar and alginates.

(ii) From sources that are completely natural, very few biopolymers are extracted. Hyaluronic acid, which is taken from newborns' umbilical cords, is one example of an exception to this rule.

(iii) Cell-free systems that use isolated enzymes to create biopolymers in vitro provide a further method for producing these materials. The use of heat-stable DNA polymerases in the polymerase chain reaction (PCR) to create monodisperse specified DNA molecules is one instance. Another illustration is dextran, which may be generated on a large scale using isolated dextran sucrase.

(iv) Fermentative biopolymer manufacturing is used in industry, such as polysaccharides. Biopolymers can be produced biotechnologically either intracellularly or extracellularly. This has a number of serious repercussions on the production and downstream processes that are required to obtain the biopolymers in a pure state [5].

Processing of biopolymers

There are many different methods and techniques used to produce biopolymers. Since most of these polymers already exist in nature or are produced by natural organisms, these processes are often a matter of extraction followed by synthesis. They may include a combination of any of fermentation, filtration, compounding/granulation, hydrolysis, esterification, poly-condensation, oxidation and dehydration. Below is an example of the production process involved in making polybutylene succinate (PBS).

Biopolymers are used in many industrial applications as well as food packaging, cosmetics and medicine. They can replace traditional petroleum-based plastics in many applications. Some biopolymers have also been applied to specific uses that other plastics would not be suitable for, such as in the creation of artificial tissue. These applications may require biocompatible and biodegradable materials with sensitivity to changes in pH as well as physicochemical and thermal fluctuations.

Biopolymers, in general, often exhibit poor mechanical properties, chemical resistance and processability in comparison to synthetic polymers. To make them more suitable for specific applications, they can be reinforced with fillers which drastically improve these properties. Biopolymers that have been reinforced in this way are called biopolymer composites. The table below is a summary of some common biopolymer composites, their properties and the industries in which they are already widely used.

Biopolymers can be classified broadly into three categories based on their monomeric units and structure:

- **Polynucleotides:** DNA (deoxyribonucleic acid) and RNA (ribonucleic acid)
- **Polysaccharides:** cellulose, chitosan, chitin, etc.
- **Polypeptides:** collagen, gelatin, gluten, whey, etc.

Biopolymers can also be categorized by other criteria such as their base materials (animal, plant or microbial), their biodegradability, their synthesis route, their applications or their properties.
Examples of some commercially-produced biopolymers include [1]:

- Bio-based polyesters such as polylactic acid (PLA), polyhydroxybutyrate (PHB), polybutylene succinate (PBS), polybutylene succinate adipate (PBSA), polytrimethylene terephthalate (PTT)
- Bio-based polyolefins such as polyethylene (Bio-PE)

- Bio-based polyamides (Bio-PA) such as homopolyamides (Bio-PA 6, Bio-PA 11) and copolyamides (Bio-PA 4.10 – Bio-PA 5.10 – Bio-PA 6.10, Bio-PA 10.10)
- Polyurethanes such as Bio-PUR
- Polysaccharide polymers such as cellulose-based polymers (regenerated cellulose, cellulose diacetate) and starch-based polymers (thermoplastic starch, starch blends).

Starch

Starch is a primary source of energy. It is composed of 60%–75% weight of grain products. It requires approximately 70%–80% of calories from the human body or living organism for consumption starch products are usually used to alter the physical properties of food. It is used as a thickening agent, adhesive, and moisture retention material in many applications. Starch is a natural biopolymer and its structure is similar to cellulose, but it differs in internal bonding. It has a D-glucose unit with an open-chain structure, it is a homopolymer of D-glucopyranose. Starch contains D-glucopyranose units, which are linked together with α(1→4) and α(1→6) glycosidic bonds. C_1 carbon of the glucopyranose ring reacts with C_4 or C_6 carbon of the glucopyranose ring to form a D-glucopyranose molecule. Starch molecules have one free reducing end due to the presence of the aldehyde group. Glucose includes two types of starch polymerization: amylose and amylopectin. Amylose is an essential carbohydrate with a linear structure, but amylopectin is a larger molecule with a highly branched structure [6].

Amylose and amylopectin

Amylose is described as an essential carbohydrate with a linear structure that consists of an α(1 → 4) glycosidic linkage[3]. It has a helical structure that possesses the H atom, but is hydrophobic in nature. During the heating of starch granules, amylose has a greater tendency to form gels [7]. It has a Dp of 1500–6000 dpi and its average molecular weight is 243,000–972,000 g/mol

Amylopectin is a larger structure and more highly branched than the amylose structure. Its molecules consist of α(1→4) and α(1→6) glycosidic linkages [70]. There are only 4%–6% of α(1→ 4) linkages and whole molecules possess an α(1→6) linkage. It exhibits excellent properties as compared to amylose due to its branched structure with a high Dp of 300,000–3,000,000 dpi [8].

Chitosan

Chitosan is a derivative of the natural polysaccharide, chitin. Chitin was first isolated and characterized from mushrooms, by French chemist Henri Braconnot in 1811. It is the second most abundant biopolymer in the world. Except celluloses, chitin is the most abundant polysaccharide in nature, being the main component of the exoskeleton of crustaceans and insects, also occurs, in nematodes and in the cell wall of yeast and fungi [9]. Chitosan is excellent in biocompatibility; high bioactivity; biodegradability; selective permeability; polyelectrolyte action; antimicrobial activity; ability to form gel and film; chelation ability and absorptive capacity. These peculiar properties provide a variety of applications to Chitosan, such as: drug carrier for controlled release [10], anti-bacterial and anti-acid;

inhibits the bacterial plaque formation and decalcification of dental enamelogenesis, fat absorbent action and promotes the healing of ulcers and lesions. Chitosan as an anti-oxidant: Chitosan has an in vivo stimulatory effect on both nitric oxide production and modulates peroxide production. Neutrophil activation was inhibited by administration of chitosans with low molecular weight and oxidation of serum albumin commonly observed in patients undergoing haemodialysis, resulting in reduction of oxidative stress associated with uremia.

Chitosan and drug delivery: It has potential to improve drug absorption and stabilization of drug components to increase drug targeting. In addition, chitosan can protect DNA and increase the expression period of genes. Chitin or chitosan derivatives, which were conjugated with some kinds of anticancer agents, can execute better anticancer effects with gradual release of free drug in the cancer tissues. Chitosan as an anti-inflammatory agent: Chitosan is confirmed to partially inhibit the secretion of both IL-8 and TNF-α from mast cells, demonstrating that water-soluble chitosan has the potential to reduce the allergic inflammatory response. Chitosan promotes phagocytosis and production of osteopontin and leukotriene B by polymorphnuclear leukocytes, production of interleukin-1, transforming growth factor b1 and platelet-derived growth factor by macrophages, and production of interleukin-8 by fibroblasts, enhancing immune responses [11].

Chitosan composite for tissue engineering: Chitosan and hydroxyapatite are one of the best bioactive biomaterials in bone tissue engineering. Different types of Marine source polysaccharides are used for management of bone diseases like Osteoporosis and arthritis. As a functional wound dressing and in order to create a moist environment for rapid wound healing, a hydrogel sheet composed of a blended powder of alginate, chitin/chitosan and fucoidan has been developed. It is highly biocompatible, biodegradable, porous structure, suitable for cell ingrowth, osteoconduction and intrinsic antibacterial nature, chitosan has been developed considerably in biomedical applications. Its application includes cartilage tissue engineering, wound healing and orthopedic applications. Degradable polymeric implants eliminate the need for a second surgical operation. Chitosan/Hydroxyapatite composite materials show promise in mimicking the organic portion as well as the inorganic portion of natural bone [12]. Chitosan as an anti-microbial agent: Chitosan shows antimicrobial action in a great variety of microorganisms, including algae, fungi and bacteria. It has shown antimicrobial activity against gram-positive bacteria and various species of yeast. The chitosan gel; derived from dilution in acetic acid is suggested as a preventive and therapeutic material for dental caries.

Cellulose

It is the most abundant naturally occurring polymer of glucose, found as the main constituent of plants and natural fibers such as cotton and linen. Some bacteria (e.g., Acetobacter xylinum) can also synthesize cellulose. Plant cellulose is chemically identical to Microbial or bacterial cellulose, although possessing different macromolecular structure and physical properties[13].

Cellulose has an organic formula $(C_6H_{10}O_5)_n$, a polysaccharide having a linear chain of several hundred to over ten thousand β (1→4) linked D-glucose units [42]. Cellulose with its derivatives is environmentally friendly. The most important cellulose fibers in medical applications are natural cotton fibers and different regenerated (man-made) cellulose fibers such as viscose, modal, and lyocell.

I. Devices for Controlled Drug Delivery: In solid tablets, cellulose ether is used which allows a swelling-driven release of the drug as physiological fluids come into contact with the tablet itself. The cellulose ether on the tablet surface starts to swell, forms chain entanglements and a physical hydrogel. As swelling proceeds from the surface to the glassy core of the tablet, the drug progressively dissolves in water and diffuses out from the polymer network[14].

II. Scaffolds for Regenerative Medicine: Due to the excellent biocompatibility of cellulose and its good mechanical properties the use of cellulose and its derivatives as biomaterials for the design of tissue engineering scaffolds has been increasing.

III. Wound Dressings: Bacterial cellulose (BC) has been widely investigated for wound healing due to its purity and high-water retention capacity.

Collagen

Collagen discovered in 1838 by Payen, is the primary structural material of vertebrates and is the most abundant mammalian protein accounting for about 20–30% of total body proteins. Collagen is synthesized by fibroblasts, which usually originates from pluripotential adventitial cells or reticulum cells. The basic collagen molecule is rod-shaped with a length and a width of about 3000 and 15 A, respectively, and has an approximate molecular weight of 300 kDa[15]. It is easily absorbable in the body and has very low antigenicity. Moreover, it is non- toxic, biocompatible and biodegradable. It has high tensile strength and high affinity with water.

Applications of collagen in biomedical science

I. **Tissue based device**: Tissue based device like prosthetic heart valves and vascular prosthesis have increased the life expectancy of many cardiac patients with lower risk of infection.

II. **Collagen-based drug delivery systems**: The main application of collagen films is as barrier membrane [14]. Collagen film/sheet/disc has been used for the treatment of tissue infection, such as infected corneal tissue or liver cancer. Soluble ophthalmic insert in the form of a wafer or a film was introduced as a drug delivery system for the treatment of infected corneal tissue using a high dose of antibiotic agents, such as gentamycin and tetracycline. Collagen film and matrix have been used as gene delivery carriers for promoting bone formation.

III. **Collagen sponges**: Collagen sponges are very useful in the management of severe burns and as a dressing for severe types of wounds. Collagen dressings are prepared in a variety of different forms including, sponges, membrane sheets and powder, having essential biological properties important for such application.

IV. **Gel, hydrogel, liposomes-collagen**: One of the successful applications of collagen for the controlled delivery systems is collagen-based gel as an injectable aqueous formulation. Collagen hydrogel was also used as gene delivery carriers[16].

V. **Nanoparticles/nanospheres:** The nanoparticles or nanospheres based biodegradable collagen are thermally stable, readily achieve their sterilization. Because of its small size, a large surface area, high adsorptive capacity and ability to disperse in water to form a clear colloidal solution, collagen- based nanoparticles have demonstrated their potential to be used as a sustained release formulation for anti-microbial agents or steroids. Applications are shown in fig.2. Nanoparticles have been used as a parenteral carrier for cytoxic agents and other therapeutic compounds, such as campthocin and hydrocortisone[16].

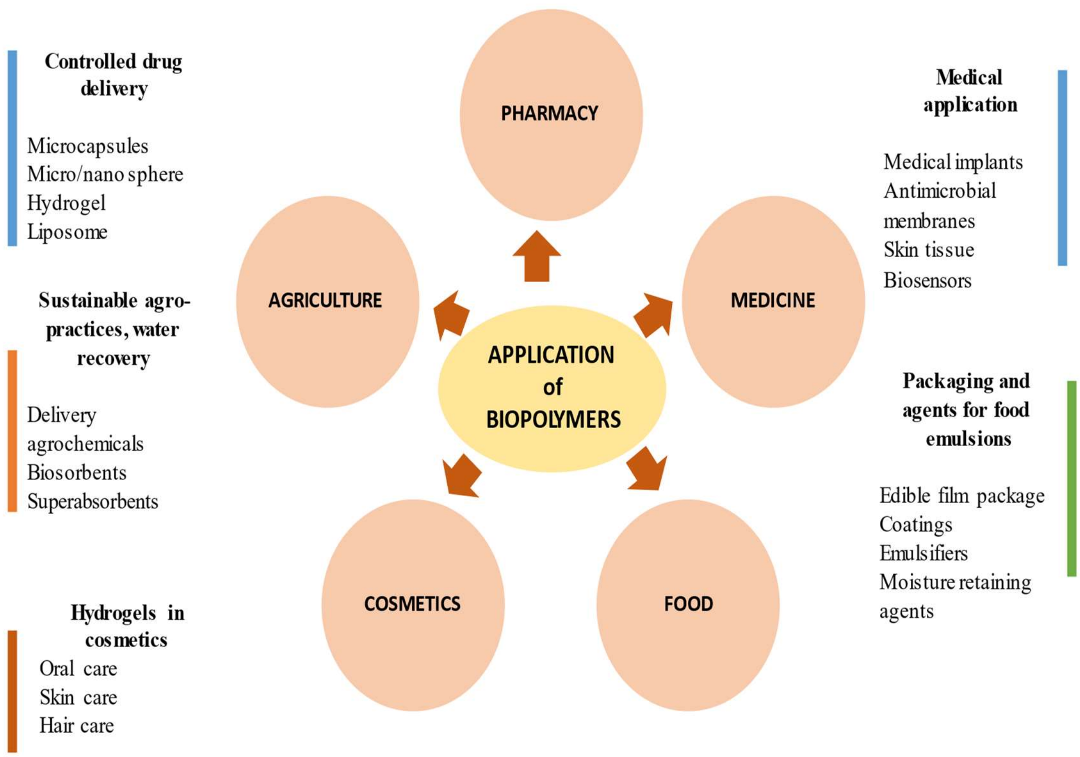

Fig.2 Applications of biopolymers

Collagen-based systems for tissue engineering

Collagen based implants have been widely used as vehicles for transportation of cultured skin cells or drug carriers for skin replacement and burn wounds. Collagen has been used as bone substitute due to its osteoinductive activity. Collagen has been used as implantable carriers for bone inducing proteins, such as bone morphogenetic protein 2 (rhBMP-2).

Collagen as a haemostat: Collagen achieves rapid coagulation of blood through its interaction with the platelets and providing a temporary framework while the host cells regenerate their own fibrous stroma. The use of collagen-based haemostats has been proposed for reducing blood loss in generalized bleeding in a wide number of tissues and management of wounds to cellular organs such as liver or spleen [17].

Gelatin

Gelatin is a water-soluble proteinaceous substance prepared by the destruction of the tertiary, secondary and to some extent the primary structure of native collagens, by the partial hydrolysis of collagen derived from the skin, white connective tissue and bones of animal. Gelatin differs from other hydrocolloids because most of them are polysaccharide, whereas gelatin is a digestible protein containing all the essential amino acids except tryptophan.

Gelatin can be made from many different sources of collagen. Cattle bones, hides, pig skins, and fish are the principle commercial sources. Gelatin is used as a foaming, emulsifying, and wetting agent in food, pharmaceutical, medical and technical applications due to its surface-active properties[18].

Xylan

Xylan, a hemicellulose largely found in nature, is considered the second most abundant polysaccharide after cellulose. Xylans are the main hemicelluloses in hardwood and they also predominate in annual plants and cereals making up to 30% of the cell wall material and one of the major constituents (25–35%) of lignocellulosic materials.

Xylan has been considered as a suitable raw material to produce colonic drug delivery systems as it is biodegraded by enzymes produced by the colonic microflora [19]. Physiological effects of Xylans: Viscous character of the fiber polysaccharides in cereals leads to the faecal bulking effect and lowering of blood cholesterol and decrease of postprandial glucose and insulin responses. Water extractable polysaccharides of cereals are claimed to alleviate alcoholic liver disorders. Arabino glucurono xylans possessing immunostimulating activities have been isolated from some herbal plants. Some of these xylans also show anti-phlogistic effect. Xylan rich hemi-celluloses extracted from plant waste such as bamboo leaves, wheat straws and corn stalks have been reported to inhibit the growth rate of sarcoma 180 and other tumours, probably due the indirect stimulation of the non-specific immunological host defense. T-lymphocytes and immunocytes are activated by Carboxymethylated xylan rich wood hemicelluloses. Pentosan polysulfate (PPS) has been known as an anti-coagulant and usually derived from beechwood glucuronoxylan. The PPS in gel form can be used in treatment of infusion thrombophlebetides[20].

Alginates

One of the most abundant biosynthesized materials, water soluble polymers extracted from brown seaweed. Alginates are hydrocolloids. Alginate is used to support matrix or delivery system for tissue repair and regeneration. Because of its biocompatibility, biodegradability, non-antigenicity and chelating ability, alginate is widely used in a variety of biomedical applications including tissue engineering, drug delivery and in some formulations preventing gastric reflux. It is an approved polymer by U.S. Food and Drug Administration (FDA), thus alginate has become one of the most important biomaterials for diverse applications in regeneration medicine, nutrition supplements etc [21]. Alginates are also widely used for impression making in the dental clinic because of its ease in handling.

I. **Wound dressings**: A mix of sodium and calcium alginate acts as a foundation for alginate dressings used for haemostasis and wound closure. They provide a moist environment at the wound bed, achieve haemostasis and absorb exudate. They also reduce wound pain, lower the bio-burden of the wound, absorb proteinases and reduce odour. Alginate-based wound dressings such as, hydrogels, electrospun mats and sponges offer many advantages including gel-forming ability upon absorption of wound exudates and haemostatic capability.
II. **Drug delivery**: Alginate is widely used as a carrier to immobilize or encapsulate drugs, for its biocompatible and biodegradable nature.

Carrageenan

Carrageenan is derived from a number of seaweeds of the class Rhodophyceae. Carrageenan is a generic name for a family of gel-forming and viscosifying polysaccharides. Carrageenan is a sulfated polygalactan with 15 to 40% of ester-sulfate content.

Anticoagulant and antithrombotic activity: The principal basis of the anticoagulant activity of carrageenan appears to be an anti-thrombic property. The mechanism underlying the anticoagulant activity of carrageenan involves thrombin inhibition. There is either anti-thrombin potentiation via heparin co-factor II (HC-II) and/ or a direct anti-thrombin effect [22].

Antiviral activity: Carrageenan is a selective inhibitor of several enveloped viruses, including such human pathogens as human immunodeficiency virus, herpes simplex virus (HSV), human cytomegalovirus, human rhinoviruses and others. Carrageenan acts primarily by preventing the binding or the entry of virions into cells.

Carrageenan is considered to be a good substitute for gelatin (animal-based product) in hard and soft gel capsules. Its incorporation in glycerin-water mixture masks the chalkiness of antacid gels. It can be used in both topical bases and suppository bases. It acts as a thickener and binder in dentifrices and prevents liquid-solid separation[23].

Gum Arabic

Gum Arabic is a dried, edible, gummy exudate from the stems and branches of Acacia Senegal and Acacia seyal that is rich in non-viscous soluble fiber. In folk medicine GA is used externally to cover inflamed surfaces and internally for the treatment of inflammation of intestinal mucosa [76]. Studies have claimed that GA possesses antioxidant and nephroprotectant properties. However, these findings are not universally accepted. Due to its physical properties, it reduces glucose absorption, increases fecal mass, bile acids and has the potential to beneficially modify the physiological state of humans. Some studies report Gum Arabic having growth inhibitory activity of certain pathogenic species (causal agent of tooth decay or agent involved in the plaque), such as *Porphyromonas gingivalis* and *Prevotella intermedia* [78]. As per the studies GA could improve dental remineralization and inhibit the formation of plaque, acting as a potential preventive agent in the formation of caries. Such effects are attributed to the high salt content of $Ca+2$, $Mg+2$ and $K+$ of polysaccharides in GA, and the effect of the gum in the metabolism of Ca and possibly phosphate.

Incorporation of Gum Arabic improves the hardness of gypsum products. Small amount of Gum Arabic plus calcium carbonate added to the hemihydrate can reduce the amount of water required for mixing of both plaster and stone [24].

Xanthan Gum

Xanthan gum is a natural polysaccharide produced by the bacterium Xanthomonas campestris. The primary structure of xanthan consists of repeating pentasaccharide units consisting of two D-glucopyranosyl units, two D-mannopyranosyl units and one D-glucopyranosyluronic unit. The thickening ability of xanthan solutions is related with viscosity; a high viscosity resists flow. Xanthan solutions are pseudoplastic, or exhibit shear thinning characteristics, and the viscosity decreases with increasing shear rate.

Xanthan gum is widely used in toothpastes and cosmetics [25]. It can be easily extruded from the tube. It also ensures that toothpaste will keep a stable stand on the brush. The shear thinning characteristics also improve the dispersion on and the rinsing from the teeth. Thickened toothpaste with xanthan gum has a bright, shiny cord with short flow behavior. In emulsions or suspensions for pharmaceutical use xanthan gum prevents the separation of insoluble ingredients.

Pectin

Pectin is a structural heteropolysaccharide contained in the primary cell walls of terrestrial plants. Pectin consists of a complex set of polysaccharides that are present in most primary cell walls and particularly abundant in the non woody parts of nearly all terrestrial plants. Commercial pectins are almost exclusively derived from citrus peel or apple pomace, both of which are by-products from juice manufacturing units. Pectin is thought to consist mainly of D-galacturonic acid (GalA) units, joined in chains by means of α-(1-4) glycosidic linkage. Pectin is used for making mucoadhesive patches in combination with carbopol and chitosan. It acts by coming in intimate contact with tissues and entanglement of polymer and mucin chains and formation of weak bonds between chains. Pectin acts as a natural prophylactic substance against poisoning with toxic cations. Pectin is effective in removing lead and mercury from the respiratory organs and gastrointestinal tract. Pectin improves the coagulation and thus useful in controlling hemorrhage.

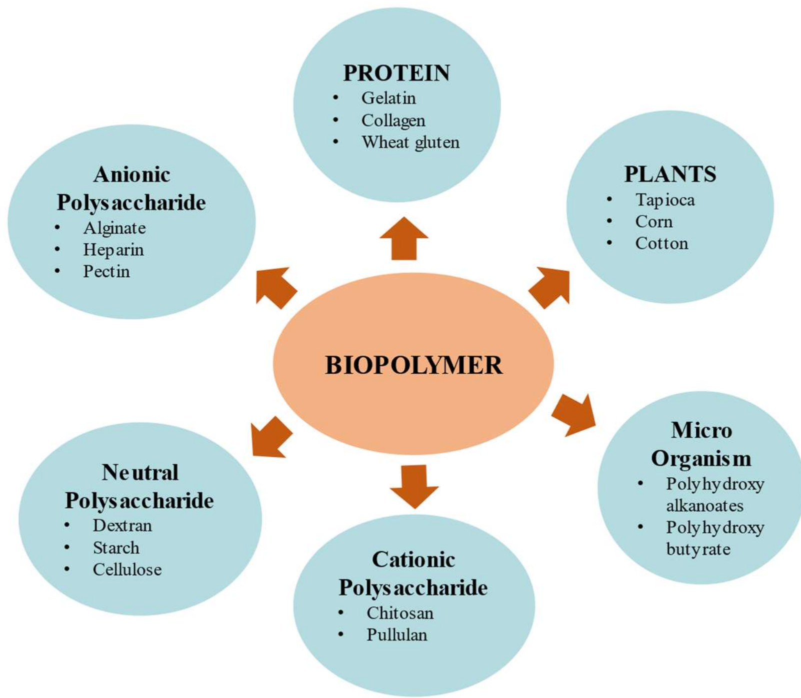

Fig.3 Types of biopolymers

Hyaluronic Acid

Hyaluronic acid is widely distributed in extracellular matrix and the joint liquid of mammals and approved for injections by the Food and Drug Administration (FDA). It is a biocompatible mucoadhesive polysaccharide with negative charge and is biodegradable. The first medical application of hyaluronan for humans was as a vitreous substitution/replacement during eye surgery in the late 1950s. Hyaluronic acid polymers are used in the preparation of gels for delivery of drugs to eye and installation into other cavities. Along with other polymers like alginic acid, HPMC (Hydroxypropyl methyl cellulose), poloxamers etc. they can be used for achieving the desired property in drug delivery systems. Corneal shields based on Hyaluronic acid have demonstrated prolonged steroid delivery, with a consummate smoothing of dosage profile. Other applications of hyaluronic acid as reviewed by Price et al., are as follows: (i) Wound healing by extracellular regeneration; (ii) Epithelial regeneration; (iii) Topical treatment of dry eye syndrome and Sjögren's syndrome; (iv) as a viscosity agent in pulmonary pathology for achieving alveolar patency; (v) Commercial preparation available for intra-articular injection; (vi) As a filler in rejuvenate medicine for wrinkles and cutaneous lines. Visco supplementation with Hyaluronic acid products helps to improve the physiological environment in an osteoarthritic joint by supplementing the shock absorption and lubrication properties of osteoarthritic synovial fluid. Different types of biopolymers are shown in fig.3. The rationale for using visco supplementation is to restore the protective viscoelasticity of synovial hyaluronan, decrease pain, and improve mobility. Esterified hyaluronic acid has also been used to prevent bacterial adhesion to dental implants, intraocular lenses, and catheters. Hyaluronic acid is an appropriate choice for a matrix to support dermal regeneration and augmentation. As a result of its ability to form hydrated, expanded matrices. Hyaluronic acid has also been successfully used in cosmetic applications such as soft tissue augmentation [26].

Properties of biopolymers

The main interest in biopolymers is to replace many of the everyday items which are made from petroleum products. This means that they will be required to exhibit similar, if not better, properties than the materials they replace to make them suitable for the various applications that they will be put to. Much of the property measurements of biopolymers have variance due to factors such as degree of polymerization, type and concentration of additives, and presence of reinforcement materials. Information about the properties of biopolymers is not as extensive as for traditional polymers, but there is still a considerable depth of investigation into their physical, mechanical, thermal properties.

Some biopolymers have been identified to possess electronic and ionic conductivity and have thus been termed electro-active biopolymers (EABP). This has given them the potential to replace other synthetic materials. These biopolymers, which include starch, cellulose, chitosan and pectin, show a wide-ranging electrical conductivity between 10-3 and 10-14 S/cm [27].

Applications

Biopolymers and their role in medicinal and pharmaceutical applications

Polymers and their composites have gained much research interest on account of their versatile and flexible nature. But most of the polymers are nonbiodegradable. Biodegradable polymers either of synthetic or natural origin have gained a lot of praise on account of their biodegradability and versatile nature. Biopolymers can be molded into scaffolds, nanocomposites, hydrogels, etc. Biopolymers have a number of applications in both medicinal and pharmaceutical applications. Biopolymers, whether of synthetic or natural origin, find use in different applications like drug delivery, tissue engineering, biomedical devices, etc.[28].

Crosslinking biopolymers for biomedical applications

Biomaterials made from proteins, polysaccharides, and synthetic biopolymers are preferred but lack the mechanical properties and stability in aqueous environments necessary for medical applications. Crosslinking improves the properties of the biomaterials, but most crosslinkers either cause undesirable changes to the functionality of the biopolymers or result in cytotoxicity. Glutaraldehyde, the most widely used crosslinking agent, is difficult to handle and contradictory views have been presented on the cytotoxicity of glutaraldehyde-crosslinked materials. Recently, poly(carboxylic acids) that can crosslink in both dry and wet conditions have been shown to provide the desired improvements in tensile properties, increase in stability under aqueous conditions, and also promote cell attachment and proliferation. Green chemicals and newer crosslinking approaches are necessary to obtain biopolymeric materials with properties desired for medical applications[29].

Biopolymers in the nutraceutical industries

Packaging is an indispensable tool for maintaining the quality of perishable food products. Petroleum-based packaging has been used as the material of choice for a long time. However, because these materials are nonbiodegradable they pose serious environmental risks. A suitable alternative is the use of biodegradable polymers. In recent years, biodegradable polymers have been found to have innumerous applications in packaging, agriculture, medicine, and other areas. In the food industry these polymers can be used as edible films and coatings, packaging materials, carriers of antimicrobial and antioxidative materials, etc. Nanocomposites can also be applied to food packaging in the future. A novel use of biopolymers is as a nanodelivery vehicle for delivering nutraceuticals and drugs orally. These are made from polysaccharides, lipids, and proteins[30].

Biopolymers for hydrogels in cosmetics

Hydrogels are cross-linked networks of macromolecular compounds characterized by high water absorption capacity. Such materials find a wide range of biomedical applications. Several polymeric hydrogels can also be used in cosmetics. Most common biopolymers used in cosmetics are presented in detail together with issues related to skin treatment and hair conditioning. Hydrogels based on collagen, chitosan, hyaluronic acid, and other polysaccharides have been characterized. New trends in the preparation of hydrogels based on biopolymer blends as well as bigels have been shown. Moreover, biopolymer hydrogels employment in encapsulation has been mentioned[31].

Application of Biopolymers in the Food Industry

Plastic materials obtained from oil are used in the food industry. These polymers are cheap and available. They have good mechanical properties, good barriers for oxygen and vaporizable aromatic substances, and they can be hot welded. However, the main disadvantage is that biopolymers are not biodegradable, and certainly not environmentally friendly. That is the reason why the application of plastic materials must be limited and gradually replaced by materials that cause fewer ecological problems. Edible and biodegradable natural polymeric materials are one of the alternatives for food usage. These are made from polysaccharides, lipids, and proteins. Their application saves money that would otherwise need to be spent on environmental protection. Biodegradable natural polymeric materials can be used as edible films and coatings, packaging materials, carriers of antimicrobial and antioxidative materials, etc. Nanocomposites will be applied for food packaging in the future. Nanoscale research, including detection of a pathogen, active packaging, antimicrobial packaging, and the formation of barriers, will improve food packaging. It may be possible to use particles that are not organic to introduce diverse components such as colors and odors. They also may be used as tanks for the controlled release of drugs or fungicides[32].

Biopolymer composites in supercapacitor and energy storage devices

Energy storage devices have a crucial role in handling energy consumption in various applications like automobiles and electronic devices. Materials used to fabricate these devices, like supercapacitors and batteries, are able to control the efficiency and lifetime of the devices. To achieve maximum efficiency and durability of the devices, the design and combination of different components of these devices are crucial. Although we are able to achieve good performance with synthetic materials, they have several drawbacks due to their synthetic background and environmental issues concerning synthetic methodology as well as processing. Production, utilization, and disposal are usually part and parcel of all kinds of technology and disposal of materials is of great concern because some are harmful to the environment. Biopolymer materials provide solutions to overcome issues produced by synthetic materials due to their availability in nature. In this chapter we discuss the utilization of biopolymer-based devices, which are also able to solve future environmental issues of these technologies[33].

Biopolymeric hydrogels: nanostructured TiO_2 hybrid materials as potential injectable scaffolds for bone regeneration

Development of novel hybrid materials from genipin crosslinked collagen or collagen/chitosan hydrogels containing various types of TiO2 nanoparticles characterized with different anatase/rutile ratios. Collagen and chitosan were selected as hydrogel components since they are biopolymers being, like collagen, the major compound present in extracellular matrix or exhibit structural similarity to glycosaminoglycans, like chitosan. TiO2 nanoparticles were introduced to the hydrogel matrices to improve their mechanical properties as well as bioactivity. A series of twelve novel hybrid materials were prepared and their physicochemical, mechanical and biological properties were evaluated. It was found that TiO2 nanostructures introduced to the hydrogels have significant influence on the swelling properties of the synthesized hybrids and their impact is strongly dependent on the type of matrices. The surfaces of hybrid materials were found to be more hydrophilic than these of corresponding hydrogel matrix. It was also observed that, the storage modulus values of the hybrids based on collagen-chitosan hydrogel are comparable to these for plain hydrogels what indicates that the mechanical properties of the materials obtained are satisfactory for possible biomedical application. The in vitro cell culture studies have shown that prepared materials are biocompatible as they can support mitochondrial activity of MEFs as well as MG-63 cells. In vitro experiments performed under simulated body fluid (SBF) conditions have revealed that all studied TiO2 nanoparticles present in hydrogel matrices, regardless of anatase/rutile ratio, successfully induced formation of apatite-like structures. The hybrid materials developed here are promising candidates for preparation of bioactive, injectable scaffolds for tissue engineering[34].

Chitosan based polymer/bioglass composites for tissue engineering applications

Composite scaffolds formed from polymers and bioglasses have been widely explored for applications in regenerative medicine as they have suitable organic/inorganic structures and properties similar to human hard tissue. Yet, these materials have only been used for non-load-bearing or low load-bearing purposes as they have limited mechanical strength while research is focused on improving their properties. One method of improving mechanical strength is by covalently bonding the organic and inorganic phases. This has been successfully achieved in Class ll hybrids which have covalent bonding between polymers and bioglasses. As well as improving mechanical strength, the chemical connection of the two phases results in simultaneous degradation. The currently available composite scaffolds use collagen for the polymer phase which can cause allergic reactions and transmit pathogens. An alternative natural polymer is chitosan which has been used to create scaffolds with bioglass avoiding the issues arising from collagen. Additionally, using cross-linking agents has been shown to strengthen chitosan hydrogels improving their mechanical properties. A promising natural cross-linker is genipin which has lower toxicity than other cross-linking agents while producing hydrogels with improved mechanical properties compared to pure chitosan. In this paper we offer an overview of requirements, structures and currently available composite scaffolds for tissue engineering applications[35].

Injectable chitosan/beta glycerophosphate hydrogels for bone tissue regeneration

Tissue engineering (TE) is a promising approach for repairing diseased and damaged bone tissue. Injectable hydrogel-based strategies offer a wide range of applications in rapid recovery of bone defects by acting as filler materials and depots for delivering various bioactive molecules and averting the need for surgical intervention. Chitosan (CS), a natural polysaccharide, forms a thermosensitive injectable hydrogel through the addition of beta-glycerophosphate (β-GP). This hybrid hydrogel possesses numerous advantages namely mimicking native extracellular matrix (ECM) and providing an amenable microenvironment for cell growth. In this review, a brief insight into the gelation mechanism of CS/GP hydrogels, modifications, bioactive additives and their applications in treating bone defects are presented[36].

Thermosensitive chitosan/glycerophosphate-based hydrogel and its derivatives in pharmaceutical and biomedical applications

Thermogelling chitosan (CS)/glycerophosphate (GP) solutions have been reported as a new type of parenteral in situ forming depot system. These free-flowing solutions at ambient temperature turn into semi-solid hydrogels after parenteral administration. Formulation parameters such as CS physico-chemical characteristics, CS/gelling agent ratio or pH of the system, were acknowledged as key parameters affecting the solution stability, the sol/gel transition behavior and/or the final hydrogel structure. We discuss also the use of the standard CS/GP thermogels for various biomedical applications, including drug delivery and tissue engineering. Furthermore, this manuscript reviews the different strategies implemented to improve the hydrogel characteristics such as combination with carrier particles, replacement of GP, addition of a second polymer and chemical modification of CS[37].

Recent advances and future prospects of cellulose, starch, chitosan, polylactic acid and polyhydroxyalkanoates for sustainable food packaging applications

Cellulose, starch, chitosan, polylactic acid, and polyhydroxyalkanoates are seen as promising alternatives to conventional plastics in food packaging. However, the application of these biopolymers in the food packaging industry on a commercial scale is limited due to their poor performance and processing characteristics and high production cost. This review aims to provide an insight into the recent advances in research that address these limitations. Loading of nanofillers into polymer matrix could improve thermal, mechanical, and barrier properties of biopolymers. Blending of biopolymers also offers the possibility of acquiring newer materials with desired characteristics. However, nanofillers tend to agglomerate when loaded above an optimum level in the polymer matrix. This article throws light on different methods adopted by researchers to achieve uniform dispersion of nanofillers in bionanocomposites. Furthermore, different processing methods available for converting biopolymers into different packaging forms are discussed. In addition, the potential utilization of agricultural, brewery, and industrial wastes as feedstock for the production of biopolymers, and integrated biorefinery concept that not only keep the total production cost of biopolymers low but are also environment-friendly, are discussed. Finally, future research prospects in this field and the possible contribution of biopolymers to sustainable development are presented. This review will certainly be helpful to researchers working on sustainable food packaging, and companies exploring pilot projects to scale up biopolymer production for industrial applications[38].

Glycerophosphate-based chitosan thermosensitive hydrogels and their biomedical applications

Chitosan is non-toxic, biocompatible and biodegradable polysaccharide composed of glucosamine and derived by deacetylation of chitin. Chitosan thermosensitive hydrogel has been developed to form a gel in situ, precluding the need for surgical implantation. In this review, the recent advances in chitosan thermosensitive hydrogels based on different glycerophosphate are summarized. The hydrogel is prepared with chitosan and β-glycerophosphate or αβ-glycerophosphate which is liquid at room temperature and transits into gel as temperature increases. The gelation mechanism may involve multiple interactions between chitosan, glycerophosphate, and water. The solution behavior, rheological and physicochemical properties, and gelation process of the hydrogel are affected not only by the molecule weight, deacetylation degree, and concentration of chitosan, but also by the kind and concentration of glycerophosphate. The properties and the three-dimensional networks of the hydrogel offer them wide applications in biomedical field including local drug delivery and tissue engineering[39].

Chitosan-Based Biomaterial Scaffolds for the Repair of Infected Bone Defects

The treatment of infected bone defects includes infection control and repair of the bone defect. The development of biomaterials with anti-infection and osteogenic ability provides a promising strategy for the repair of infected bone defects. Owing to its antibacterial properties, chitosan (an emerging natural polymer) has been widely studied in bone tissue engineering. Moreover, it has been shown that chitosan promotes the adhesion and proliferation of osteoblast-related cells, and can serve as an ideal carrier for bone-promoting substances. In this review, the specific molecular mechanisms underlying the antibacterial effects of chitosan and its ability to promote bone repair are discussed. Furthermore, the properties of several kinds of functionalized chitosan are analyzed and compared with those of pure chitosan. The latest research on the combination of chitosan with different types of functionalized materials and biomolecules for the treatment of infected bone defects is also summarized. Finally, the current shortcomings of chitosan-based biomaterials for the treatment of infected bone defects and future research directions are discussed. This review provides a theoretical basis and advanced design strategies for the use of chitosan-based biomaterials in the treatment of infected bone defects.

Biopolymers produced from microorganisms

A range of biopolymers like polysaccharides, polyamides, and polyesters are naturally produced by microorganisms. Genetic engineering of microorganisms opens up vast prospective for the synthesis of biopolymers with tailored properties suitable for desired applications, including food and nutraceuticals. Some examples of biopolymers from microbes are exopolysaccharide xanthan gum from Xanthomonas, alginate, bacterial cellulose, polyamide cyanophycin, poly-γ-glutamic acid, etc. Secondary metabolites produced by many bacteria have been proven to be valuable for human use. Some microbial by-products have been functional in biopolymer synthesis. One such example is (PHAs) synthesized from microorganisms. PHA is a group of carbon and energy sources synthesized and stored in many bacteria such as Escherichia coli. Some examples of PHAs include poly-3-hydroxybutyrate and poly(hydroxyoctanoate-co-hydroxydecanoate). The literature provides many works directed toward the development of biodegradable and biocompatible materials from PHAs. Also, the functional groups of unconventional PHAs provide sites for chemical modifications helping the polymers to be consumer friendly. However, much research is still needed to produce PHAs that have properties comparable to conventional plastics like polyethylene or polystyrene.

Biopolymers synthesized from bioderived monomers

PLA is a commonly used biopolymer derived from monomers like lactic acid and lactide. PLA is generally prepared by polymerization of lactide, a cyclic dimer synthesized by depolymerization of lactic acid, which, in turn, is obtained by the microbial fermentation of annual renewable sugar-based materials such as cellulose or starch. PLA has comparable mechanical properties to petroleum-based polymers like polyesters. PLA/starch composites find applications such as mulch films for agriculture, trash bags, fast-food utensils, package containers, and single- or short-term usage items. Sandwiched PLA/starch/PLA laminate sheets are used for food packaging, controlled release of drugs, pesticides, insect diets, etc. [40]. Another example of a biopolymer from bioderived monomers is poly(glycolic acid), which is polymerized from glycolic acid monomers. Polycaprolactone (PCL) is a biodegradable polyester with widespread utilization in the production of specialty polyurethanes. Addition of PCL results in superior resistance to water, oil, solvent, and chlorine to the developed polyurethane. PCL is generally used along with resins to improve their processing characteristics and their end-use characteristics like impact resistance. It is compatible with a wide range of other materials, for example, PCL can be mixed with starch to lower its cost and improve biodegradability or it can be added as a polymeric plasticizer to polyvinyl chloride. PCL has also been approved by the Food and Drug Administration for drug delivery platforms.

Biopolymers extracted from biomass

Biopolymers such as proteins and polysaccharides can be extracted directly from plant or animal biomass. Extensive research is being done on polysaccharides like cellulose, starch, alginate, carrageenan, PLA, PCL to derive desirable biopolymers. In fact, the first commercially available biodegradable film was a composite synthesized from granular starch and synthetic polymers. Starch-based films have been formed for enhancing the life of strawberries from 14 to 21 days. Chitosan is another polysaccharide commercially produced by alkali deacetylation of chitin. Chitosan-based biopolymers have remarkable mechanical properties, selective permeability against gases like carbon dioxide and oxygen, and wide antimicrobial properties. Chitosan has been used to prepare composite coatings and films for shelf-life extension of a wide variety of food products like banana, mango, and capsicum. However, chitosan-based biopolymers have poor water vapor permeability. Chitin/cellulose composite films are known to possess properties pertaining to chitin-based films, while the addition of cellulose improves water vapor permeability. Chitosan/methyl cellulose-based composite film demonstrated antimicrobial activity against E. coli and Staphylococcus aureus on fresh-cut cantaloupe and watermelons. Chitin/cellulose composite films were also demonstrated to be effective against Listeria monocytogenes. Cellulose has also been incorporated into composite films synthesized using methylcellulose, PCL, and alginate containing antimicrobial agents, including acetic acid, rosemary extract, and Asian spice essential oil. Alginate is extracted from seaweed composed of a linear copolymer of d-mannuronic and l-guluronic acid monomers. These films are demonstrated to be effective against L. monocytogenes, E. coli, and Salmonella typhimurium[41].

Biopolymer films

Packaging made from biodegradable biopolymers such as proteins, polysaccharides and lipids is a promising alternative to synthetic polymers. Films made from these biopolymers exhibit certain disadvantages in terms of their mechanical, barrier and physicochemical properties. Plasticizer's, nanoparticles, lipids and antimicrobial compounds can be added to them to improve these properties. The tendency of biopolymer films to brittleness can be mitigated by adding plasticizers and/or nanoparticles. These films also tend to have high water vapour permeability, which can be reduced by adding lipids and/or nanoparticles. Incorporating natural compounds with antimicrobial activity into biopolymer films can provide them the advantages of maintaining food safety and extending shelf life. Addition of plasticizers, nanoparticles, lipids and/or antimicrobial compounds to biopolymer films can help to make them comparable to conventional synthetic films with the advantages that they reduce pollution and are biodegradable.

Table 1. Physical, mechanical and thermal properties of some commercial biopolymers.
(You can also compare these materials visually on the Matmatch comparison page)

Biopolymer	**Density at 23 °C**	**Tensile strength at 23 °C**	**Flexural modulus at 23 °C**	**Melting point**	**Elongation at 23 °C**
PLA Luminy® LX530	1.24 g/cm³	50 MPa	N/A	165 °C	5 %
Rilsan® BMNO	1.03 g/cm³	N/A	N/A	189 °C	50 %

NuPlastiQ®BC 27240	1.3 g/cm³	12MPa	0.24 GPa	140 - 160 °C	272 %
Extrudr Wood Filament	1.23 g/cm³	40 MPa	3.2 GPa	150 - 170 °C	N/A
DuraSense Eco PP L40 Food	1.06 g/cm³	49 MPa	4 GPa	N/A	3.5 %

Future of biopolymers

Increase in bio-based polymer production between 2017 and what is estimated to be the case in 2022. Furthermore, it is projected that biodegradable biopolymers will constitute a larger percentage of biopolymer production in the coming years. It is clear to see that biopolymer production is on an upward trajectory. While it has a long way to go, if it is to take over from petroleum products, production is forecasted to increase from 2.27 million tonnes in 2017 to 4.31 million tonnes in 2022. This is at least partly a result of public demand and government regulations, which will continue to have a significant impact.

Biopolymers/bioplastics suppliers

The following companies provide different biopolymer grades that can be found on Matmatch. You can contact the suppliers from the links below:

- Arkema: High Performance Polymers: some bio-based materials from Arkema include grades in their Rilsan® and Pebax® Rnew® ranges
- DSM Engineering Materials: check out DSM's EcoPaXX® polyamide 410 and Arnitel® TPC materials
- Stora Enso Biocomposites: Stora Enso has a wide range of renewable materials, for example DuraSense Eco PP S40, which combines bio-based polypropylene and S-Wood fiber
- Total Corbion PLA: Total Corbion is a leader in Polylactic Acid (PLA) materials, which they market under the name PLA Luminy®
- RadiciGroup High Performance Polymers: under the RADILON brand, RadiciGroup offers PA610 materials with 60% renewable-sourced materials
- Extrudr
- Great Eastern Resins Industrial Co. Ltd.
- Feconix[42-43]

References

[1] Babu, A. K., Teja, N. B., Ramakrishna, B., Kumar, B. B., & Reddy, G. V. (2011). Formulation and evaluation of double walled microspheres loaded with pantoprazole. METHODS, 15, 28.
[2] Babu, K., & Ramana, M. V. (2016). Development and in vivo evaluation of gastro retentive floating tablets of antipsychotic drug risperidone. Int J Pharm Pharm Sci, 11, 43-52.
[3] Babu, A. K., Reddy, V. R., Reddy, N., & Vidyasagar, J. (2010). Evaluating the post compression parameter of ibuprofen by using super disintegrants. An Int J Adv Pharm Sci, 1(2), 247-53.
[4] Tatipamula, V. B., Polimati, H., Gopaiah, K. V., Babu, A. K., Vantaku, S., Rao, P. R., & Killari, K. N. (2020). Bioactive Metabolites from Manglicolous Lichen Ramalina leiodea (Nyl.) Nyl. Indian Journal of Pharmaceutical Sciences, 82(2), 379-384.
[5] Babu, A. K., & Ramana, M. V. (2016). In vitro and in vivo evaluation of quetiapine fumarate controlled gastro retentive floating drug delivery system. International Journal of Drug Delivery, 8(1), 12-22.
[6] Babu, A. K., & Ramana, M. V. A review on floating drug delivery system. 7(1), 75-99.
[7] Thadanki, M., & Babu, A. K. (2015). Review on Ethosomes: A novel approach of Liposomes. International Journal of Pharmacy & Life Sciences, 6(1), 85-99.
[8] Ramana, M., Babu, A., & Thadanki, M. (2014). Formulation Development And Evaluation Of Omeprazole Microspheres by Using the pH sensitive enteric polymers (LB590). The FASEB Journal, 28, LB590.
[9] Babu, A. K., Sree, S. N., & Chandralekha, S. P. (2019). A Review on Benign Prostatic Hyperplasia. World Journal of Current Medical and Pharmaceutical Research, 192-197.
[10] Babu, A. K., & Mamatha, P. (2022). Formulation And Optimization Of Ceritinib Loaded Nanobubbles By Box-Behnken Design. International Journal of Applied Pharmaceutics, 14(4), 219–226. Https://Doi.Org/10.22159/Ijap.2022v14i4.44388
[11] Ponnaganti, M., & Babu, A. K. (2021). Preparation, Characterization And Evaluation Of Chitosan Nanobubbles For The Targeted Delivery Of Ibrutinib. Nveo-natural volatiles & essential oils Journal| NVEO, 5017-5037.
[12] Babu, A. K. (2018). Development and Characterization of Orlistat Floating Microballoons. Int. J. Res. Pharm, L. Sci, 6(2), 55-60.
[13] Babu, A. K., Kumar, M. P., Krupavaram, B., Mandadi, S. R., Lakshmi, L., Manikandhan, R., Sultana, R. (2022) Diabetic foot ulcer, antimicrobial remedies and emerging strategies for the treatment: An overview. International Journal of Health Sciences, (III), 2835-2850.
[14] Morgado, P.I.; Aguiar-Ricardo, A.; Correia, I.J.(2015). Asymmetric membranes as ideal wound dressings:An overview on production methods, structure, properties and performance relationship. J. Membr. Sci. 490, 139–151.
[15] Manimalha, B.; Ravi, K.T.; Mary, B. (2001). Skin substitutes: A review. Burns, 27, 534–544.
[16] Norouzi, M.; Boroujeni, S.M.; Omidvarkordshouli, N.; Soleimani, M. Advances in skin regeneration: Application of electrospun scaffolds. Adv. Healthc. Mater. 8, 1114–1133.

[17] Chaudhari, A.A.; Vig, K.; Baganizi, D.R.; Sahu, R.; Dixit, S.; Dennis, V.; Pillai, S.R. (2016) Future prospects for scaffolding methods and biomaterials in skin tissue engineering: A review. Int. J. Mol. Sci. 17, 1974.

[18] Capanema, N.S.; Mansur, A.A.; de Jesus, A.C.; Carvalho, S.M.; de Oliveira, L.C.; Mansur, H.S. (2018). Superabsorbent cross-linked carboxymethyl cellulose-PEG hydrogels for potential wound dressing applications. Int. J. Biol. Macromol. 106, 1218–1234.

[19] Madaghiele, M.; Demitri, C.; Sannino, A.; Ambrosio, L. (2014). Polymeric hydrogels for burn wound care: Advanced skin wound dressings and regenerative templates. Burns Trauma, 2, 153–161.

[20] Ravichandiran, P.; Masłyk, M.; Sheet, S.; Janeczko, M.; Premnath, D.; Kim, A.R.; Park, B.; Han, M.; Yoo, D.J.(2019).Synthesis and Antimicrobial Evaluation of 1,4-Naphthoquinone Derivatives as Potential Antibacterial Agents. ChemistryOpen 2019, 8, 589–600.

[20] Ravichandiran, P.; Sheet, S.; Premnath, D.; Kim, A.R.; Yoo (2019) D.J. 1,4-Naphthoquinone Analogues: Potent Antibacterial Agents and Mode of Action Evaluation. Molecules 24, 1437.

[21] Ravichandiran, P.; Athinarayanan, J.; Premnath, D.; Periasamy, V.S.; Alshatwi, A.A.; Vasanthkumar, S. (2015). Synthesis, molecular docking and biological evaluation of novel 6-(4-(4-aminophenylsulfonyl) phenylamino)-5H-benzo [a] phenothiazin-5-one derivatives. Spectrochim. Acta A Mol. Biomol. Spectrosc. 139, 477–487.

[22] Dhivya, S.; Padma, V.V.; Santhini, E. (2015). Wound dressings A review. BioMedicine, 22.

[23] Parani, M.; Lokhande, G.; Singh, A.; Gaharwar, A. (2022). Engineered Nanomaterials for Infection Control and Healing Acute and Chronic Wounds. ACS Appl. Mater. Interfaces 2016, 8, 10049–10069.

[24] Stefanov, I.; Pérez-Rafael, S.; Hoyo, J.; Cailloux, J.; Pérez, O.O.S.; Hinojosa-Caballero, D.; Tzanov, T. (2017). Multifunctional Enzymatically Generated Hydrogels for Chronic Wound Application. Biomacromolecule, 18, 1544–1555.

[25] Varaprasad, K.; Jayaramudu, T.; Kanikireddy, V.; Toro, C.; Sadiku, E.R. (2020). Alginate-based composite materials for wound dressing application: A mini review. Carbohydr. Polym, 236, 116025.

[26] Shitole, A.A.; Raut, P.W.; Khandwekar, A.; Sharma, N.; Baruah, M. (2019). Design and engineering of polyvinyl alcohol based bi-omimetic hydrogels for wound healing and repair. J. Polym. Res, 26, 201.

[27] Kenawy, E.; Omer, A.M.; Tamer, T.M.; Elmeligy (2019), M.A.; Eldin, M.M. Fabrication of biodegradable gela-tin/chitosan/cinnamaldehyde crosslinked membranes for antibacterial wound dressing applications. Int. J. Biol. Macromol. 139, 440–448.
[PubMed]

[28] Poonguzhali, R.; Basha, S.K.; Kumari, V.S. (2018). Novel asymmetric chitosan/PVP/nanocellulose wound dressing: In vitro and in vivo evaluation. Int. J. Biol. Macromol, 112, 1300–130.

[29] Jafari, A.; Hassanajili, S.; Karimi, M.B.; Emami, A.; Ghaffari, F.; Azarpira, N. (2018). Effect of organic/inorganic nanoparticles on performance of polyurethane nanocomposites for potential wound dressing applications. J. Mech. Behav. Biomed. Mate, 88, 395–405.

[30] Nethi, S.K.; Das, S.; Patra, C.R.; (2019). Mukherjee, S. Recent advances in inorganic nanomaterials for wound-healing applications. Biomater. Sci. 2019, 7, 2652–2674.

[31] Parham, S.; Wicaksono, D.H.; Bagherbaigi, S.; Lee, S.L.; Nur, H. Antimicrobial treatment of different metal oxide nanoparti-cles: A critical review. J. Chin. Chem. Soc. 2016, 63, 385–393.

[32] Nikolova, M.P.; Chavali, M.S. (2020). Metal Oxide Nanoparticles as Biomedical Materials. Biomimetics, 5, 27.

[33] Stoica, A.E.; Chircov, C.; Grumezescu, A.M. (2020). Nanomaterials for Wound Dressings: An Up-to-Date Overview. Molecules, 25, 2699.

[34] Kalashnikova, I.; Das, S.; Seal, S. (2015). Nanomaterials for wound healing: Scope and advancement. Nanomedicine, 10, 2593–2612.

[35] Wells, A.; Nuschke, A.; Yates, C.C. (2016). Skin tissue repair: Matrix microenvironmental influences. Matrix Biol, 49, 25–36.

[36] Dumville, J.C.; Gray, T.A.; Walter, C.J.; Sharp, C.A.; Page, T.; Macefield, R.; Blazeby, J. (2016). Dressings for the prevention of surgical site infection. Cochrane Database Syst. Rev, 12,

[37] Rakhshaei, R.; Namazi, H. (2017) A potential bioactive wound dressing based on carboxymethyl cellulose/ZnO impregnated MCM-41 nanocomposite hydrogel. Mater. Sci. Eng, 73, 456–464.

[38] Khorasani, M.T.; Joorabloo, A.; Moghaddam, A.; Shamsi, H.; MansooriMoghadam, Z. (2018). Incorporation of ZnO nanoparticles into heparinized polyvinyl alcohol/chitosan hydrogels for wound dressing application. Int. J. Biol. Macromol, 114, 1203–1215.

[39] Joorabloo, A.; Khorasani, M.T.; Adeli, H.; Mansoori-Moghadam, Z.; Moghaddam, A. (2019). Fabrication of heparinized nano ZnO/poly(vinylalcohol)/carboxymethyl cellulose bionanocomposite hydrogels using artificial neural network for wound dressing application. J. Ind. Eng. Chem, 70, 253–263.

[40] Rao, K.M.; Suneetha, M.; Zo, S.; Duck, K.H.; Han, S.S. (2019). One-pot synthesis of ZnO nanobelt-like structures in hyaluronan hydrogels for wound dressing applications. Carbohydr. Polym, 223, 115124.

[41] Jatoi, A.W. (2020). Polyurethane nanofibers incorporated with ZnAg composite nanoparticles for antibacterial wound dressing applications. Compos. Commun, 19, 103–107.

[42] Majumder, S.; Dahiya, U.R.; Yadav, S.; Sharma, P.; Ghosh, D.; Rao, G.K.; Rawat, V.; Kumar, G.; Kumar, A.; Srivastava, C.M. (2020). Zinc Oxide Nanoparticles Functionalized on Hydrogel Grafted Silk Fibroin Fabrics as Efficient Composite Dressing. Biomolecules, 10, 710.

[43] Naseri-Nosar, M.; Farzamfar, S.; Sahrapeyma, H.; Ghorbani, S.; Bastami, F.; Vaez, A.; (2017). Salehi, M. Cerium oxide nanoparti-clecontaining poly (ε-caprolactone)/gelatin electrospun film as a potential wound dressing material: In vitro and in vivo evaluation. Mater. Sci. Eng. C, 81, 366–372.