A Natural Polymer Used in Novel Drug Delivery System

Jyotsana Sonkar, Rahul Deo Yadav, Pradeep Kumar Niranjan

[Jyotsanasonkar85@gmail.com](mailto:Jyotsanasonkar85@gmail.com,%20rahulyadav246@gmail.com)

**ABSTRACT**

Natural polymers have received a great deal of attention as potential carriers for the delivery of drugs and other medicinal compounds. Natural polymers are versatile in drug administration due to their inherent advantages in exceptional biocompatibility, controlled enzyme degradation, specific interactions with various biomolecules, and ease of modification. The two essential components of any pharmaceutical formulation are the active ingredient and excipients. Excipients assist in the production of dosage forms and enhance their physicochemical properties. As excipients, polymers are essential in all dosage forms. Through the release of two different drug types, hydrophilic and hydrophobic, polymers play a significant part in the development of drug delivery technology. Due to some of the negative side effects and toxicity of synthetic drugs, products from natural sources have become an essential component of the human health care system. In solid oral dosage forms, polymers have been widely utilized as binders, diluents, disintegrants, and matrix agents. Nanotechnology has just begun to make considerable strides in biomedical applications, including more modern medication delivery methods. Because, since that natural polymers are abundant in nature, generally biocompatible, biodegradable, safe, and non-immunogenic, there has been extensive research into producing biocompatible, biodegradable submicron devices as drug delivery systems. The most extensively researched and used natural materials for application in new drug delivery systems include polysaccharides, resins, and tannins.

1. **INTRODUCTION**

The development of drug delivery systems has received a lot of interest recently. For various routes of administration, several drug delivery methods have been hypothesized because they need less frequent drug administration, produce more effective therapeutic effects, and cause less side effects. [[1](#_ENREF_1)] Typically, a polymer is made up of (at least) five repeating chemical units, or "mers," that are strung together. Polymers typically include more than five monomers, and some polymers may have hundreds or thousands of monomers in each chain. Polymers are classified depending on the molecular weight of each chain [[2](#_ENREF_2)] therapeutic compounds, polymers have a significant function in new drug delivery methods. The primary function of the polymer is to regulate the dosage form's medication release pattern. Exploration of diffusion-controlled and solvent-activated formulations in drug delivery has resulted in tremendous advancement. Numerous polymers have a natural origin, such as minerals, chitin from animals, or cellulose from plants. Many of these have been around for ages. Because of their well-known biodegradability and biocompatibility, biodegradable polymers have been employed extensively in biomedical applications.

In the biomedical field, polymers are employed in long-term therapies to increase their efficacy, lessen their negative effects, and improve patient compliance. Polymers have a variety of roles in the pharmaceutical industry, including binders in tablet formulations and viscosity and flow control agents in liquid formulations. Manage the extended, pulsatile, and targeted drug delivery systems, drug release rates. The polymer can be applied as a film coating to hide the drug's disagreeable flavor. In a sustained release drug delivery system, the initial drug concentration and polymer chain relaxation determines the rate of drug release from the matrix.(polymer4) The natural polymers chitosan, alginate, gelatin, collagen, cellulose, and starch are frequently employed in the administration of pharmaceuticals. To deliver medications to certain locations within the body, these polymers can be processed into a variety of forms, including nanoparticles, microparticles, hydrogels, and films. The effectiveness, bioavailability, and toxicity of natural polymer-based drug delivery systems are strongly influenced by their surface qualities. Natural polymers, however, have limits in their usage for drug administration since it can be challenging to manage their surface properties. As a result, altering the surface of natural polymers has become a crucial field of drug delivery research.[[3](#_ENREF_3)]

Polymeric nanoparticles are defined as submicron (size˂1µm) colloidal carriers. It is necessary to ensure that the nanoparticles are carefully delivered only to the infected region of the body without affecting the surrounding healthy tissue. Nanoparticles can escape from the bloodstream at the continuous vascular endothelium *via*. paracellular pathway, transcellular process or trans cellular pathway. It is different the age gap between the fenestration sites on endothelium is much larger(100nm-2µm)than in healthy tissues(2-6nm).therefore, nanoparticles can go through the fenestration thus enhancing drug penetration in the tissues and accumulating the drug in tumors site to provide a better therapeutic effect which is called enhanced penetration and retention effect. [[2](#_ENREF_2)]

1. **ADVANTAGES AND DRAWBACKS OF NATURAL POLYMERS**
2. **Advantages**

Natural polymer-based innovative drug delivery systems have several benefits that enhance pharmacokinetics and boost the biodistribution of medicinal drugs to target organs. [[4](#_ENREF_4), [5](#_ENREF_5)]

* Stabilization of the drug:The polymer can shield the medicine from the physiological setting, improving its in vivo stability.[[4](#_ENREF_4)]
* Localized delivery of drug:Systemic exposure of the drug can be decreased since the product can be implanted directly at the location where drug activity is required. [[4](#_ENREF_4)]
* Sustained delivery of drug:The medication is released from the capsule over time, and transdermal drug delivery systems, focused, and insulin are only a few examples of novel drug delivery systems.[[6](#_ENREF_6)]
* Safety:Their readily available nature, they provide the necessary security without posing any negative risks.[[7](#_ENREF_7)]
* Availability:They are abundantly available throughout the world; for example, huge amounts of cellulose may be easily harvested**.**[[7](#_ENREF_7)]

1. **Drawbacks** [[8](#_ENREF_8)]

* Microbial contamination:During production, they are exposed to the external environment hence there are chances of microbial contamination.
* Batch- to- batch variation:Natural polymer formation is reliant on the environment and numerous biotic and abiotic elements, whereas synthetic manufacturing is a regulated process with defined number of materials.
* The uncontrolled rate of hydration:The number of chemical elements existing in a specific substance may vary due to differences in the collection of natural materials at various times, as well as differences in geography, species, and climate conditions.
* Slow Process:Natural polymers have a slow rate of production as the production rate depends upon the environment and many other factors.
* Heavy metal contamination:There are chances of Heavy metal contamination often associated with herbal excipients.

1. **CLASSIFICATION**
2. **GENERAL MECHANISMS OF DRUG DELIVERY FROM POLYMER**  [[9](#_ENREF_9)]

There are three primary mechanisms by which active agents can be released from a delivery system namely.

1. **Diffusion**

When a medication or other active substance flows through the polymer that makes up the controlled-release device, diffusion takes place. When a drug diffuses, it leaves the polymer matrix and enters the surrounding environment. Since the active agent has a gradually increasing distance to travel and needs a longer diffusion time to release, using this type of system, the release rate typically declines over time. When a delivery system is introduced into a biological environment, the chosen combinations of polymer matrices and bioactive agents must permit the drug to diffuse through the pores or macromolecular structure of the polymer without causing any change in the polymer itself.

1. **Degradation**

The necessity to remove a drug delivery system once the active agent has been released is eliminated by biodegradable polymers, which break down inside the body as a result of normal biological processes. The majority of biodegradable polymers are made to break down into biologically acceptable and progressively smaller molecules through hydrolysis of the polymer chains. A release rate that is proportional to the surface area of the drug delivery system is achieved by some degradable polymers, most notably the poly anhydrides and polyorthoesters, in which the degradation only takes place at the surface of the polymer.

1. **Swelling**

Initially dry, they will absorb water or other body fluids when implanted within the body and swell. The medicine can diffuse through the swelled network into the surrounding environment because the swelling increases the formulation's aqueous solvent concentration and polymer mesh size.

1. **Classes of Natural Polymers**

Natural polymers can be facilitated in a variety of ways. These polymers are recognized to be important in the realm of pharmaceutical medication research and technology and act as protein carriers. Natural polymers are important in drug delivery systems because they have reactive sites that can be used for cross-linking, legends conjugation, and other changes, which makes them perfect drug carriers for a variety of therapeutic property. [[10](#_ENREF_10)]

1. **Starch**

Starch is produced by plants and stored in their structures as a source of energy. Starch is the most prevalent carbohydrate found in the plant world as a raw material, second only to cellulose. The primary source of carbohydrates in plants, starch serves as a reserve food source during times of germination, development, and dormancy. Each starch's characteristics are closely related to its plant source. A heterogeneous polymer of α -D-glucose unit is starch. The anhydrous glucose units are mostly connected by α - (1, 4) bonds, with α-(1, 6) connections playing a smaller role. Amylose and amylopectin are two distinct structural types that make up the biopolymer. Amylopectin is a branching molecule comprised of several thousand glucose units, whereas amylose is a linear chain of several hundred glucose molecules.[[11](#_ENREF_11)]

Due to the starch's biodegradability, low cost, and wide availability, thermoplastic starch films are one of the most promising replacements for synthetic polymers in the packaging industry. However, several film properties are influenced by the makeup of the starch granules, as measured by the amylose content and phosphate monoesters, as well as the starch's molecular weight. This work used the casting method to create biodegradable thermoplastic starch films from potato, maize, wheat, and rice starch. It was assessed how each starch's grain structure affected the microstructure, transparency, hydration characteristics, crystallinity, and mechanical properties of the films. The most translucent and opaque starch films were made of potato and corn respectively. All of the films exhibited uniform interior structures that were highly amorphous and free of pores.[[12](#_ENREF_12)]

Starch is a frequently utilized mucoadhesive carrier for nasal medication delivery that has been shown to improve the absorption of both tiny hydrophobic medicines and hydrophilic macromolecular pharmaceuticals. Maize starch is the most favored class for pharmaceutical applications, with drum-dried waxy maize starch being considered the best due to its superior bioadhesive characteristic when compared to starch treated in other ways.[[13](#_ENREF_13)]

Advantages: Simple tablet preparation, the potential for a steady release rate (zero-order) over time, and the capacity to combine significant concentrations of medications with various physicochemical features.[[11](#_ENREF_11)]

1. **Pectin**

Pectins are biopolymers with numerous uses due to their complexity and structural variety. Even though, although pectins from various sources have similar structural traits, many of these features vary depending on the species and physiological stage of the plant. Additionally, the chemical characteristics of pectin, such as the amounts of galacturonic acid, methoxyl, and acetylation, influence how it is used.[[14](#_ENREF_14)]

The pectin backbone is a linear chain of α-(1- 4)-linked D-galacturonic acid that is found in the pectin family of complex polysaccharides. Pectins can thicken, bind to water, and stabilize in addition to being employed as gelling agents. [[15](#_ENREF_15)]Pectin is found in the cell walls of developing and dividing plants. Additionally, xylem and fiber cells in woody tissue's junctional zone between cells within secondary cell walls contain it. Pectin has been studied as an excipient in a variety of dosage forms, including microparticulate delivery systems for ocular preparations, matrix-style transdermal patches, and film coating for colon-specific drug delivery systems when combined with ethyl cellulose. Depending on the botanical source, pectin's chemical makeup might change. For instance, pectin from citrus has a smaller molecular size and fewer neutral sugars than pectin from apples. [[16](#_ENREF_16)] Pectin gel beads are an effective medium for controlling the release of a drug within the gastrointestinal tract.[[17](#_ENREF_17)] Pectic compounds are typically classified into four groups: protopectin, pectic acid, pectinic acid, and Pec. Pec is one of the many different biopolymers and is a type of water-soluble anionic heteropolysaccharide that is recovered chemically or enzymatically from the main cell walls of terrestrial plants. Due to their various sources and techniques of extraction, Pec has a higher spectrum of structural variability. Due to its outstanding qualities, including non-toxicity, biocompatibility, biodegradability, affordability, antibacterial, and anti-inflammatory capabilities, pec is regarded as a viable contender in the drug delivery sector. Pec can be obtained from a variety of sources, including apple pomace, citrus peels, and more recently, sugar beet pulp. Undoubtedly, the main source of Pec comes from the by-products of tropical and subtropical fruit. However, it is crucial to note that the extraction methods as well as additional factors like the extraction duration, type of acid, pH, temperature, and liquid-solid ratios have an impact on the Pec yield and physicochemical attributes of Pec. [[18](#_ENREF_18), [19](#_ENREF_19)]

1. **Carrageenans**

Carrageenans are sulfated polysaccharides that come in a variety of forms prefixed with lota (i-), Kappa (j-), and Lambda (k)-carrageenan. K-carrageenan predominates in the tough and meaty red algae kappaphycus alvarezzi. There are many Kappaphycus spp. on reef flats and reef edges that are between almost 1 and 17 m deep.[[20](#_ENREF_20)]

While the lota type is elastic and creates a gel, the Gamma type produces viscosity. It is utilized in the formulation of controlled- release tablets as well as hydrogel beads and tablet excipients. Alginate, potassium, and calcium can all be used to cross-link it. Additionally, it is utilized in the creation of innovative sustainable release products[[21](#_ENREF_21)] used especially as thickeners or gelling polymers. [[22](#_ENREF_22)]

Carrageenan is recognised as a potential biomaterial for producing food packaging films because of its distinctive mechanical behaviour, water vapour barrier, surface hydrophobicity, light protection, and thermal characteristics. In light of growing environmental protection awareness, an alternative bio-based, polymer-based food packaging material has gained a lot of interest since it is freely accessible, non-toxic, and biodegrades over of a few weeks at a specific temperature and humidity level. Polysaccharides, lipids, and proteins are frequently used as film-forming substrates for biodegradable packaging materials. In this context, hydroxyl-rich carrageenan is thought to be a particularly promising material due to its remarkable gelling and film-forming abilities. To make carrageenan-based composite films, functional substances like polyphenols and enzymes are frequently added to carrageenan substrates.[[23](#_ENREF_23)]

1. **Hyaluronic acid**

The linear polysaccharide hyaluronic acid (HA), also known as hyaluronan and hyaluronate, is biodegradable, biocompatible, and viscoelastic. It is a naturally occurring biopolymer, and higher animals' tissues may contain naturally occurring hyaluronic acid. The concentrations are highest in the synovial fluid of articular joints and the vitreous humour of the eye. The linear, unbranching polyanionic disaccharide units that make up hyaluronic acid are made of glucuronic acid (GlcUA) and N-acetyl glucosamine (GlcNAc), which are alternatively connected by β-1-3 and β-1-4 glycosidic linkages. The concentration and molecular weight of the hyaluronic acid chains regulate the viscoelastic behaviour of hyaluronic acid solutions, which is crucial for its usage as a biomaterial.[[24](#_ENREF_24)]

The production of HA rises during tissue damage and wound healing, and HA controls several elements of tissue repair, such as the immunological response to injury, the response of fibroblasts and epithelial cells to injury, and the activation of inflammatory cells. HA synthases (HAS) are specialized enzymes that produce HA. These are membrane-bound enzymes that produce HA on the plasma membrane's inner surface.[[25](#_ENREF_25)] Due to its purported pharmacological effects, which include anti-ageing, anti-inflammatory, skin healing, tissue regeneration, and wound recovery qualities, hyaluronic acid (HA), a significant component of extracellular matrix, has been widely used in the pharmaceutical and cosmetic sectors. At the moment, HA is frequently used in transdermal administration systems to improve drug penetration in the treatment of psoriasis. To improve medication permeation through and into the intact skin for psoriasis treatment, several drug delivery technologies have been developed, including ethosomes, cryogels, microneedle patches, and HA-based nanoparticles. A key topical carrier for the targeted delivery of medications to the skin, as well as a drug delivery agent for ocular, nasal, pulmonary, parenteral, and topical routes of administration, HA was developed as a result of its remarkable solubility qualities. HA, functions as a mucoadhesive, keeping the medication at the intended site of action or absorption. Additionally, it can alter the therapeutic agent's rate of release and absorption in vivo and localize drug delivery to the epidermis. Methotrexate, tacrolimus, and corticosteroids are among the psoriasis medications that have been included in these HA-based delivery systems; they are all first-line therapies for moderate to severe psoriasis.[[26](#_ENREF_26)] Depending on the size of the polymer, hyaluronan (HA) has varied effects on different types of cells. The discovery that tiny chains or oligosaccharides of HA (6–18 sugar units) but not big polymers can kill a variety of cancer cells by inducing apoptosis while sparing normal cells is one of the more intriguing ones. When HA oligosaccharides are added to the treatment, even chemoresistant cells become drug-sensitive.[[27](#_ENREF_27)]

1. **Cyclodextrin**

A family of cyclic oligosaccharides having a lipophilic inside and a hydrophilic exterior is known as cyclodextrins (CDs). Due to their size and abundance of hydrogen donors and acceptors, CD molecules typically do not pass through lipophilic membranes. CDs have mostly been employed as complexing agents in the pharmaceutical industry to improve the bioavailability and stability of poorly soluble medicines by making them more soluble in water. Numerous pharmaceutical applications use CDs, including ones that increase the bioavailability of medications.[[28](#_ENREF_28)] CD comprised of six to eight glucose units linked together at the α-1,4 position by glucosidic connections.[[11](#_ENREF_11)] , which are the native CDs gamma-cyclodextrin(γ-CD),α -CD, and β-CD, respectively. Native CDs are soluble in water to varying degrees, with γ-CD being the most soluble (232.0 g/L), followed by α-CD (145.0 g/L), and β-CD (18.5 g/L), which is the least soluble. Strong intramolecular hydrogen bonds in β-CD are thought to be the cause of the compound's low water solubility and its ability to inhibit hydrationand so restrict its use, especially in parenteral preparations. This issue was resolved by substituting the hydroxyl groups in β-CD that produces the hydrogen bonds, which significantly increased its water solubility. This led to the creation of numerous other water-soluble CD derivatives. Due to their torus-like form, CDs have the unusual capacity to serve as molecular containers by trapping outside molecules inside their internal cavity [[29](#_ENREF_29)] When a drug CD complex forms, no covalent bonds are created or destroyed, and in an aqueous solution,Free drug molecules and those bound inside the CD cavity maintain equilibrium as the complexes easily dissolve. [[30](#_ENREF_30)]Cyclodextrins are not digested in the stomach or small intestine of the GI tract. They are converted by the big colonic bacteria present in the colon into minute monosaccharides, which are then absorbed from these regions. The large intestine completely digests cyclodextrins, but the small intestine only marginally degrades them.[[11](#_ENREF_11)] CDs have been used to prevent drug-drug or drug additive interactions, lessen or eliminate disagreeable tastes or odours, lessen or eliminate gastrointestinal or ocular irritation, and even transform oils and liquid medications into microcrystalline or amorphous powders.[[30](#_ENREF_30)] Since most parenteral formulations are aqueous solutions, CDs are an ideal strategy for allowing their preparation with poorly water-soluble drugs. As a result, the formation of water-soluble drug-CD inclusion complexes is very advantageous because it increases the drug's solubilization, improves its stability, and also increases its bioavailability by lengthening its circulation time.[[29](#_ENREF_29)]

1. **Proteins**

Numerous amino acid units connected by peptide bonds make up proteins. They are present as structural units in people, animals, and plants. [[31](#_ENREF_31)]

1. **Chitosan**

Chitosan is an abundant natural-based polymer[[32](#_ENREF_32)] Chitosan is a linear copolymer consisting of glucosamine and N-acetyl glucosamine units connected by 2-amino-2-deoxy-D-glucan (GlcN). The water-soluble chitosan derivatives, which include chitosan salts, zwitterionic chitosan, and chitosan oligomers, have recently piqued interest due to their water-solubility. Chitosan possesses many of chitosan's beneficial properties but may be dissolved in neutral aqueous solutions. They are both intricate biomaterials as a result, and their applications in bioengineering and biopharmaceuticals are both significant [[33](#_ENREF_33)] It has been frequently employed to create polyelectrolyte complexes with polyanions for drug administration since it is a cationic polymer with advantageous properties.[[19](#_ENREF_19)] Several colloidal systems based on chitosan are currently promising carriers for bioactive compounds. Chitosan is a promising candidate for drug delivery in the oral cavity since it is a bioadhesive polymer and has antibacterial properties[[32](#_ENREF_32)] .It has beneficial biological characteristics like mucoadhesion, biocompatibility, non-toxicity, and, most importantly, biodegradability.[[33](#_ENREF_33)] Chitosan microspheres enable stomach-specific drug delivery and can stay in the stomach for a longer period. Chitosan increases the residence time of dosage forms at mucosal locations, inhibits proteolytic enzymes, and increases the permeability of protein and peptide medicines across mucosal membranes to enhance absorption in the intestine. According to research, the bacteria that live in the colon break down chitosan. This polymer may therefore have a potential future in colon-specific medication delivery. Numerous in vitro and in vivo investigations demonstrated that chitosan is an effective medium for the delivery of nonviral genes and DNA vaccines. Due to its unique physical, chemical, and biological characteristics, chitosan has been used into a variety of formulations for the gastrointestinal track delivery of drugs and genes.[[32](#_ENREF_32)]

1. **Albumin**

Albumin is a predominant protein found in the blood plasma, representing 60% of the total serum protein. In the body, it functions as a means of transportation and disposal of drugs that bind to it. Therefore, albumin’s extreme binding capability can help increase the distribution of drugs, which is why it is extensively used in drug delivery development.[[34](#_ENREF_34)]  Human serum albumin (HSA) is a plentiful, multifunctional, non-glycosylated, negatively charged plasma protein that has been shown to have antioxidant and enzymatic capabilities in addition to its ligand-binding and transport properties. Preproalbumin, which has an N-terminal peptide, is the form in which it is largely produced in the liver. A globular, water-soluble, and un-glycosylated serum protein is albumin.[[2](#_ENREF_2)]

1. **Aginates**

Brown algae are often extracted to make alginate, either sodium chloride or calcium chloride must be added. Sodium alginate is a typical excipient used in pharmaceutical products. ALG has a variety of biological uses because of its low toxicity, biocompatibility, and reasonably low cost. Alginates may produce a "raft" of low-density viscous gel that acts as a barrier at the low pH of the stomach, easing the symptoms of reflux. [[34](#_ENREF_34)]Alginate is a non-branched, binary copolymer made up of b-D-mannuronic acid and a-L-guluronic acid monomers that are (1-4) glycosidically connected.[[35](#_ENREF_35)] As a result, the physical characteristics of alginate and the resulting hydrogels are influenced by the composition, sequence, block length, and molecular weight. Commercially accessible sodium alginates have molecular weights between 32,000 and 400,000 g/mol and come in low, medium, and high viscosities. The ideal viscosity for the transport of proteins. Alginates have been studied and used as emulsion stabilizers, tablet binders, tablet disintegrants, and suspending agents. Guluronic residues in alginate can gel in the presence of polyvalent ions like calcium or aluminium. It is possible to create matrices, films, beads, pellets, microparticles, and nanoparticles using this cross-linking and the ensuing gel formation**. [**[**5**](#_ENREF_5)**]** The fundamental drawback of employing alginate-based materials is that they cannot be degraded enzymatically by mammals.[[35](#_ENREF_35)]

1. **Xanthan Gum**

Gums are polysaccharide substances that come from living things including plants, algae, and bacteria. They are viewed as intriguing potential drug carriers due to their superior biocompatibility and biodegradability, swelling capacity, and sensitivity to colon microbiota destruction. [[36](#_ENREF_36)] Xantan gum (XG) is a high molecular weight natural anionic exo-polysaccharide that has five repeating units, including two units of glucose, two units of mannose, and one unit of glucuronic acid. XG's structural backbone is comparable to that of cellulose. Its terminal D-mannose is linked to D-glucuronic acid via β-(1-4) and to D-mannose via α-(1-2) in the branching chain. Depending on the type of microbial strain, pyruvate or acetate groups are used to attach D-mannose units in XG. While the five-fold helical helix of XG's secondary structure appears to be sustained by a non-covalent link. [[37](#_ENREF_37)] It has a wide range of therapeutic applications including food, cosmetics, and pharmaceuticals. Despite being used for the delivery of non-proteinous drugs, XG has also been evaluated for the delivery of therapeutic proteins and peptides. [[38](#_ENREF_38)] Since XG is a non-toxic substance, it doesn't irritate the skin or the eyes. Additionally, the US Food and Drug Administration (FDA) authorized the use of XG in food items in any quantity (without any restrictions) in 1969 as a safe food additive (stabilizer and emulsifier). Additionally, XG has a registration in the CFR as a stabilizer and thickening agent. Additionally, XG was approved by the European Commission (EC) in 1980 under the designation E415 in the list of permissible stabilizers and thickeners. Since the recommended daily intake of XG was modified to a non-quantitative limit of "not specified," it was proven that XG is a safe food additive. The lack of antimicrobial characteristics, poor workability, small surface area, and sluggish dissolving rate of XG limit its use in industrial applications. Due to these limitations, there are suitable chemical alterations that may be made to the XG structure to address them and make XG usable for specific drug delivery systems and wastewater treatment.[[37](#_ENREF_37)]

1. **Inulin**

It is a polysaccharide derived from the roots of dendelion, Taraxacum officinale (Compositae), and the bulbs of dehlia, Inula Helenium (Compositae). A variety of oligomers make up inulin, and each inulin molecule contains two to more than 60 fructose molecules connected by β-2,1-glycosidic bonds. In the upper gastrointestinal tract, inulin is resistant to digestion; however, colonic bacteria break it down. Using Eudragit® RS and inulin with a high degree of polymerization, biodegradable colon-specific films that could withstand digestion by gastric and intestinal fluids were created. When a mixture of Eudragit® RS and Eudragit® RL was mixed with inulin, it demonstrated greater swelling and penetration qualities in the colonic medium than other gastrointestinal media. Eudragits® were developed as films with inulin. [[39](#_ENREF_39)] Inherent therapeutic effects of inulin (INU) include decreased tumour risk, assistance with calcium ion absorption and anti-inflammatory and antioxidant characteristics, among others. In addition to these, INU has been employed in a variety of medicinal applications as a drug carrier, stabilizer, cryoprotectant, and a substitute for fats and sugars [[40](#_ENREF_40)]

1. **Cellulose**

The most prevalent polysaccharide in nature is cellulose, which serves as the primary structural element of plant cell walls. It offers a variety of benefits, including excellent thermal and mechanical qualities, as well as cost-effectiveness, biocompatibility, and biodegradability. When it comes to cellulose's fundamental composition, it is a straight forward polysaccharide with a homogenous backbone devoid of branching or substituents. Elementary fibrils make up the morphological hierarchy of cellulose, which packs into larger units termed microfibrils, which are then put together to form fibres. There are areas of the cellulose fibrils that are highly organized (crystallites) and areas that are disordered (amorphous-like) in terms of how the cellulose chains are arranged. Nanocrystalline cellulose is produced by extracting the crystalline areas, although different interactions between intra- and intermolecular networks might result in cellulose polymorphs or allomorphs. [[41](#_ENREF_41)]

To make cellulose more processable and to create cellulose derivatives (cellulosic) like carboxymethyl cellulose, methylcellulose, hydroxyethylcellulose, etc. that can be customized for certain industrial purposes, chemicals are added to cellulose. Cellulose has a wide range of uses in the cosmetic, medicinal, hygiene, food, and pharmaceutical industries. While the intermolecular links allow the linear polymers to form sheet shapes, the intramolecular bonds give the polymer chain its stiffness. This biopolymer can be a promising nanoscale reinforcing material for polymers because it is readily available in nature, inexpensive, and biodegradable. [[42](#_ENREF_42)]

**Table 1: Various natural polymers and their applications**

|  |  |  |  |
| --- | --- | --- | --- |
| **Polymer** | **Source** | **Applications** | **References** |
| Agar – agar | Gelidium amansii, grailaria, and pterocladia | Emulsifying agents, tablet disintegrants, suspending agents | [[10](#_ENREF_10)] |
| Cellulose | Present in cell wall of green plants, algae and Oomycetes | Mucoadhesive delivery system, and in the monolithic matrix system | [[43](#_ENREF_43)] |
| Tamarind | Tamarinds indicia | Hydrogels,ocular mucoadhesive drug delivery | [[44](#_ENREF_44)] |
| Pectin | Citrus aurantium | Beads, floating beads, colon drug delivery, pelletization | [[44](#_ENREF_44)] |
| Gum arabic | Acacia trees | Matrix microencapsulating agent | [[45](#_ENREF_45)] |
| Xanthan gum | Xanthomonas campestris | High thickening capacity | [[31](#_ENREF_31)] |
| Carrageenan | Extracted from red sdible sea weeds | Thickening properties Stabilizing properties Binding property | [[43](#_ENREF_43)] |
| Starch | Maize,rice, wheat, potato | Dis-integrant, binder | [[46](#_ENREF_46)] |
| Gum acacia | Acacia senegal | Suspending and expanding agent | [[47](#_ENREF_47)] |
| Alginates | Brown seaweed and algae | Matrixing agent | [[48](#_ENREF_48)], [[49](#_ENREF_49)] |

**Table 2: List drugs and natural polymer combinations used in drug delivery**

|  |  |  |
| --- | --- | --- |
| **Drug** | **Polymer used** | **References** |
| Furosemide | Guar gum, pectin, xanthum gum | [[50](#_ENREF_50)] |
| Atenolol | Xathum gum, Guar gum | [[50](#_ENREF_50)] |
| Cinnarizine | Chitin and chitosan | [[51](#_ENREF_51)] |
| Metformin hydrochloride | Fenugreek seed mucilage | [[51](#_ENREF_51)] |
| amoxicillin trihydrate | chitosan | [[52](#_ENREF_52)] |
| Nimesulide | Locust bean gum | [[51](#_ENREF_51)] |
| Ciprofloxacin Riboflavin | Ovomucin | [[33](#_ENREF_33)] |
| Silver saccharinate (AgS) | Alginate | [[33](#_ENREF_33)] |
| Ornidazole | Chitosan | [[44](#_ENREF_44)] |
| Venlaflexine | Beeswax, carnauba wax | [[53](#_ENREF_53)] |
| Indomethacin | Egg albumin | [[54](#_ENREF_54)] |
| zidovudine | chitosan | [[55](#_ENREF_55)] |
| Scopolamine, broxaterol | Soybean lecithin (Epikuron 200) | [[56](#_ENREF_56)] |
| Metoclopramide | starch | [[57](#_ENREF_57)] |
| Metronidazole | pectin | [[58](#_ENREF_58)] |
| Bromazepam, ibuprofen | Cyclodextrin | [[30](#_ENREF_30)] |
| Famotidine | Xanthum gum | [[59](#_ENREF_59)] |

1. **APPLICATIONS OF NATURAL POLYMERS IN DRUG DELIVERY SYSTEM**
2. **Tablets**

Polymers have long been employed as an excipient in both the traditional and immediate-release oral dose forms. Either to help with a manufacturing process or to keep the medicine from deteriorating while it is being stored. The powder particles in dump mass, such as gelatin, starch, alginic acid, etc., are bound by the polymers as a binder. In tablet formulations, starch is employed as a disintegrant. When these tablets come into contact with water, they burst and expand the surface area of the medicine by enhancing dissolving properties[[53](#_ENREF_53)]

1. **Capsules**

Gelatine has been utilized only as a shell material for hard (two‐piece) and delicate (one‐piece) capsules. [[60](#_ENREF_60)] There have been created polymeric capsule shells with a range of compositions. These shell compositions may contain just one type of natural polymer, like chitosan or albumin, or a composite of several different types of natural polymers, like BSA-alginate natural polymers functionalized by other materials, like inorganic nanoparticles, functionalizing polymers, antibodies, and a variety of other materials. These shells have diverse core materials encapsulated inside them, either directly made of the solid or liquid active pharmaceutical cargo or as transporters for various forms of APC. Depending on the sort of core desired, a solid core made of different natural and synthetic polymers, metallic particles, and composites has been constructed the precursor materials' moieties and the demands based on the application. Additionally, liquid cores of various aqueous media, oils, and organic solvents have been created to distribute either hydrophobic or hydrophilic pharmaceutical cargo. Additionally, natural polymer-made hollow/porous capsules have also been produced. The cargo may be distributed or dissolved in the liquid/solid core acting as a reservoir or matrix, or it may be implanted in the shell of the capsules with a liquid/solid/hollow core, depending on the biomedical uses. The encapsulated cargo may include pharmaceuticals, growth factors, stem cells, progenitor cells, probiotic bacterial strains, nutritional compounds (such as vitamins), hormones (such as insulin), and a variety of other substances, depending on the desired applications[[8](#_ENREF_8)]

1. **Emulsions**

Natural polymers can create films with a high tensile strength that can resist coalescence among the droplets and stabilize emulsions due to their interfacial absorption. [[61](#_ENREF_61)]

1. **Topical delivery**

Families of sulfated polysaccharides called carrageenans, which are obtained from red marine algae, are frequently used in the industry because they can create gels that are relatively stiff and thermally reversible**.[**[**4**](#_ENREF_4)**]**

1. **Transdermal drug delivery**

Studies on the use of chitosan gel as a drug reservoir and various natural polymers with varying crosslink densities as drug release regulating membranes for the administration of propranolol hydrochloride have been conducted.[[4](#_ENREF_4)]

1. **Gastro retentive Dosage form**

An alternate method for generating an extended- release profile is to use gastro retentive dosage forms. In this method, the formulation will stay in the stomach for an extended amount of time, releasing the medication in situ. The drug will then dissolve in the liquid contents and slowly travel into the small intestine.[[62](#_ENREF_62)]

1. **Polymers as floating drug delivery systems**

Polymers are frequently used in floating drug delivery systems to direct medication administration to the stomach, a particular area of the gastrointestinal tract. Chitosan, pectin, xanthan gum, guar gum, gellangum, karkaya gum, psyllium, starch, husk, starch, alginates, and other natural polymers have all been investigated for their intriguing potential in stomach-specific medication delivery. [[63](#_ENREF_63)]

1. **Fast Dissolving Tablets**

Based on established biocompatibility and safety, the use of natural polymers is advantageous. Due to their affordability and regulatory approval, natural gums are among the most widely used hydrophilic polymers. To target the distribution of drugs to a specific area in the gastrointestinal tract, namely the stomach, polymers are typically used in floating drug delivery systems. These polymers can also be chemically modified and formed into gels, and they are secure, nontoxic, and safe.[[51](#_ENREF_51)]

1. **Ocular delivery**

Chitosan along with an excellent film capability make chitosan suitable for the development of ocular bandage lenses.[[4](#_ENREF_4)]

1. **Wound - dressing**

Recently, a class of newly developed porous crystalline polymers, particularly nanoscale covalent organic frameworks and metal-organic frameworks, have attracted significant attention for effective wound dressing applications. These highly ordered porous materials have many desirable properties, including high specific surface areas, high porosity, excellent thermal stability, simple functionalization, good biocompatibility, and promising biodegradation ability. They are composed of inorganic metal ions and organic ligands. In the biomedical field, this newly developing family of porous multifunctional materials has promise for drug delivery, high loading capacity, and loading of many tiny molecular medicines.[[64](#_ENREF_64)]

1. **Conclusions**

Because they are non-toxic, easily accessible, cheap, and naturally extracted to offer dietary supplements, natural polymers are chosen over synthetic polymers. Faster medication dissolution and greater bioavailability are characteristics of natural super disintegrants, which contribute to more effective therapy and better patient compliance. Polymer plays a significant function in medication delivery. Because of the degree of toxicity, pattern of degradation, and nature of polymer incompatibility with pharmaceuticals, polymer selection is essential for the manufacturing of pharmaceutical products. The review's final analysis shows that natural polymers are useful in the formulation of pharmacological dosages. The bioavailability and residence time of the medicine at the site of action are enhanced by the natural polymer. Additionally, it aids in the advancement of the use of innovative natural polymers in drug delivery systems.

**REFERENCES**

1. Pahwa, R., et al., *Role of natural polymers in the development of floating drug delivery systems.* Journal of Pharmacy Research, 2010. **3**(6): p. 1312-1318.

2. Prabu Lakshmana , a.S., *Role of Natural Polymers in Drug Delivery Systems as Challenging Ailments.* Novel approaches in drug designing and development, November 13, 2017.

3. Bhatt, P., et al., *Plasma Modification Techniques for Natural Polymer-Based Drug Delivery Systems.* Pharmaceutics, 2023. **15**(8): p. 2066.

4. Deb, J., M. Das, and A. Das, *Excellency of natural polymer in drug delivery system: A Review.* International Journal of Pharmaceutical and Biological Science Archive, 2017. **5**: p. 17-22.

5. Berardi, A., et al., *Alginates as tablet disintegrants: Understanding disintegration mechanisms and defining ranges of applications.* International Journal of Pharmaceutics, 2021. **601**: p. 120512.

6. Shaikh Ashiya K. , J.D.A., Gali vidyasagar , Bavage Shyamlila B. , Bavage Nandkishor B, *A Polymer Used in the Novel Drug Delivery System.* INTERNATIONAL JOURNAL OF INNOVATIVE RESEARCH IN TECHNOLOGY May 2020 **Volume 6**(Issue 12 ).

7. S, M.Y.a.S., *Application of Plant Based Natural Polymer in Drug Delivery System-A Critical Overview.* Open Access of Journal of Pharmaceutical research, April 19, 2022. **Volume 6** (Issue 2).

8. Kaushik, K., R.B. Sharma, and S. Agarwal, *Natural polymers and their applications.* International Journal of Pharmaceutical Sciences Review and Research, 2016. **37**: p. 30-36.

9. Rajeswari, S., et al., *Natural polymers: A recent review.* World J. Pharm. Pharm. Sci, 2017. **6**: p. 472-494.

10. Muhammad Sajid Hamid Akash, K.R.S.C., *Natural and Synthetic Polymers as Drug Carriers*

*for Delivery of Therapeutic Proteins.* 2015.

11. Prajapati1, T.K., M.K.S.P. , and D.s.s. , *Natural and synthetic polymers used in Bioadhesive delivery system.* INTERNATIONAL JOURNAL FOR INNOVATIVE RESEARCH IN MULTIDISCIPLINARY FIELD, 2017. **Volume - 3,**(9).

12. Domene-López, D., et al., *Influence of Starch Composition and Molecular Weight on Physicochemical Properties of Biodegradable Films.* Polymers, 2019. **11**(7): p. 1084.

13. Chaturvedi, M., M. Kumar, and K. Pathak, *A review on mucoadhesive polymer used in nasal drug delivery system.* J Adv Pharm Technol Res, 2011. **2**(4): p. 215-22.

14. Minzanova, S.T., et al., *Biological Activity and Pharmacological Application of Pectic Polysaccharides: A Review.* Polymers (Basel), 2018. **10**(12).

15. Malviya, R. and G.T. Kulkarni, *Extraction and characterization of mango peel pectin as pharmaceutical excipient.* Polim Med, 2012. **42**(3-4): p. 185-90.

16. Krushnakumar J Gandhi\*, S.V.D., Kailash R Biya, *POLYMERS IN PHARMACEUTICAL DRUG DELIVERY SYSTEM: A REVIEW.* Int. J. Pharm. Sci. Rev. Res., 14(2), 2012; nᵒ 10, 57‐66 Accepted on: 10‐04‐2012; Finalized on: 25‐05‐2012.

17. Murata, Y., et al., *Drug release properties of a gel bead prepared with pectin and hydrolysate.* J Control Release, 2004. **95**(1): p. 61-6.

18. Han, S.S., et al., *Pectin Based Hydrogels for Drug Delivery Applications: A Mini Review.* Gels, 2022. **8**(12).

19. Sung, Y.K. and S.W. Kim, *Recent advances in polymeric drug delivery systems.* Biomaterials Research, 2020. **24**(1): p. 12.

20. Shanmuga SI, S.M.a. and S. S, *Synthesis and Characterization of Carrageenan Coated Magnetic Nanoparticles for Drug Delivery Applications.* iMedPub Journals, 2015**Vol. 6 No. 3:19**

21. Mohammed, M.A., et al., *An Overview of Chitosan Nanoparticles and Its Application in Non-Parenteral Drug Delivery.* Pharmaceutics, 2017. **9**(4).

22. Priscilla B.S. Albuquerque1, Luana C.B.B. Coelho2, et al., *Approaches in biotechnological applications of natural polymers.* AIMS Molecular Science,, 2016: p. 386-425.

23. Cheng, C., et al., *Recent advances in carrageenan-based films for food packaging applications.* Frontiers in Nutrition, 2022. **9**.

24. Liu, L., et al., *Microbial production of hyaluronic acid: current state, challenges, and perspectives.* Microbial Cell Factories, 2011. **10**(1): p. 99.

25. Papakonstantinou, E., M. Roth, and G. Karakiulakis, *Hyaluronic acid: A key molecule in skin aging.* Dermatoendocrinol, 2012. **4**(3): p. 253-8.

26. How, K.N., et al., *Hyaluronic Acid-Mediated Drug Delivery System Targeting for Inflammatory Skin Diseases: A Mini Review.* Frontiers in Pharmacology, 2020. **11**.

27. Toole, B.P., S. Ghatak, and S. Misra, *Hyaluronan oligosaccharides as a potential anticancer therapeutic.* Curr Pharm Biotechnol, 2008. **9**(4): p. 249-52.

28. Tiwari, G., R. Tiwari, and A.K. Rai, *Cyclodextrins in delivery systems: Applications.* Journal of Pharmacy and Bioallied Sciences, 2010. **2**(2): p. 72.

29. Laura Ferreira, J.C., Francisco Veiga,Catarina Cardoso,Ana Cláudia Paiva-Santos https://doi.org/10.1016/j.ejpb.2022.07.007, *Cyclodextrin-based delivery systems in parenteral formulations: A critical update review.* European journal of pharmaceutics and biopharmaceutics, 2022. **vol.178**: p. 35-52.

30. Tiwari, G., R. Tiwari, and A.K. Rai, *Cyclodextrins in delivery systems: Applications.* J Pharm Bioallied Sci, 2010. **2**(2): p. 72-9.

31. Prakash, U., D.R.L. Singh, and D. Sharma, *ROLE OF XANTHAN GUM (XANTHOMONAS COMPESTRIS) IN GASTRORETENTIVE DRUG DELIVERY SYSTEM: AN OVERVIEW.* International Research Journal of Pharmacy, 2013. **2013**: p. 35-38.

32. Prabaharan, M. and J.F. Mano, *Chitosan-Based Particles as Controlled Drug Delivery Systems.* Drug Delivery, 2004. **12**(1): p. 41-57.

33. Leyva-Gómez, G., et al., *Approaches in Polymeric Nanoparticles for Vaginal Drug Delivery: A Review of the State of the Art.* Int J Mol Sci, 2018. **19**(6).

34. Pápay, Z.E., et al., *Optimization and Development of Albumin-Biopolymer Bioconjugates with Solubility-Improving Properties.* Biomedicines, 2021. **9**(7).

35. Naira, L.S. and C.T.L. , *Biodegradable polymers as biomaterials.* Prog. Polym. Sci. 32 (2007) 762–798, 11 June 2007.

36. Froelich, A., et al., *Natural Gums in Drug-Loaded Micro- and Nanogels.* Pharmaceutics, 2023. **15**(3).

37. Abu Elella, M.H., *Synthesis and Potential Applications of Modified Xanthan Gum.* Journal of Chemical Engineering Research Updates, 2021. **8**: p. 73-97.

38. Akash, M.S.H., K. Rehman, and c. shuqing, *Natural and Synthetic Polymers as Drug Carriers for Delivery of Therapeutic Proteins.* Polymer Reviews, 2015. **55**.

39. Kulkarni Vishakha, S., D. Butte Kishor, and S. Rathod Sudha, *Natural polymers–A comprehensive review.* Int. J. Res. Pharm. Biomed. Sci, 2012. **3**(4): p. 1597-1613.

40. Gupta, N., et al., *Inulin: A novel and stretchy polysaccharide tool for biomedical and nutritional applications.* International Journal of Biological Macromolecules, 2019. **132**: p. 852-863.

41. Albuquerque, P., et al., *Approaches in biotechnological applications of natural polymers.* 2016.

42. Benabid, F. and F. Zouai, *Natural polymers: Cellulose, chitin, chitosan, gelatin, starch, carrageenan, xylan and dextran.* Algerian Journal of Natural Products, 2016. **4**(3): p. 348-357.

43. Pranati, S. and K. Syed Abul, *Natural Polymers as Potential Antiaging Constituents*, in *Pharmacognosy*, P. Shagufta and A.-T. Areej, Editors. 2019, IntechOpen: Rijeka. p. Ch. 11.

44. Rishi Kumar, R.M.a.P.K.S., *Pharmaceutical Applications and Patents in*

*Natural Polymer Based Drug Delivery System.* Advances in Biological Research 9 (1): 24-32, 2015, 2015.

45. Chranioti, C. and C. Tzia, *Arabic Gum Mixtures as Encapsulating Agents of Freeze-Dried Fennel Oleoresin Products.* Food and Bioprocess Technology, 2014. **7**.

46. Sivamaruthi, B.S., et al., *Pharmaceutical and biomedical applications of starch-based drug delivery system: A review.* Journal of Drug Delivery Science and Technology, 2022: p. 103890.

47. Brhane, Y., A. Shibeshi, and T. Gebre-Mariam, *Evaluation of Local Gum of Acacia polyacantha as a Suspending Agent in Metronidazole Benzoate Suspension Formulations.* Ethiopian Pharmaceutical Journal, 2014. **30**: p. 33.

48. Tuğcu-Demiröz, F., et al., *Evaluation of alginate based mesalazine tablets for intestinal drug delivery.* European Journal of Pharmaceutics and Biopharmaceutics, 2007. **67**(2): p. 491-497.

49. Kumar, S. and S.K. Gupta, *Natural polymers, gums and mucilages as excipients in drug delivery.* Polim. Med, 2012. **42**(3-4): p. 191-197.

50. Chandal Priya, R., Kapoor Ankita, *, POLYMER: A BOON TO CONTROLLED DRUG DELIVERY SYSTEM,.* International Research Journal of pharmacy, 2013.

51. Alam, M.T., N. Parvez, and P.K. Sharma, *FDA-Approved Natural Polymers for Fast Dissolving Tablets.* Journal of Pharmaceutics, 2014. **2014**: p. 952970.

52. Rossi, S., et al., *Chitosan Ascorbate Nanoparticles for the Vaginal Delivery of Antibiotic Drugs in Atrophic Vaginitis.* Mar Drugs, 2017. **15**(10).

53. Pagar, U.N., Pansare Jagruti J., Mogal Prasad S., Dode Raj H., Surawase Rajendra K, *Applications of Polymer in Dosage Form Development.* International Journal of pharmacy and Pharmaceutical research, Human Journals May 2021 **Vol.:21,**( Issue:2. ).

54. B.\*1, C.G., et al., *Formulation and Evaluation of Indomethacin Microspheres using naturaland synthetic polymers as Controlled Release Dosage Forms* International Journal of Drug Discovery, 2010. **Volume 2**( 1): p. pp-08-16.

55. Asha Kesari, V., *Formulation and evaluation of Zidovudine loaded chitosan Microspheres for controlled release.* International Journal of Drug Development & Research January-March 2012 **Vol. 4** ( Issue 1 ).

56. Lucia Montenegro a, et al., *From nanoemulsions to nanostructured lipid carriers: A relevant development in dermal delivery of drugs and cosmetics.* Journal of Drug Delivery Science and Technology, 2015.

57. Kapoor D, V.R., Lad C, Patel M, Lal B, *SITESPECIFIC DRUG DELIVERY THROUGH NASAL ROUTE USING BIOADHESIVE POLYMERS.* Journal of Drug Delivery and Therapeutics, 2015;: p. 1-9.

58. Ganguly, D.P.a.M., *FORMULATION AND EVALUATION OF A PECTIN BASED CONTROLLED DRUG DELIVERY SYSTEM CONTAINING METRONIDAZOLE.* RJLBPCS, 2017.

59. Mohammed Muqtader\*, F.F.a.S.A., *DEVELOPMENT OF FAMOTIDINE FLOATING DRUG DELIVERY SYSTEM USING NATURAL POLYMERS.* INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH, 2012: p. 863-867.

60. Pawar, K., et al., *Natural polymers in pharmaceutical drug delivery: A review.* World Journal of Biology Pharmacy and Health Sciences, 2020. **4**: p. 082-090.

61. Tamang, N., et al., *A review of biopolymers’ utility as emulsion stabilizers.* Polymers, 2021. **14**(1): p. 127.

62. Thahera, P., et al., *Formulation and evaluation of Norfloxacin gastro retentive drug delivery systems using natural polymers.* International Current Pharmaceutical Journal, 2012. **1**(7): p. 155-164.

63. Prasanthi, N.L., et al., *A review on polymorphism perpetuates pharmaceuticals.* Am. J. Adv. Drug Deliv, 2016. **4**: p. 58-63.

64. Kuddushi, M., et al., *Recent advances in novel materials and techniques for developing transparent wound dressings.* Journal of Materials Chemistry B, 2023. **11**(27): p. 6201-6224.