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ROLE OF POLYMERS IN SUSTAINED RELEASED MICROBEADS FORMULATION: A REVIEW

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ABSTRACT: The aim of this article is to provide a wide-angle prospect of the detailed information of pharmaceutical polymers in sustained released micro-beads dosage forms. Polymers have played an integral role in the advanced drug delivery technology by providing controlled release of therapeutic agents in constant doses over long periods, cyclic dosage, and constant release of both hydrophilic and hydrophobic drugs. When formulating challenging molecules into solid oral dosage forms, polymeric pharmaceutical excipients permit masking undesired physico-chemical properties of drugs and, consequently, altering their pharmacokinetic profiles to improve the therapeutic effect. The number of synthetic and natural polymers available commercially as pharmaceutical recipients have increased dramatically, offering potential solutions to various difficulties. The different polymers may allow increased solubility, swell ability, viscosity, biodegradability, advanced coatings, pH dependency, mucodhesion, and inhibition of crystallization. Biodegradable polymers attract the attention of its use as they can be degraded to non-toxic monomers and most important, a constant rate of drug release can be achieved from a biodegradable polymer-based controlled release device. Natural polymers can be used as the means of achieving predetermined rates of drug delivery, and their physicochemical characteristics with the ease of availability provide a platform to use it as a polymer for drug delivery systems. The main role of polymer is to protect the drug from the physiological environment and prolong release of drug to improve its stability. The objective of this review is to summarize the applications of the different polymers and its derivatives and also to elaborate the importance of polymers in the pharmaceutical field.

INTRODUCTION: Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. Development of new drug entities and pharma-ceutical formulations, mainly because of patient acceptance, convenience and cost effective manufacturing process.

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For many drug substances, conventional immediate release formulations provide clinically effective therapy while maintaining the required balance of pharmacokinetic and pharmacodynamic profiles with an acceptable level of safety to the patient.

In recent years a wide variety of newer oral drug delivery systems like sustained/controlled release dosage forms are designed and evaluated in order to overcome the limitations of conventional therapy. Recently, several technical advancements have been made. They have resulted in the development of a new technique for drug delivery. These techniques are capable of controlling the rate of drug delivery, sustaining the duration of

therapeutic activity, and or targeting the drug to tissue. A non-immediate release dosage form alters the release rate by affecting the value of kinetic release [1, 2, 3, 4, 5]. A non-immediate release dosage form may be conveniently divided into four categories:

1. Delayed-release
2. Sustained release
3. Controlled release
4. Prolonged-release
5. Site-specific release
6. Receptor release

Delayed-release employs repetitive, intermittent dosing of drugs from one or more immediate release units incorporated into a single dosage form. These types of dosage forms include repeat action tablets and capsules and enteric-coated tablets where the timed release is achieved by barrier coating. Sustained-release dosages are drug delivery systems that achieve slow release of the drug over an extended period of time. If the system is successful in sustaining a constant drug level in the body or target tissue, it is considered a controlled release system.

If it is unsuccessful in providing a constant level but extends the duration of action over that which is achieved by conventional delivery, it is known as a prolonged-release system.

Site-specific and receptor release refers to the targeting of a drug directly to a certain biological location. For site-specific release, the target should be a certain organ or tissue. For receptor release, the target should be the particular receptor for the drug within an organ or tissue [4, 6, 10]. In general, the active substances may not be easily administered and absorbed by the human body; they need to be put in some appropriate form with the help of suitable polymers and Excipients. Synthetic and natural-based polymers have found their way into the pharmaceutical and biomedical industries, and their applications are growing at a fast pace.

Polymers: Polymers are substances containing a large number of structural units joined by the same type of linkage. These substances often form into a chain-like structure starch, cellulose, and rubber all posses polymeric properties. Polymers have found applications in diverse biomedical fields such as drug-delivering systems, developing scaffolds in tissue engineering, implantation of medical devices and artificial organs, prosthesis, ophthalmology, dentistry, bone repair, and many other medical fields.

In a traditional pharmaceutics area, such as tablet manufacturing, polymers are used as tablet binders to bind the excipients of the tablet. Modern or advanced pharmaceutical dosage forms utilize polymers for drug protection, taste masking, controlled release of a given drug, targeted delivery, increase drug bioavailability.

A major application of polymers in the current pharmaceutical field is for controlled drug release, which will be discussed in detail in the following sections. In the biomedical area, polymers are generally used as implants and are expected to perform long term service. This requires that the polymers have unique properties that are not offered by polymers intended for general applications.

In general, the desired polymer properties in pharmaceutical applications are film-forming (coating), thickening (rheology modifier), gelling (controlled release), adhesion (binding), pH-dependent solubility (controlled release), solubility in organic solvents (taste masking), and barrier properties (protection and packaging). From the solubility standpoint, pharmaceutical polymers can be classified as water-soluble and water-insoluble (oil soluble or organic soluble).

The cellulose ethers with methyl and hydroxypropyl substitutions are water-soluble, whereas ethyl cellulose and a group of cellulose esters such as cellulose acetate butyrate or phthalate are organic soluble. Hydrocolloid gums are also used when solubility in water is desirable.

The synthetic water-soluble polymers have also found extensive applications in pharmaceutical industries, among them polyethylene glycol, polyethylene glycol vinyl alcohol polymers, polyethylene oxide, polyvinyl pyrrolidone and polyacrylate or polymethacrylate esters containing anionic and cationic functionalities are well-established [4, 6, 7, 8, 9].

TABLE 1: POLYMERS IN PHARMACEUTICAL AND BIOMEDICAL APPLICATIONS [7, 8, 9, 11]

Water-soluble polymers	
Poly (acrylic acid)	Cosmetic, pharmaceuticals, immobilization of cationic drugs, the base for Carbopol polymers
Poly (ethylene oxide)	Coagulant, flocculent, very high molecular-weight, swelling agent.
Poly (ethylene glycol)	plasticizer, used as a base for suppositories
Poly (vinyl pyrrolidone)	Used to make betadine (iodine complex of PVP) with less toxicity than iodine, plasma replacement, tablet granulation
Poly (vinyl alcohol)	Water-soluble packaging, tablet binder, tablet coating
Polyacrylamide	Gel electrophoresis to separate proteins based on their molecular weights, coagulant, absorbent
Poly (isopropyl acrylamide) and poly (cyclopropyl methacrylamide)	Thermo gelling acrylamide derivatives, its balance of hydrogen bonding, and hydrophobic association changes with temperature
Cellulose-Based Polymers	
Ethylcellulose	Insoluble but dispersible in water, aqueous coating system for sustained release applications
Carboxymethyl cellulose	Superdisintegrant, emulsion stabilizer
Hydroxyethyl and hydroxypropyl celluloses	Soluble in water and in alcohol, tablet coating
Hydroxypropyl methylcellulose	Binder for tablet matrix and tablet coating, gelatin alternative as capsule material
Cellulose acetate phthalate	Enteric coating
Hydrocolloids	
Alginic acid	Oral and topical pharmaceutical products; thickening and suspending agent in a variety of pastes, creams, and gels, as well as a stabilizing agent for oil-in-water emulsions; binder and disintegrant
Carrageenan	Modified release, viscosifier
Chitosan	Cosmetics and controlled drug delivery applications, mucoadhesive dosage forms, rapid release dosage forms
Hyaluronic acid	Reduction of scar tissue, cosmetics
Pectinic acid	Drug delivery
Water-Insoluble Biodegradable Polymers	
(Lactide-co-glycolide) polymers	Microparticle nanoparticle for protein delivery
Starch-Based Polymers	
Starch Glidant, Sodium starch	a diluent in tablets and capsules, a disintegrant in tablets and capsules, a tablet binder glycolate Superdisintegrant for tablets and capsules in oral delivery

Criteria followed in Polymer Selection: [3, 4, 12, 13]

- The polymer should be soluble and easy to synthesis.
- It should have finite molecular weight.
- It should be compatible with the biological environment.
- It should be biodegradable.
- It should provide good drug-polymer linkage.

Important Properties of Polymer: [3, 7, 11, 12] Properties of polymer that must be fulfilled before going for usage in biomedical treatment are given below:

1. Capability of maintaining good mechanical integrity until degraded.
2. Capability of controlled rates of degradation.
3. The material should not arouse a sustained inflammatory or toxic response upon implantation *in-vivo*.
4. The material should have an acceptable shelf life. Should possess a degradation time concurring with their function and the degradation time of the material should match the healing or regeneration process.
5. The material should have appropriate mechanical properties as per as application criteria, and any variation in mechanical properties with degradation should be compatible with the healing or regeneration process.
6. Degradation products should be non-toxic, and easily metabolized and cleared from the body.
7. The material should have appropriate permeability and processibility for the intended application.

8. In the case of scaffold-guided tissue engineering, the biodegradable polymer should be processable into a proper shape fitting the defect's site, with a proper micro-nanostructure.
9. The polymeric materials should be designed into a scaffold structure so as to carry mechanical properties and degradation rate suitable to maintain the spaces required for cell ingrowth and matrix creation, and to bear stresses and loading.

Polymers used for the Preparation of Microbeads [11, 12, 13, 14] A number of different substances, both biodegradable as well as non-biodegradable have been investigated for the preparation of microbeads. These materials include polymers of natural and synthetic origin and also modified natural substances. Some examples of polymers are Albumin, Gelatin, Sodium alginate, Chitosan, Starch, Dextran, Polylactide, and olyglycolide Polyanhydride, Polyphosphazene, etc. Sodium alginate micro Beads are one of the multiparticulate drug delivery systems and are prepared to obtain prolonged or controlled drug delivery, to improve bioavailability or stability, and to target a drug to specific sites. Multiple unit dosage forms such as microspheres or beads have gained in popularity as oral drug delivery systems because of more uniform distribution of the drug in the gastrointestinal tract, more uniform drug absorption, reduced local irritation, and elimination of unwanted intestinal retention of polymeric material when compared to non-disintegrating single unit dosage form.

Sodium Alginate: [11, 12, 13, 14, 15] Chemically alginates are linear, unbanked polysaccharide composed of monomers of b-D Mannuronic acid (M) and it's C-5epimer a –l guluronic acid(G) residues joined together by (1-4) glycoside linkages The residues generally vary widely in composition and sequence and are arranged in a pattern of blocks along the chain.

The sehomopolymeric regions of b-D mannuronic acid blocks and a-Lguluronic acid blocks are inter-dispersed with regions of alternating structure (b-D-mannuronic acid a-l-guluronic acid blocks). The composition and extent of the sequences and the molecular weight determine the physical properties of the alginates. The molecular variability is dependent on the organism and tissue from which the alginates are isolated. Sodium alginate is a polysaccharide composed of thousands of oxidized sugar "units" joined together to form an ionic polymer. The repeating units are six-membered rings containing negatively charged $–CO_2$ – groups. The C-1 carbon atom of one ring is connected via an oxygen atom to the C-4 carbon atom of the next ring in the polymer chain.

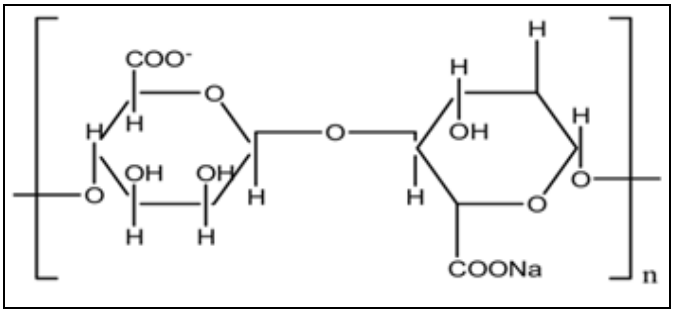

FIG. 1: CHEMICAL STRUCTURE OF SODIUM ALGINATE

The presence of ionic CO2 side chains, as well as numerous OH groups, makes this natural polymer extremely hydrophilic or water-loving. Sodium alginate is used as a "thickening agent" in many processed foods. Sodium Alginate and Calcium Alginate has a number of uses in the medical and pharmaceutical industries. It is used to make wound dressings, dental impression materials, as a radiography agent, and to diagnose and treat intestinal or gastric diseases.

Solubility: Sodium alginate is slowly soluble in cold water, forming a viscous, colloidal solution. It is insoluble in alcohol and hydroalcoholic solutions in which alcohol content is greater than 30% by weight. It is also insoluble in other organic solvents *viz.* Chloroform and ether, and in acids where the PH of the resulting solution falls below 3.0.

Application of Alginate as Matrix for Controlled Drug Delivery: Alginates have been widely used as a tablet disintegrant, binding agent, viscosity modifying agent, as a stabilizer in disperse system in the production of suspension and emulsion, and also as a thickening agent.

The most important advantage of using alginate as a matrix for Controlled release (CR) formulations, because it is degraded and is absorbed by the body during and/or after drug release without any toxic

effects. This allows bypass of surgical removal of the device. Hence, it can be a suitable matrix for the sustained release of various drugs. Several drugs have been incorporated into alginate matrices in a variety of forms (*e.g.*, beads, microspheres, films, and tablets), for Controlled release therapies. The following properties of alginates have enabled it to be used as the most acceptable matrix for controlled drug delivery.

1. It is readily available and is relatively inexpensive.
2. It contains ingredients that are accepted food additives.
3. It is non-toxic when taken orally and also has a protective effect on mucous membranes of the upper gastrointestinal tract.
4. It is haemo-compatible and does not accumulate in any organ of the human body.
5. It is biodegradable, so there is no need for surgical removal after the drug is exhausted.
6. It can form hydrogels under mild conditions.
7. It is water-soluble, so it eliminates the use of noxious solvents during processing, and hence stability, toxicological and environmental problem associated with solvents can be minimized.
8. It forms a gel at room temperature and hence reduces the chances of destroying the activity of sensitive drugs at elevated temperatures.
9. Soluble sodium alginate cross-linked with a variety of cross-linking agents forms insoluble gel, which is used to delay release of some drugs.
10. Flow properties of drugs with needlelike crystals (*e.g.*, Sulfadiazine) can be improved by incorporating in alginate beads. This method of agglomeration also avoids polymorphic transformations as agglomerates are formed from drug dispersions.
11. Sodium alginate beads formed are mechanically strong so they could be coated with enteric polymers to prepare enteric drug delivery systems.

There have been several investigations for the use of alginate gels as carriers for a variety of drugs. Alginate beads can be administered by filling in capsules or by compressing into a tablet. The successive sections will throw light on the use of alginate as a controlled drug delivery carrier for several drugs of different characteristics.

Pectin: [16, 17, 18] Pectin is a naturally occurring biopolymer that is finding increasing applications in the pharmaceutical and biotechnology industry. Pectin has been widely studied and published but is difficult to characterize as a model system due to the heterogeneous nature of the polymer.

Chemical Structure: Pectin is an essentially linear polysaccharide. The structure of pectin is very difficult to determine because pectin can change during isolation from plants, storage, and processing of plant material. At present, pectin is thought to consist mainly of D-galacturonic acid units joined in chains by means of a-(1-4) glycosidic linkage. These uronic acids have carboxyl groups, some of which are naturally present as methyl esters, and others which are commercially treated with ammonia to produce carboxamide groups. Pectin contains from a few hundred to about 1000 saccharide units in a chain-like configuration; this corresponds to average molecular weights from about 50,000 to 150,000 daltons. Large differences may exist between samples and between molecules within a sample, and estimates may differ between methods of measurement.

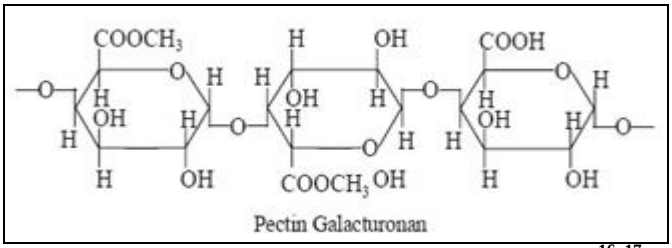

FIG. 2: CHEMICAL STRUCTURE OF PECTIN [16, 17]

Solubility: Completely soluble in 20 parts of water forming a solution containing negatively charged and very much hydrated particles. Dissolves more swiftly in water, if previously moistened with sugar syrup, alcohol, and glycerol or if first mixed with 3 or more parts of sucrose. Viscosity, solubility, and gelation are generally related. For example, factors that increase gel strength will increase the tendency to gel, decrease solubility and increase viscosity, and *vice versa*.

Pharmaceutical Applications of Pectin: Pectin is an interesting candidate for pharmaceutical use, *e.g*., as a carrier of a variety of drugs for controlled release applications. Many techniques have been used to manufacture the pectin-based delivery systems, especially ion tropic gelation and gel coating.

These simple techniques, together with the very safe toxicity profile, make pectin an exciting and promising excipient for the pharmaceutical industry for present and future applications.

Chitosan: [18, 19, 20] Chitin is a white, hard, inelastic mucopolysaccharide that is the supporting material of crustaceans and insects. It is a homopolymer consisting of N-acetyl glucosamine units linked through a β (1-4) linkage and has a 3D α-helical configuration, which is stabilized by hydrogen bonding.

Chitosan, a copolymer comprising of glucosamine and N-acetyl glucosamine, is produced by the partial deacetylation of chitin and comprises a series of polymers with different molecular weights (50 kDa to 2000 kDa), viscosities, and degrees of deacetylation (40-98%). The nitrogen atom of chitosan is a primary aliphatic amine, and it is soluble in organic acids such as acetic and formic acids. Chitosan has been primarily formulated as microparticles for injectable and topical applications.

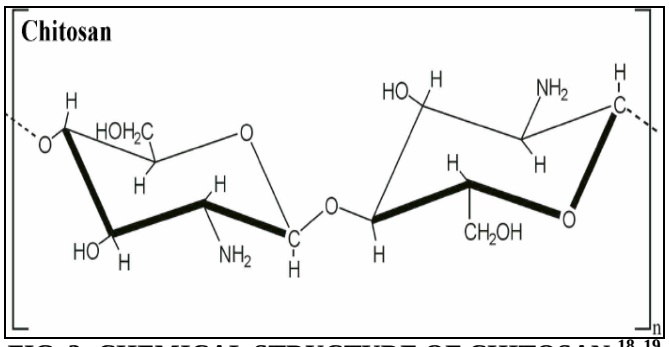

FIG. 3: CHEMICAL STRUCTURE OF CHITOSAN [18, 19]

Solubility: Chitin is insoluble in water and most organic solvents and accordingly the pharma-ceutical uses of this polymer are limited.

Pharmaceutical Applications of Chitosan:

1. Drug delivery (cationic nature allows the formation of complexes with the drug/excipient molecules)
2. Controlled drug release. (gel-forming ability in low pH media, has a high charge density at pH < 6.5)
3. Fast drug release dosage forms
4. Peptide delivery Adsorption enhancer for hydrophilic drugs.

Xanthum Gum: [21, 22, 23] The primary structure of xanthan consists of repeating pentasaccharide units are consisting of two D-glucopyranosyl units, two D-mannopyranosyl units, and one D-glucopyranosyluronic unit. Its industrial importance is based upon its ability to control the rheology of water-based systems.

It is a very effective thickener and stabilizer because it gives highly viscous solutions even at low concentrations as compared to other polysaccharide solutions. Xanthan gum solutions exhibit pseudoplastic behavior (viscosity is regained immediately, even at high shear rates). Its pseudoplastic property enhances the mouthfeel effect and flavor release. Xanthan gum solutions offer very good stability. They are least affected by changes in pH and are stable in both alkaline and acidic conditions. The solution properties of xanthan are not affected in a pH range of 1-13. Xanthan is compatible with most commercially available thickeners such as sodium alginate, carboxymethyl cellulose, and starch.

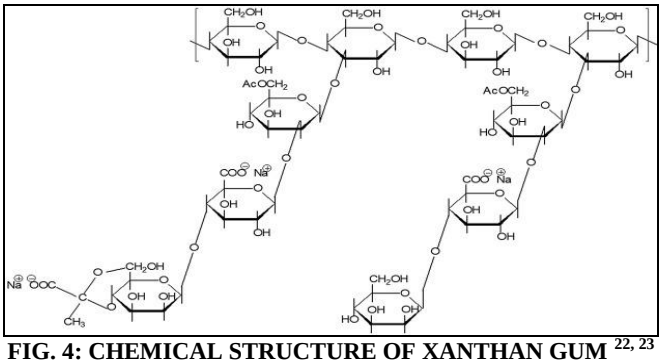

FIG. 4: CHEMICAL STRUCTURE OF XANTHAN GUM [22, 23]

Solubility: Xanthan is highly soluble in cold and hot water, and this behavior is related to the polyelectrolyte nature of the xanthan molecule. Xanthan gum is mainly considered to be no gelling and used for viscosity.

It hydrates rapidly in cold water without lumping to give reliable viscosity encouraging its use as a thickener stabilizer, emulsifier, and foaming agent.

Advantages of Xanthan Gum: Xanthum Gum is used as an excipient to increase or decrease the drug release, but not much has been reported concerning its use for sustained drug release.

Xanthan has the potential advantage of drug release with zero-order release kinetics. However, its major drawback is that the drug release is influenced by the pH and the presence of ions in the medium.

Carrageenan: [24, 25, 26] Carrageenan, naturally occurring repeating units of galactose and 3, 6-anhydrogalactose high molecular weight anionic gel-forming polysaccharides, extracted from red seaweeds species such as Euchema, Chondrus crispus, Iridaea and Gigartina stellate.

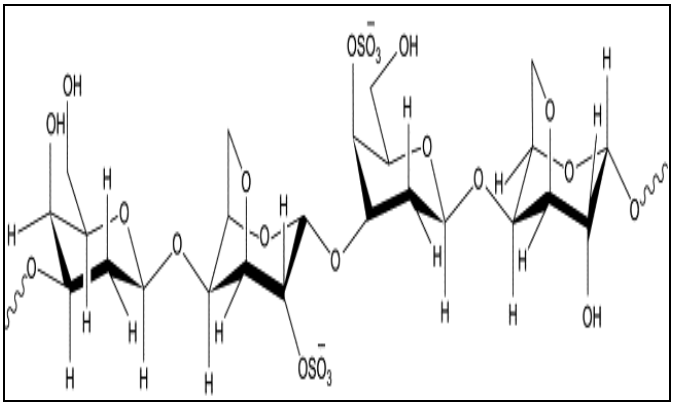

FIG. 5: CHEMICAL STRUCTURE OF CARRAGEENAN [24, 25]

Depending on degree of sulfation are classified into different types: λ-carrageenan (three-sulfate), κ-carrageenan (di-sulfate) and ι-carrageenan (monosulfate). Highly sulfated λ-carrageenan is a thickener agent and does not form gel while κ- and ι-carrageenan forms gel, which influences their release kinetics. Carrageenans are mostly utilized because of their superb physical functional properties in food industries, such as bulking agent, thickening, stabilizing abilities and gelling. Because of the high robustness, good compatibility and persistent viscoelasticity of the tablet during granulation and compression, it proved to be useful as tablet excipient agents. Hence, for sustained release formulations, carrageenans are suitable excipients. The chemical reactivity of carrageenans is primarily due to their half-ester sulfate groups, which are strongly anionic, being comparable to inorganic sulfate in this respect. The free acid is unstable and commercial carrageenans are available as stable sodium potassium and calcium salts or, most commonly, as a mixture of these. The associated cations together with the conformation of the sugar units in the polymer chain, determine the physical properties of the carrageenans. The functionality of carrageenans in various applications depends largely on their rheological properties. Viscosity depends on concentration, temperature, the presence of other solutes, and the type of carrageenan, and its molecular weight. Viscosity increases nearly exponentially with concentration

Solubility: Carrageenans are commercially important hydrophilic colloids (water-soluble gums) which occur as matrix material in numerous species of red seaweeds (Rhodophyta) wherein they serve a structural function analogous to that of cellulose in land plants. Chemically they are highly sulfated galactans. Due to their half-ester sulfate moieties, they are strongly anionic polymers.

Applications of Carrageenans: Carrageenan is a selective inhibitor of several enveloped viruses, such as human pathogens as human immunodeficiency virus, herpes simplex virus (HSV), human cytomegalovirus, human rhinoviruses, and others. A study showed Carrageenan-based bio-nano-composites, which has been used as a drug deliverytool. It can be used in both topical bases and suppository bases. It has excellent thickening and binding properties, for which carrageenan is being used in dentifrices and prevents solid-liquid separation.

TABLE 2: EXAMPLES OF POLYMERS USED IN MICROBEADS [27, 28, 29, 30, 31, 32, 33, 34, 35]

Polymers	Physicochemical Properties	Applications
Sodium Alginate [27, 28]	Water soluble, anioniccoacervation with ions(Ca^{2+}, Sr^{2+}, Ba^{2+}), polycations (chitosan)or poly-l-lysine	Swelling ability (200–300_of its own weight fromwater) pH-dependent swelling nontoxic, non-irritant low density (capable offloading in gastric juice)
Chitosan [29, 30]	disintegrant, binder, viscosity increasing. Soluble in weak acids, mucoadhesive reacts with negatively charged surfaces	Diffusion, erosion,in situ forming hydrogels. Antifungal, antibacterial, reduces LDL (low-density lipoprotein), tissue regenerative, pulmonarydelivery, Ion tropic gelation, coacervation with anions, modified emulsification

Pectin [31]	Negatively charged molecule, Gelation depends on the degree of esterification, cation (Ca, Zn) concentration in solution, temperature and pH In situ gelling,	Sustained delivery, dietary fiber, drug delivery in colorectal carcinoma (5-FU),antiviral activity.
Guar gum [30]	Water-soluble, nonionic, galactomannanforms a thixotropic solution, stable atpH 4–10.5	Controlled-release, colon-targeted release, appetite suppressant, thermoreversible
Xanthan gum [33]	Soluble in warm and cold water, not affected by pH anionic polyelectrolyte. No gelation at room temp, cryogelation possible, stable viscosity over wide pH range, surface activity	Emulsion stabilizer, controlled-release, colon-targeted, swelling, diffusion, matrix erosion.
Carrageenan [34, 35]	Anionic polymer, Carrageenan: shear thinning thixotropic gel-forming	Carrageenan: elastic gel is formed with K^+, $Ca^{2+,}$ thermoreversible gel Forming Release by erosion (physical contact-Scentcaps®), effective against HPV(human papilloma virus)

CONCLUSION: This review has covered the major concerns about natural and synthetic polymers, their types, uses, and degradability. Polymers have been used as a main tool to control the drug release rate from the formulations. Polymersaremacromolecules having very large chains, contain a variety of functional groups, can be blended with other low and high molecular-weight materials, and can be tailored for any application.

The purpose of this article is to explore and constitute the concepts that a biomaterial can change with the radically new types of substance that we are using, in many new ways, in medical technology so that it will attract the attention of specialists in the study of natural-based biopolymers. Polymers, particularly in the formulation of microbeads, microspheres, nanoshperes are used in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted, specific and effective *in-vivo* delivery, and supplements as miniature versions of diseased organ and tissues in the body.

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